Cross-education of wrist extensor strength is not influenced by non-dominant training in right-handers.

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Running title: Corticospinal inhibition and cross-education of strength.

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ABSTRACT

Purpose: Cross-education of strength has been proposed to be greater when completed by the dominant limb in right handed humans. We investigated whether the direction of cross-education of strength and corticospinal plasticity are different following right or left limb strength training in right-handed participants. **Methods:** Changes in strength, muscle thickness and indices of corticospinal plasticity were analyzed in 23 adults who were exposed to 3-weeks of either right-hand strength training (RHT) or left-hand strength training (LHT). **Results:** Maximum voluntary wrist extensor strength in both the trained and untrained limb increased, irrespective of which limb was trained, with TMS revealing reduced corticospinal inhibition. **Conclusions:** Cross-education of strength was not limited by which limb was trained and reduced corticospinal inhibition was not just confined to the trained limb. Critically, from a behavioral perspective, the magnitude of cross-education was not limited by which limb was trained.

ABREVIATIONS

AMT: Active motor threshold

CON: Control

ECR: Extensor carpi radialis muscle

IHI: Interhemispheric inhibition

LHT: Left hand training

MEP: Motor-evoked potential

M_{MAX}: Maximum compound action potential

M1: Motor cortex

MVIC: Maximum voluntary isometric contraction

1RM: One-repetition maximum

RHT: Right hand training

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

sEMG: Surface electromyography

SICI: Short-interval intracortical inhibition

TMS: Transcranial magnetic stimulation

INTRODUCTION

It is well recognized that unilateral strength training improves motor performance of not only the practiced limb, but also in the unpracticed contralateral homologous limb (Farthing and Zehr 2014; Ruddy and Carson 2013). Meta-analyses have shown that, on average, an 8% increase in strength of the untrained limb is observed following unilateral strength training and that the magnitude of cross-education is associated with the quantity of practice (Carroll et al. 2006; Zult et al. 2014).

Although the exact locus of neural adaptation that underpin cross-education remain unresolved, previous studies showed changes in the primary motor cortex (M1), ipsilateral to the trained limb in the form of increased corticospinal excitability (Goodwill et al. 2012; Kidgell et al. 2011), reduced short-interval intracortical inhibition (SICI) (Goodwill et al. 2012), reduced interhemsipheric inhibition (IHI) (Hortobagyi et al. 2011) and increases in voluntary activation (Lee et al. 2009). Recently, it has been speculated that cross-education may be induced by either 'cross-activation' (a spill-over of neural drive from the active to the inactive hemisphere), or 'bilateral access' (development of motor engrams that can be accessed by either hemisphere) (Ruddy and Carson 2013; Lee et al. 2010). Although these theoretical models are not mutually exclusive, they do suggest that the 'untrained' M1, ipsilateral to the trained limb, plays a critical role in mediating the cross-education effect (Ruddy and Carson 2013). An interesting question to address regarding the directionality effects of cross-education, is that no previous studies have addressed whether there are hemispheric differences in the extent of corticospinal excitability and inhibition and whether these responses differ when using the dominant or non-dominant limb in right-handed individuals. Interestingly, the representation of upper limb muscles and synaptic connectivity within the M1 is larger in the dominant hemisphere than the non-dominant hemisphere in right-handed individuals (Hammond 2002) and as such, it is possible that the extent of corticospinal excitability and or inhibition, may differ following unilateral strength training of either the dominant or non-dominant limb in right-handed individuals.

Research shows that following motor skill training, certain motor skills only transfer in one direction, either direction or not at all (Criscimagna-hemminger et al. 2003; Hinder et al. 2013), suggesting that the novelty and complexity of the motor task might be important (Holper et al. 2009). With regards to the cross-education of strength, only one study has investigated the directionality effects of cross-education in right-handed individuals (Farthing et al. 2005). In this study, right-handed participants completed a 6-week training program of maximal isometric ulnar deviation training. Participants who trained their dominant right arm exhibited a significant cross-education of strength (~39%) to the untrained non-dominant left arm. However, those that trained their non-dominant left arm showed a non-significant rise in the cross-education effects to their untrained dominant right arm (~9%).

The clinical efficacy of cross-education has been utilised in immobilization studies (Farthing et al. 2009; Farthing et al. 2011; Magnus et al. 2010; Pearce et al. 2012) and following distal wrist fracture (Magnus et al. 2013). However, if directionality of cross-education is unidirectional, as previously described (Farthing et al. 2005), then one must reconsider the clinical efficacy for the use of cross-education as an intervention following unilateral injury to the dominant right limb. Given that much of the cross-education literature has only considered cross-education

effects following unilateral strength training of the dominant right limb (Farthing et al. 2007; Hortobagyi et al. 2011; Kidgell et al. 2011; Lee et al. 2009), the objective of this study was to examine the directionality effects of cross-education following unilateral strength training of either the dominant or non-dominant wrist in right-handed individuals. A secondary objective was to examine the corticospinal responses associated with unilateral strength training and cross-education. Specifically, we hypothesised that, in right limb dominant participants, cross-education of strength would be greater following right limb training to the left non-trained limb compared to non-dominant left limb training. Furthermore we hypothesised that changes in TMS parameters (MEP amplitude and silent period duration) would change in both trained and untrained limbs to reflect the cross-education of strength.

METHODS

Participants

23 right handed (assessed by the Edinburgh handedness questionnaire; laterality quotient of 85.0 ± 2.0) males (n =11) and females (n = 12) aged 18-36 years were selected on a voluntary basis, and provided written informed consent. All participants had not participated in strength training for a minimum of 12 months, and were free from any known history of peripheral or neurological impairment, as assessed by pre-screening TMS questionnaire. Seven participants (3 males and 4 females, aged 25.20 ± 2.71 years) were randomly allocated to the control group, eight participants (4 males and 4 females, 22.20 ± 2.06 years) to right hand training (RHT) and eight participants (4 males and 4 females, aged 21.00 ± 2.21 years) to the left hand training (LHT). The study complied with the Declaration of Helsinki and was approved by the University Human Research Ethics Committee.

Experimental design

Participants were required to attend a familiarisation session to introduce testing procedures. Following the familiarisation session, which involved exposure to TMS (establishment of active motor threshold) and strength testing, 3 days prior to baseline testing, participants were allocated to either a control (CON), left-hand training (LHT) or right-hand training (RHT) group based upon baseline strength. Figure 1 outlines the experimental protocol. Participants in the training groups underwent TMS and one repetition maximum (dynamic concentric 1RM) strength testing before and after a 3-week supervised strength training program. Control participants only undertook pre- and post-testing for TMS and 1RM strength, but were instructed to not specifically strength train, but to maintain their current level of physical activity. Post-training testing was carried out between 24 and 36 hours after the final training session. Measures of corticospinal excitability and corticospinal inhibition preceded all performance testing to ensure that any neurophysiological changes were as a result of the training intervention and not due to the test order.

Strength training protocol

Participants allocated to the LHT and RHT groups participated in supervised strength training 3 times per week (9 sessions in total) on non-consecutive days for 3-weeks, which required flexion/extension of the wrist with a weighted dumbbell. Training was performed in a seated position with the left or right forearm pronated and rested on a horizontal bench, with posture identical to pre and post strength testing procedures. The training took place under supervision, and consisted of 4 sets of 6-8 repetitions at 70% 1-RM, with 3 min recovery between sets; an electronic metronome guided the repetition timing of 3 s for the concentric phase and 4 s for the eccentric phase (Hendy and Kidgell 2013). The duration of each strength training sessions was approximately 20 min. When participants were able to complete 4 sets of 8 repetitions, through 20° of wrist flexion /extension, the training load was increased by 5%. The control group continued performing typical daily activities without undertaking any additional training.

Dynamic strength testing

Maximal voluntary dynamic strength of the wrist extensors was determined by a standard unilateral single repetition maximum (1RM) test with an adjustable weighted dumbbell. Participants were seated in the isokinetic dynamometer, shoulders relaxed and elbow flexed at 90°, with the forearm pronated and fastened firmly on the arm rest. The dynamometer attachment was removed and a weighted dumbbell was used to allow for a more functional measure of dynamic strength. The wrist was positioned such that the styloid process sat just beyond the edge of the arm rest, and the relaxed hand hung free. The researcher placed the dumbbell in the participant's hand, and instructed them to grasp the dumbbell and completely extend the wrist, moving the hand upwards. A trial was considered successful when the participant was able to lift the weight from a rested position hanging below the arm rest between 15-20° of wrist flexion, to at least 15° beyond horizontal, measured by an electromagnetic goniometer (3DM-GX2®, Williston, Vermont, USA). The starting weight of the dumbbell was estimated by the researcher, and the weight was increased in increments of 0.25 kg or 0.5 kg as appropriate, until the participant could no longer produce a successful trial. Each trial was separated by 3 min rest to prevent fatigue.

Surface electromyography

The area of electrode placement was shaved, abraded and cleaned with 70% isopropyl alcohol. Surface electromyography (sEMG) was recorded from the right and left extensor carpi radialis (ECR) muscles using bipolar Ag-AgCl electrodes. The electrodes for the ECR 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 (Selvanayagam et al. 2012). A common ground was placed on the wrist. sEMG signals were amplified (x1000), band pass filtered (high pass at 13 Hz, low pass at 1000 Hz), digitized online at 2 kHz, recorded (1 sec) and analysed using Power Lab 4/35 (AD Instruments, Bella Vista, Australia). Pre-stimulus root mean square EMG (*rms*EMG) activity was determined in the wrist extensors 100 ms prior to each TMS stimulus during pre and post testing. Any trial in which pre-stimulus *rms*EMG exceeded 5 ± 2% of maximal *rms*EMG was discarded and the trial repeated.

Transcranial magnetic stimulation

TMS was delivered using two Magstim 200^2 stimulators (Magstim Co, Dyfed, UK) connected via a Bistim unit and a single 70 mm figure of eight coil. The motor hotspot for the ECR was determined and active motor threshold (AMT) was established as the intensity at which at least five of 10 stimuli produced MEP amplitudes of greater than 200 μV in the right and left ECR muscle. To ensure all stimuli were delivered to the optimal motor hotspot throughout testing, participants wore a tight fitting cap marked with a latitude-longitude matrix, positioned with reference to the nasion-inion and interaural lines. Single-pulse recruitment curves were collected during low level isometric contractions of the wrist extensors. Low level contractions were performed by maintaining a straight (180˚) wrist and fingers[22], which equated to 5 ± 2% of *rms*EMG maximum, which was obtained during MVIC testing. Consistent muscle activation was confirmed and consistent between testing sessions, by recording pre stimulus *rms*EMG throughout the session. For a single recruitment curve, 10 stimuli were delivered at each intensity (10% stimulator output steps) up to 40% above AMT.

Corticospinal excitability was determined from the peak-to-peak amplitude of MEPs evoked as a result of stimulation and was measured in the left and right ECR muscle, contralateral to the cortex being stimulated. All MEP amplitudes were analysed (LabChart 8 software, ADInstruments, Bella Vista, NSW, Australia) after each stimulus was automatically flagged with a cursor, providing peak-to-peak values in μV, which were then averaged and normalized to the maximal compound action potential (M_{MAX}).

Corticospinal inhibition was determined by applying ten TMS pulses over the right and left motor cortex at each stimulus intensity above AMT (10% stimulator output steps), to evoke a silent period in the left and right ECR, during low level voluntary activity (5% ± 2% of *rms*EMG maximum). The average duration of the silent period over the ten trials was calculated. The beginning of the MEP preceding the silent period and the subsequent onset of the EMG signal were manually selected and used to indicate the beginning and end of the silent period, respectively Shorter silent period durations imply a reduction in intracortical inhibition, thereby contributing to increased net corticospinal excitability, whereas longer silent period durations demonstrate greater intracortical inhibition (Calancie et al. 1987). All processing was completed by the same investigator who was blinded to each condition (Christie and Kamen 2014).

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 for the test intensity was set at 120% of AMT, which was determined during familiarisation and adjusted if there was a change in AMT following training. The conditioning stimulus for paired-pulse stimulation was set at 80% of AMT, the inter-stimulus interval was 3 ms (Kidgell et al. 2015). The conditioned MEP amplitude was expressed as a percentage of the unconditioned test MEP amplitude to calculate the level of intracortical inhibition.

Maximum compound muscle action potential

Direct muscle responses were obtained from the left and right ECR muscle by supramaximal electrical stimulation (pulse width 1 ms) of the radial nerve under resting conditions (DS7A, Digitimer, UK). The site of stimulation that produced the largest M-wave was located by positioning the bipolar electrodes in the radial groove

on the posterior surface of the humerus. An increase in current strength was applied to the radial nerve until no further increase was observed in the sEMG amplitude (M_{MAX}). To ensure maximal responses, the current was increased an additional 20% and the average M_{MAX} was obtained from five stimuli each separated by 6-9 sec. M_{MAX} was recorded at baseline and following the training intervention, to control for possible changes in peripheral muscle excitability that could influence MEP amplitude.

Muscle thickness

Thickness of the wrist extensors (a combined measure of the posterior forearm musculature in cm) was measured with a portable ultrasound device (Sonosite Ultrasound, Springfield, NJ) after a protocol adapted from Magnus et al. (2010). The site of measurement was determined by marking the skin two thirds of the distance between the styloid process and the lateral epicondyle while the participant rested their forearm on a bench in a pronated position, with the elbow flexed at 90°. The 8- to 15-Hz transducer probe was lubricated with transmission gel and placed lightly on the marked area of the skin, ensuring minimal compression of the muscle before measurement. The average of six readings served as the final value for muscle thickness. Reproducibility of wrist extensor muscle thickness was completed on a subsample of eight participants on two separate occasions, 1 week apart (Coefficient of variation of 2.4%). Ultrasonography was performed by the same sonographer who was blinded to the training conditions.

Statistical analysis

All data was screened for normality using Mauchly's Test of Sphericity, specifically looking at Greenhouse-Geisser and Huynh-Feldt correction to test the equality of variance. To ensure that there were no significant differences between groups at baseline, a one-way analysis of variance (ANOVA) was used for all dependent variables (1-RM wrist extension strength, rmsEMG, muscle thickness, corticospinal excitability, inhibition and SICI. A 3 (group) x 2 (time) multivariate analysis appropriate for multiple dependent variables with repeated measure was used to determine any differences between groups for the variables, rmsEMG, M_{MAX}, muscle thickness, corticospinal excitability, cortical silent period duration and SICI. If significant main effects were found, a Bonferroni correction was used for *post-hoc* testing to compare group interaction (control, LHT and RHT) by time (pre, post) for each dependent variable. The level of significance was set at $P < 0.05$. SPSS version 23.0 (SPSS Inc., Chicago, III) was used for the statistical analysis. All data are presented as mean ± standard deviation (SD).

RESULTS

Voluntary dynamic strength (1-RM)

At baseline there were no differences in 1-RM strength between limbs ($P = 0.54$). Following unilateral strength training there was a significant main effect for TIME ($P <0.001$) and a GROUP x TIME interaction ($P < 0.001$). For the *trained limb*, Post hoc analyses showed a 22% increase in strength (pre 8.90 ± 2.50 kg compared to post 10.80 ± 2.80 kg) following LHT and an 18% increase (pre 9.80 ± 3.00 kg compared to post 11.20 ± 2.60 kg) following RHT compared to control (both, $P < 0.001$). For the *untrained limb*, Post hoc analyses revealed a 15% increase in strength (pre 8.80 ± 2.70 kg compared to post 10.20 ± 3.60 kg) following LHT and a 10% increase (pre

7.90 ± 2.90 kg compared to post 8.74 ± 3.10 kg) following RHT compared to a 1% change in the control (pre 8.40 ± 2.60 to post pre 8.50 ± 2.62; both, $P < 0.001$; Figure 2B).There was no difference in the magnitude of strength gain overtime for the trained limb ($P = 0.42$) or the untrained limb between LHT and RHT ($P = 0.29$).

Muscle thickness

There was no TIME effect ($P = 0.25$) or GROUP x TIME interaction for muscle thickness ($P = 0.192$). Muscle thickness for the control group was 1.67 ± 0.09 cm pre and 1.68 ± 0.09 cm post, LHT pre 1.60 ± 0.13 cm pre and 1.64 ± 0.14 cm post, RHT pre 1.81 ± 0.13 cm pre and 1.89 ± 0.13 cm post, respectively for the *trained wrist extensors*. For the *untrained wrist extensors*, muscle thickness was 1.67 ± 0.09 cm pre and 1.69 ± 0.10 cm post, LHT pre 1.61 ± 0.12 cm pre and 1.67 ± 0.12 cm post and for RHT pre 1.80± 0.15 cm pre and 1.75 ± 0.15 cm post, respectively.

Surface electromyography and M_{MAX}

Average *rms*EMG as a percentage of maximal voluntary EMG was calculated 100 ms before TMS stimulus trigger for each stimulus intensity for both single and paired-pulse TMS. At baseline there were no differences in average *rms*EMG between groups for single-pulse TMS or paired-pulse TMS (all P >0.05) and there were no GROUP x TIME interactions ($P > 0.05$; Table 1) for *rms*EMG for single-pulse TMS. For paired-pulse *rms*EMG, there were also no GROUP x TIME interactions ($P > 0.05$; Table 1).

At baseline there were no differences in M_{MAX} between groups ($P > 0.05$) and no GROUP x TIME interaction ($P > 0.05$; Table 1).

Corticospinal excitability

Figure 3A-C display MEP amplitude as a percentage of M_{MAX} for the contralateral trained M1. For the *trained wrist extensors*, no differences in MEP amplitude at 10% above AMT (expressed as a percentage of M_{MAX}) was detected (Mean MEP amplitude 11.50 ± 7.80% of M_{MAX}) between groups at baseline ($P = 0.16$) and there were no GROUP x TIME interactions ($P = 0.06$). There were no differences in MEP amplitude at 20% above AMT (Mean MEP amplitude 22.70 ± 11.10% of M_{MAX}) between groups at baseline ($P = 0.73$) and no GROUP x TIME interactions present ($P = 0.11$). Again, there were no differences in MEP amplitude at 30% above AMT (Mean MEP amplitude 26.40 ± 10.30% of M_{MAX}) between groups at baseline ($P = 0.92$) and there were no GROUP x TIME interactions ($P = 0.08$). Finally, there were no differences in MEP amplitude at 40% above AMT (Mean MEP amplitude 31.50 ± 12.10% of M_{MAX}) between groups at baseline ($P = 0.96$) and there were no GROUP x TIME interactions ($P = 0.21$, Table 1).

Figure 4A-C displays MEP amplitude as a percentage of M_{MAX} for the ipsilateral untrained M1. For the *untrained wrist extensors*, no differences in MEP amplitude at 10% above AMT was detected (Mean MEP amplitude 11.80 ± 11.90% of M_{MAX}) between groups at baseline ($P = 0.90$) and there were no GROUP x TIME interactions ($P = 0.27$). There were no differences in MEP amplitude at 20% above AMT (Mean MEP amplitude 21 ± 14.50% of M_{MAX}) between groups at baseline ($P = 0.96$) and there were no GROUP x TIME interactions ($P =$

0.78). Again, no differences in MEP amplitude at 30% above AMT was detected (Mean MEP amplitude 26.60 ± 16.60% of M_{MAX}) between groups at baseline ($P = 0.72$) and there were no GROUP x TIME interactions ($P = 0.36$). Finally, there were no differences in MEP amplitude at 40% above AMT (Mean MEP amplitude 38.80 ± 18.40% of M_{MAX}) between groups at baseline ($P = 0.85$) and there were no GROUP x TIME interactions ($P = 0.59$, Table 1).

Corticospinal inhibition

Silent period duration for the contralateral 'trained' and ipsilateral 'untrained' M1 for the control, LHT and RHT groups are presented in Figure 5A-C and 6A-C respectively. Silent period duration for the contralateral 'trained' M1 for the control, LHT and RHT groups are presented in Figure 5A-C. For the *trained wrist extensors*, no differences in silent period duration were detected at 10% above AMT (Mean SP duration 113 ± 40 ms) between groups at baseline ($P = 0.80$) and there were no GROUP x TIME interactions ($P = 0.81$). There were no differences in SP duration at 20% above AMT (Mean SP duration 157 ± 34 ms) between groups at baseline, $P = 0.26$), however there was a main effect for TIME ($P = 0.049$), but no GROUP x TIME interaction ($P = 0.13$). Post hoc testing showed that only following LHT, silent period duration reduced by 22 ms (from 172 ± 37 ms to 150 ± 18 ms, $P = 0.01$), despite RHT reducing the silent period duration by 12 ms (144 ± 28 ms to 132 ± 35 ms, $P = 0.21$). The magnitude of change in silent period duration following LHT was not different RHT (P = 0.11) or the control group ($P= 0.24$). Again, there were no differences in silent period duration at 30% above AMT was detected (Mean SP duration 183 ± 27 ms) between groups at baseline ($P = 0.34$) and there were no GROUP x TIME interactions ($P = 0.22$). There was a trend over time for a reduction in silent period duration following LHT, with a reduction of 20 ms (196 ± 30 ms to 176 ± 27 ms, $P = 0.059$), and a 10 ms reduction following RHT (176 ± 27 ms to 166 ± 40 ms). Finally, there were no differences in silent period duration at 40% above AMT (Mean SP duration 183 ± 27 ms) between groups at baseline ($P = 0.93$), however, there was a main effects for TIME ($P = 0.002$), but no GROUP x TIME interaction ($P = 0.15$). Following LHT, silent period duration reduced by 14 ms (from 196 ± 35 ms to 182 ± 30 ms) and RHT reduced the silent period duration by 22 ms (194 ± 15 ms to 1172 ± 28 ms). There was no difference in the magnitude of reduction in silent period duration following left or right limb unilateral strength training (group effect; $P = 0.89$).

Silent period duration for the ipsilateral 'untrained' M1 for the control, LHT and RHT groups are presented in Figure 6A-C. For the *untrained wrist extensors*, no differences in silent period duration were detected at 10% above AMT (Mean SP duration 98 ± 39 ms) between groups at baseline ($P = 0.89$) and there were no GROUP x TIME interactions ($P = 0.43$). There were no differences detected in silent period duration at 20% above AMT (Mean SP duration 147 ± 41 ms) between groups at baseline ($P = 0.84$) and there were no GROUP x TIME interactions ($P = 0.36$). There were no differences detected in SP duration at 30% above AMT (Mean SP duration 169 ± 31 ms) between groups at baseline ($P = 0.32$), however, there was a GROUP x TIME interaction ($P = 0.004$). *Post hoc* analysis showed that following RHT, silent period duration reduced by 22 ms (154 ± 20 ms to 132 ± 25 ms, $P = 0.001$), which was different to the control group ($P = 0.001$), but not different to the LHT group ($P = 0.07$). However, there was a trend for a reduction in silent period duration following LHT with a reduction of 10 ms (from 177 ± 332 ms to 167 ± 35 ms, $P = 0.07$). Finally, there were no differences in silent period duration at 40% above

AMT (Mean SP duration 183 ± 30 ms) between groups at baseline (P = 0.47), but there was a GROUP x TIME interaction (P < 0.001). *Post hoc* analysis revealed that silent period duration reduced by 47 ms (171 ± 28 ms to124 ± 29 ms) in the left untrained limb following RHT compared to a 2 ms (188 ± 19 ms to186 ± 26 ms) reduction following LHT (P = 0.001) and compared to the control group (P = 0.001).

Intracortical Inhibition

For the *trained wrist extensors*, no differences were detected in short-interval intracortical inhibition (mean 42 ± 29% expressed as a percentage of the test response) between groups at baseline (P = 0.36) and there were no GROUP x TIME interactions (P = 0.32). Similarly, for the *untrained wrist extensors*, there were no differences in SICI (mean 40 ± 30% as a percentage of the test response) between groups at baseline (P = 0.86) and there were no GROUP x TIME interactions (P = 0.74).

DISCUSSION

The main objective of the present study was to determine the directionality of transfer effects following unilateral strength training of the dominant and non-dominant limb in right-handed individuals. We also examined the neural mechanisms thought to be implicated in the cross-education of strength and whether they are implicated by strength training either the dominant or non-dominant limb in right-handed individuals. Most notably this study provides new information that the cross-education of strength occurred after training the dominant *and* non-dominant wrist extensors in right-handed individuals, and that unilateral strength training reduced corticospinal inhibition (time effect) depending on the limb trained (group interaction effect). These data contend previous initial suggestions that the cross-education of strength is unidirectional (Farthing et al. 2005), however more recently Farthing and Zehr (2014) suggested that the effect varies greatly depending on the task and that training the dominant side may enhance the effect. Based upon the present experimental design, our findings support the bi-directional nature of cross-education in right hand dominant participants.

The Cross-education of strength is similar between dominant and non-dominant sides in right-handed individuals.

The increase in the cross-education of strength observed in the current study is larger than previously suggested (7.6%) in a meta-analysis (Carroll et al. 2006); with several other recent cross-education studies showing much greater cross-education effects than the aforementioned meta-analysis (Hortobágyi et al. 2011; Kidgell et al. 2015; Goodwill et al. 2012; Kidgell et al. 2011). Following our training program, the untrained limb increased in strength by 10% and 15% for RHT and LHT, respectively, and the magnitude of strength gain for the trained limbs were 22% for LHT and 18% for RHT. The large cross-education of strength exhibited in this study, may be related to the motor learning effects that are associated with dynamic muscle actions. For example, the change in contralateral strength (irrespective of which limb was trained in right-handed individuals) is larger than previous studies that did isometric training (Lee et al. 2009; Munn et al. 2005). A previous study employed isometric contractions of the ECR, while the current study adopted a dynamic strength training protocol, whereby the timing of each repetition was controlled and as such may have resulted in the observed differences (Lee et al. 2009).

Dynamic strength training that involves both concentric and eccentric contractions has been shown to increase strength when compared with isometric strength training alone and this may also account for the observed differences in contralateral strength **(**Brown et al. 1990). Dynamic contractions might provide more afferent feedback that transfers strength uniformly well in both directions in right-handed individuals.

It is not entirely clear why the current results differ to Farthing et al. (2005), but it might be related to the strength training task performed. This is particularly interesting, given that our study used a less intense strength training stimulus, a shorter duration of intervention, a lower training percentage of maximum strength and less number of sets compared to the study by Farthing et al. (2005). The degree of asymmetry in the cross-education of motor skills depends on several factors, including how skilled, or complex a task is, and theoretically how novel it is to those performing it (Holper et al. 2009; Ruddy and Carson 2013). Therefore, unilateral strength training that encompasses a component of task complexity (i.e. performing a paced strength training task), conceptually could transfer uniformly between limbs, and is evident in the current study. The inclusion of paced repetitions was used to add an element of novelty and conceivably task complexity to each repetition via participants pacing their movement to an external stimulus provided by a metronome (Holper et al. 2009; Ackerly et al. 2011; Thaut et al. 2002; Leung et al. 2015). Farthing et al. (2005) suggested that for cross-education to occur in both directions, the task must be unfamiliar to both limbs. In the case of that study, isometric ulnar deviation is not a common strength exercise, but the exercise failed to transfer strength in both directions. This is confusing because the current study used a similar task that required a gripping action; however, the complexity of guided wrist extension coupled with dynamic externally paced repetitions might be the determining point to explain differences between studies, outside of the different training intensities and duration of the training period. The rationale for using a slow controlled repetition protocol has been based primarily on previous research suggesting greatest cross-education of strength from slower controlled repetitions and the changes in cortical activation following the complexity of a task (Hortobágyi et al. 1997; Holper et al. 2009).There is evidence to show that metronome-paced motor training compared to self-paced training of the upper limb is associated with greater use-dependent adaptation of the target muscle (Ackerley et al. 2011; Leung et al. 2015).We suspect that the strength training task performed in the current study that used different muscles and training task may have resulted in a different motor learning outcome compared to previous work, but is not limited to the task alone (Farthing et al. 2005). Although, during maximal unilateral muscle contractions, the untrained muscle can exhibit up to greater than 20% of mirror EMG activity (Zijdewind et al. 2006), a limitation to the present study was mirror EMG activity was not measured during training. However, we have previously reported during maximal concentric training of the wrist, mirror sEMG activity is only 1.5% of maximum EMG activity (Kidgell et al. 2015). A further limitation could be that measuring dynamic strength, via the 1-RM method, is not as sensitive as using torque measures such as dynamometry. Nonetheless, dynamic strength is often used clinically to assess voluntary strength and in this instance under the constraints of the current experimental design, the cross-education of strength appears to be bi-directional in right-handed individuals. The current findings also support the directionality effects of cross-education in the clinical setting following wrist fracture (Magnus et al. 2013).

Corticospinal inhibition is reduced following unilateral strength training.

TMS studies have shown increased corticospinal excitability, reduced cortical inhibition and reduced interhemispheric inhibition in the ipsilateral M1 during varying levels of unilateral muscle activity (Hortobágyi et al. 2003; Perez and Cohen 2008; Zijdewind et al. 2006; Hortobágyi et al. 2011; Howatson et al. 2011). We did not detect any training-related change in MEP amplitude in either the contralateral 'trained' or ipsilateral 'untrained'M1, showing that strength training had no effect on corticospinal excitability. The results suggest that the strength training program used in this study did not increase the neural excitability of the contralateral untrained muscle due to chronic changes in synaptic connectivity within specific neural circuits between hemispheres that contribute to the ability to generate force. It is important to recognize that the amplitude of MEPs evoked by single-pulse TMS is not only affected by the excitability of corticospinal cells at the level of the M1 but also at the level of the spinal cord by the excitability of motoneurons innervating the target muscle. In the present study, the excitability of the spinal H-reflex pathway was not assessed, however, based upon previous lower-limb cross-education studies in healthy participants, the H-reflex remains unchanged following unilateral training (Lagerquist et al. 2005; Fimland et al. 2009), but increases following stroke (Dragert and Zehr 2013). The results of the current study in healthy participants, shows that unilateral strength training of the left or right limb in right-handed participants did not alter cortical excitability of the trained and the untrained limb.

A distinctive contribution of the present study is that we have extended knowledge surrounding the potential neural mechanisms contributing to both strength development and the cross-education of strength, as we observed a training-related reduction in corticospinal inhibition that was more pronounced in the ipsilateral "untrained" M1 following RHT. At a minimum, this suggests there are asymmetries in the neural adaptations to cross-education of strength following dominant and non-dominant strength training in right-handed participants. It seems that unilateral strength training of the dominant right limb induces a selective change in the excitability of corticospinal cells controlling the intrinsic muscles of the wrist engaged in the task. However, as there were no distinct difference in the transfer of strength following RHT or LHT training, this asymmetry in corticospinal activity does not seem to underpin the magnitude of change in strength of the untrained limbs respectively. However, because the duration of the silent period is proportional to the stimulus intensity and independent of MEP amplitude, the large reduction in silent period duration reported in the untrained limb following RHT training at higher intensities, shows that interhemsipheric plasticity is greater from the trained M1 to the untrained M1, at least in right-hand dominant participants at higher stimulus intensities.

The result of a reduced silent period duration at several points along the MEP recruitment curve, strongly implicates that adjustments in $GABA_B$ may form an important neural adaptation that contributes to both strength of the trained limb and the cross-education of strength to the untrained limb. Of noticeable importance, the strength training program has affected a specific population of GABAergic cortical neurons, confined to the ipsilateral 'untrained' M1. $GABA_B$ are the most widely distributed GABAergic cortical neurons in the M1 and activation of $GABA_B$ results in the generation of an inhibitory post synaptic potential which hyperpolarizes the postsynaptic neuron and makes it more difficult for the initial axon segment to reach the firing threshold required for the generation of an action potential in corticospinal cells (Watanabe et al. 2002). At least, for the right hand training

group at higher stimulus intensities (i.e. 30 and 40% above AMT), the current findings support a role for reduced synaptic efficacy between intracortical inhibitory neurons and corticospinal neurons, showing that the change in strength in both limbs are, at least in part, due to modulation of the GABAergic projections within the M1.

Although the motor system between left and right brain hemispheres are known to be asymmetrical with physiological differences between sides contributing to asymmetries in hand function (Amunts et al. 1996), we did not observe any difference in motor performance (i.e. voluntary muscle strength) between left and right hand training. While the ipsilateral 'untrained' M1 in right-handed people differentially modulated corticospinal inhibition only at higher TMS intensities, it did not influence the magnitude of cross-education, suggesting that other sites within the cerebral cortex, such as cingulate motor areas, dorsal pre-motor cortices and temporal lobe regions may contribute to the cross-education of strength following dominant and non-dominant limb training (Ruddy and Carson 2013; (Farthing et al. 2007).

There are several limitations to the present study. The addition of measures at a segmental level, particularly cervicomedullary MEPs and H-reflexes, would provide additional information as to the site of adaptation within the corticospinal tract following unilateral strength training. Despite these limitations, the current data can be extended in the broader context to have important implications in the management of injury (i.e. immobilization, stroke) and in attenuating losses in muscle strength across the population (young and older adults) irrespective of which limb is trained in right-handed individuals.

CONCLUSION

The present findings support the notion that the cross-education of strength is not unidirectional and that the magnitude of cross-education was not limited by which limb was trained in right-handed individuals; rather, it appears to be dependent upon the type of strength training task (i.e. dynamic externally paced contractions). Importantly, we have shown that corticospinal inhibition was reduced following RHT at higher TMS intensities, indicating that reduced cortical inhibition is an important early neural adaptation following unilateral strength training that is not just confined to the trained limb. At least in the current experimental design, cortical inhibition plays a greater role than excitability at higher TMS stimulus intensities following RHT compared to LHT. Despite this asymmetry in neural adaptation, it had no effect on the directionality of the cross-education of muscle strength in right-handed participants. These findings have important clinical relevance for cross-education, showing that the transfer of wrist extension strength is not influenced by which limb is trained in right-handed humans, thus being particularly important for upper limb stroke rehabilitation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1: Mean (± SE) for AMT, M_{MAX}, single-pulse TMS pre-stimulus rmsEMG, paired-pulse TMS pre-stimulus at 80% and 120% AMT (CS, TS respectively) prior to and following 3 weeks of unilateral strength training.

		Control (n = 7)		LHT (n = 8)		RHT (n = 8)		
		Pre	Post	Pre	Post	Pre	Post	P value
AMT	cM1	29.38 ±1.54	29.13 ± 1.42	34.50 ± 4.27	31.88 ± 2.45	31.00 ± 2.75	32.00 ± 3.14	0.24
SI	iM1	29.00 ± 1.67	28.38 ± 1.77	29.50 ± 2.20	31.25 ± 2.80	33.43 ± 2.70	32.86 ± 3.07	0.23
CS	cM1	23.63 ± 1.18	23.38 ± 1.07	27.63 ± 3.42	25.50 ± 1.95	24.71 ± 2.25	25.43 ± 2.51	0.24
	iM1	23.13 ±1.38	23.88 ± 1.44	24.25 ± 1.69	25.63 ±2.10	26.86 ± 2.19	26.29 ± 2.44	0.25
TS	cM1	35.13 ± 1.89	34.88 ±1.78	41.38 ± 5.12	38.25 ± 2.94	37.29 ± 3.26	38.57 ±3.78	0.23
	iM1	34.88 ± 1.96	32.88 ± 2.84	35.38 ± 2.63	37.50 ± 3.39	40.00 ± 3.21	40.57 ± 3.65	0.22
Mwave (mV)	cM1	15.04 ± 4.36	15.39 ± 4.31	16.70 ± 4.12	16.60 ± 4.27	19.33 ± 2.76	19.88 ± 2.79	0.58
	iM1	17.54 ± 4.17	17.87 ± 4.10	17.07 ± 3.47	17.60 ± 3.46	20.31 ± 3.37	19.94 ± 3.81	0.44
SP rmsEMG ($\%MVC_{MAX}$)	cM1	4.40 ± 0.67	3.97 ± 0.76	4.82 ± 0.92	4.24 ± 0.70	5.57 ± 0.81	5.78 ± 1.05	0.53
	iM1	4.05 ± 0.74	3.64 ± 0.57	4.21 ± 0.68	4.93 ± 0.32	4.43 ± 0.52	4.18 ± 0.24	0.38
PP rmsEMG ($\%MVC_{MAX}$)	cM1	3.29 ± 0.60	3.09 ± 0.62	3.11 ± 0.55	3.25 ± 0.61	4.50 ± 0.89	4.54 ± 1.07	0.71
	iM1	3.09 ± 0.38	2.90 ± 0.50	2.41 ± 0.19	3.27 ± 0.50	3.03 ± 0.20	4.16 ± 0.40	0.11

cM1: contralateral cortex (trained limb); iM1: ipsilateral cortex (untrained limb); SI: stimulus intensity; CS: conditioning stimulus intensity; TS: test stimulus intensity; Mwave: maximum compound action potential; Single pulse (SP) rmsEMG was pooled across all four stimulus intensities (AMT +10, 20, 30 & 40). *P* values represent the repeted-measures ANOVA for AMT, SI, CS, TS, Mwave, SP rmsEMG, PP rmsEMG for the cMI and iMI.

FIGURE LEGENDS

Figure 1: Schematic representation of the experimental design with measures obtained prior and following three weeks of unilateral strength training. Pre and post measures included assessment of peripheral muscle excitability (M-waves), corticospinal excitability and inhibition recruitment curves, short-interval intracortical inhibition (SICI) and one-repetition maximum (1RM) strength test of the right and left wrist extensors.

Figure 2A-B: Mean (± SE) changes in 1-RM strength of the right and left wrist extensors following three weeks of unilateral strength training. **(A)** Trained limb; **(B)** Untrained limb. $^{+}$ denotes significant to baseline; * denotes significant control group.

Figure 3A-C: Mean (± SE) change in MEP amplitude (% M_{MAX}) of the contralateral (trained) motor cortex following three weeks of unilateral strength training of the wrist extensors. **(A)** Right hand trained wrist extensors **(B)** Left hand trained wrist extensors **(C)** Control (no training).

Figure 4A-C: Mean (± SE) change in MEP amplitude (% M_{MAX}) of the ipsilateral (untrained) motor cortex following three weeks of unilateral strength training of the wrist extensors. **(A)** Right hand trained wrist extensors **(B)** Left hand trained wrist extensors **(C)** Control (no training).

Figure 5A-C: Mean (± SE) changes in silent period duration of the contralateral (trained) motor cortex following three weeks of unilateral strength training of the wrist extensors. **(A)** Right hand trained wrist extensors **(B)** Left hand trained wrist extensors **(C)** Control (no training). $^{+}$ denotes significant to baseline.

Figure 6A-C: Mean (± SE) changes in silent period duration of the ipsilateral (untrained) motor cortex following three weeks of unilateral strength training of the wrist extensors. **(A)** Right hand trained wrist extensors **(B)** Left hand trained wrist extensors **(C)** Control (no training). $^{+}$ denotes significant to baseline; * denotes significant control group; $^{\wedge}$ denotes significant to left hand trained.

Figure 1

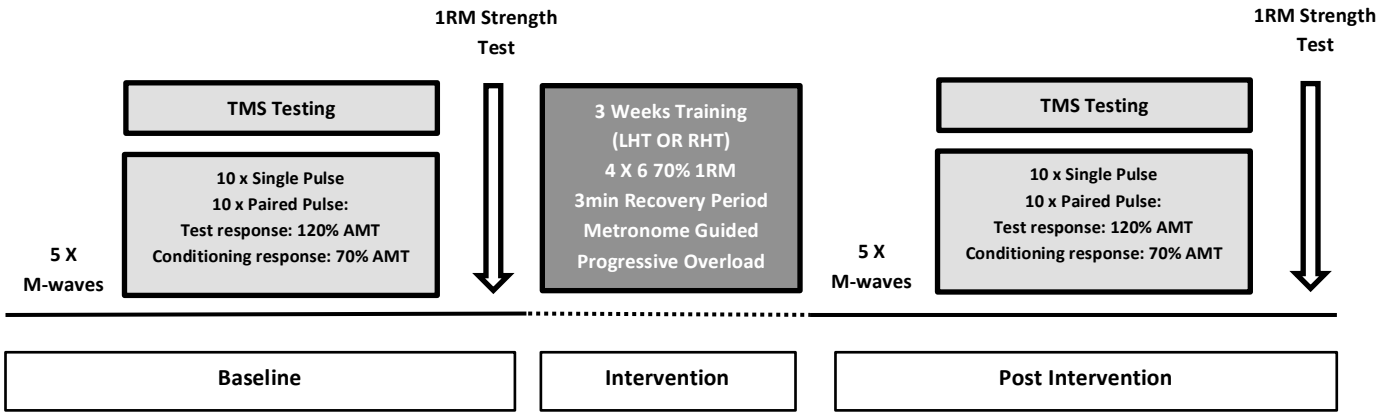
1RM Strength Test
1RM Strength Test
TMS Testing
TMS Testing
10 x Single Pulse
10 x Paired Pulse:
Test response: 120% AMT
Conditioning response: 70% AMT
3 Weeks Training
(LHT OR RHT)
4 X 6 70% 1RM
3min Recovery Period
Metronome Guided
Progressive Overload
10 x Single Pulse
10 x Paired Pulse:
Test response: 120% AMT
Conditioning response: 70% AMT
5 X
M-waves
5 X
M-waves
Baseline
Intervention
Post Intervention

Figure 2

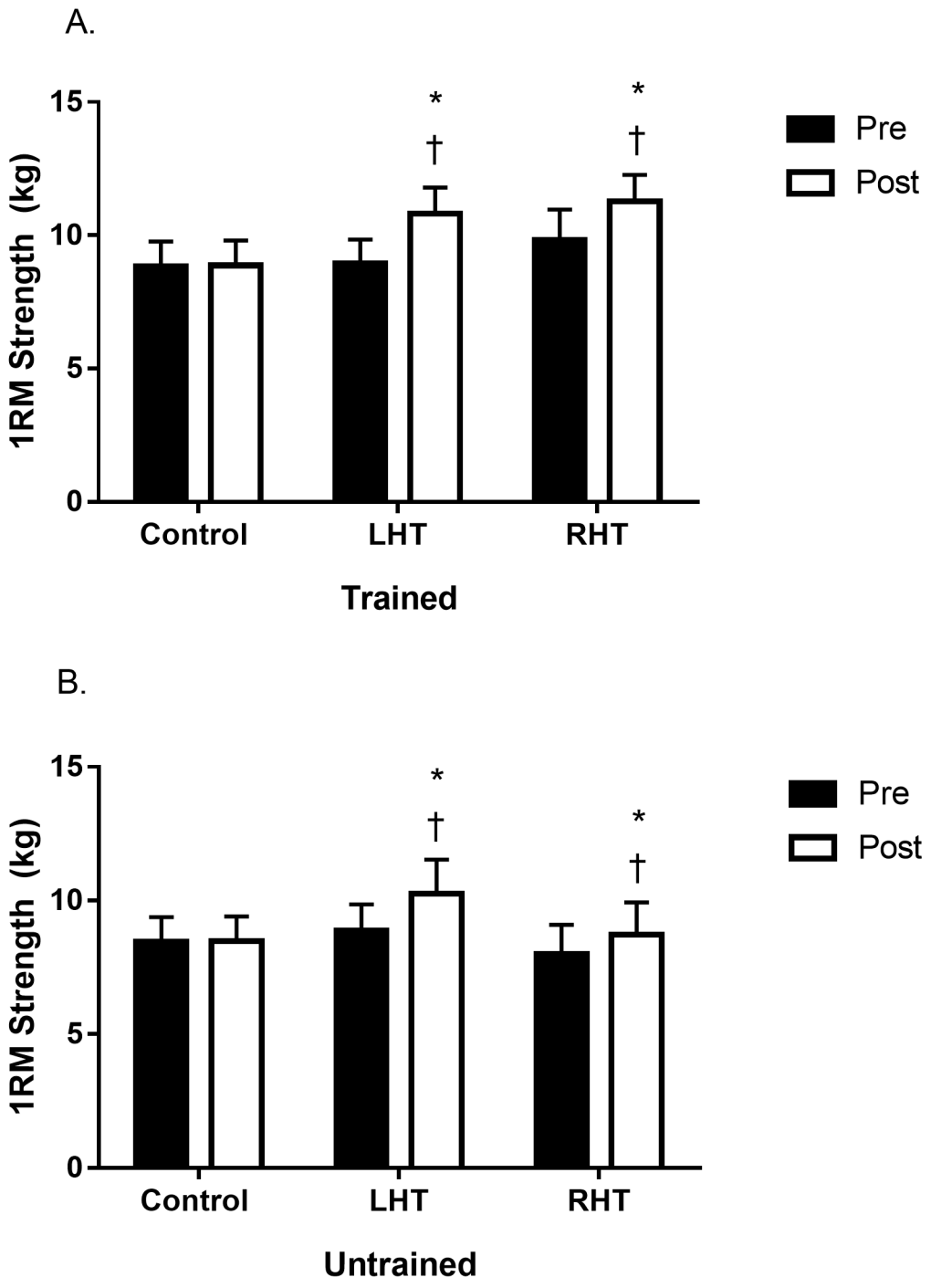
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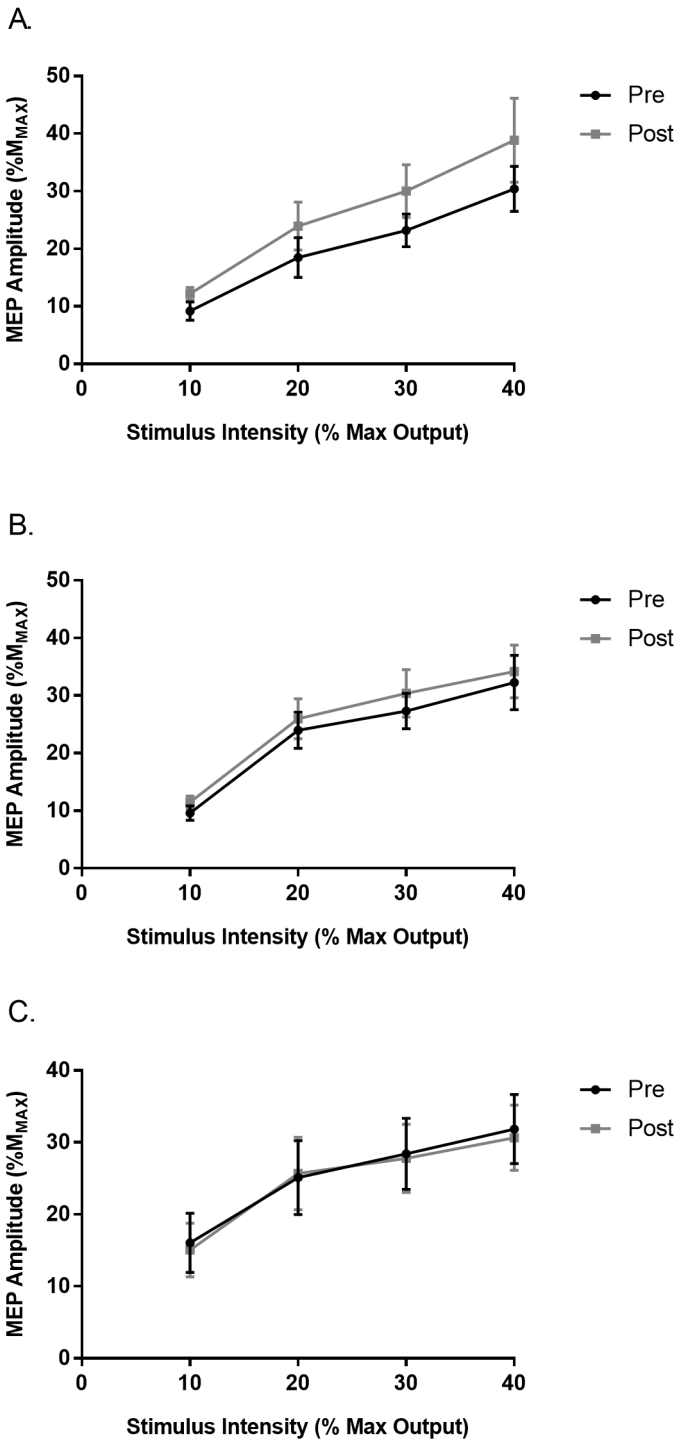
Figure 3


A.
MEP Amplitude (%M$_{MAX}$)
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MEP Amplitude (%M$_{MAX}$)
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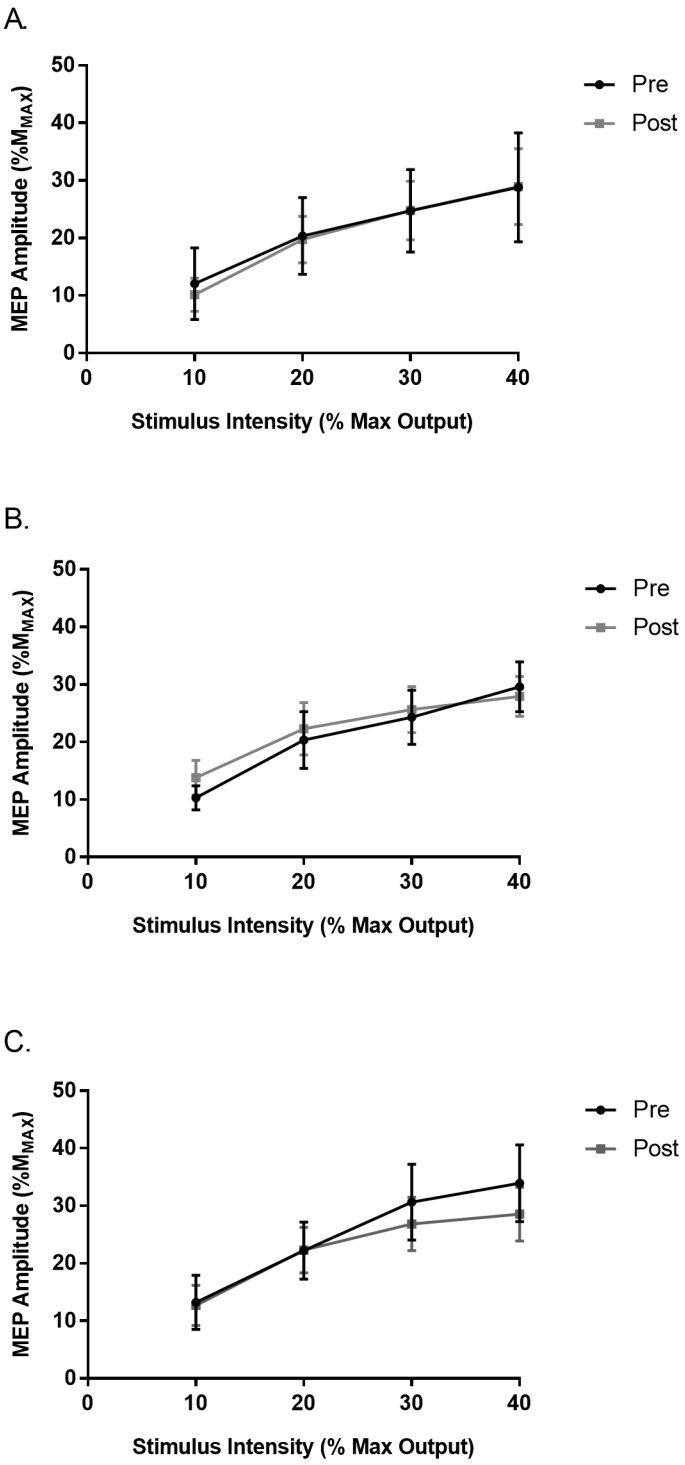
C.
MEP Amplitude (%M$_{MAX}$)
Stimulus Intensity (% Max Output)
Pre
Post

Figure 4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Stimulus Intensity (% Max Output)
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B.
MEP Amplitude (%M$_{MAX}$)
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Stimulus Intensity (% Max Output)
Pre
Post
C.
MEP Amplitude (%M$_{MAX}$)
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Stimulus Intensity (% Max Output)
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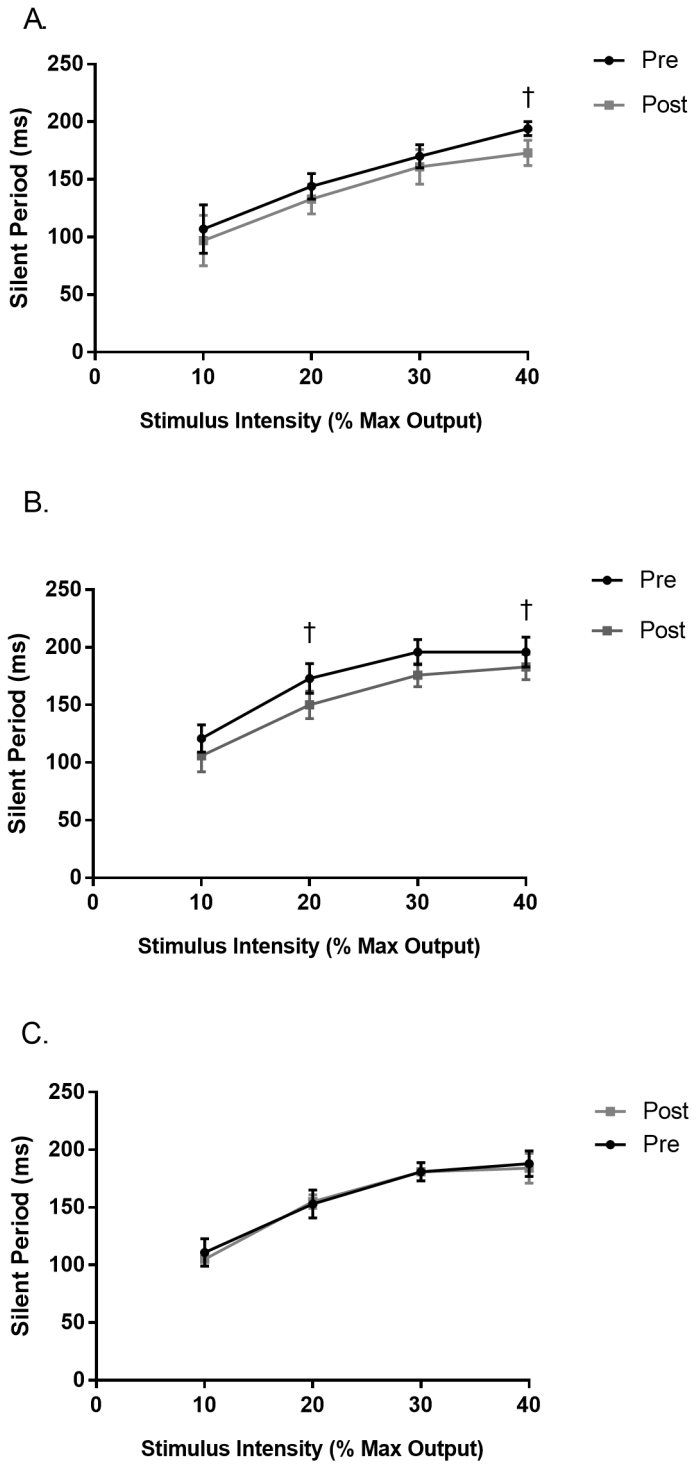
Figure 5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Silent Period (ms)
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Stimulus Intensity (% Max Output)
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B.
Silent Period (ms)
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Stimulus Intensity (% Max Output)
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Pre
Post
C.
Silent Period (ms)
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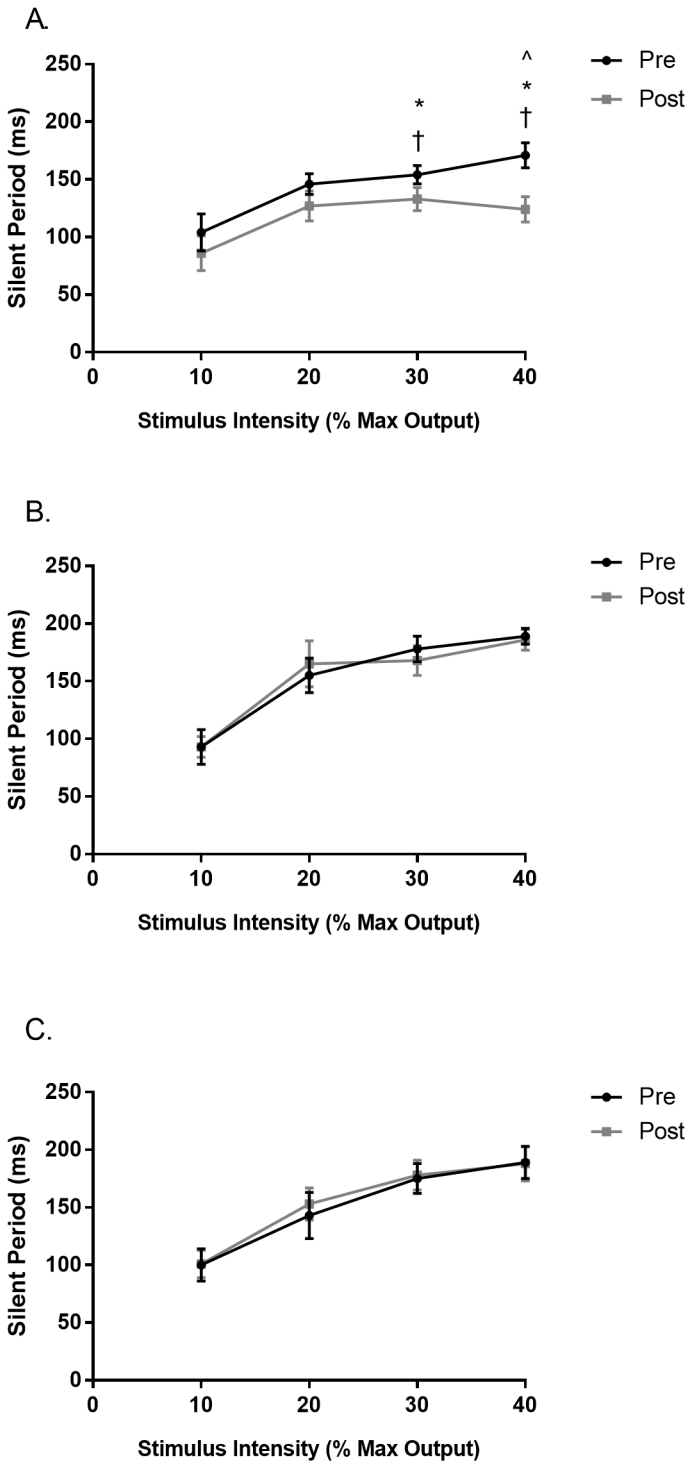
Stimulus Intensity (% Max Output)
Post
Pre

Figure 6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Stimulus Intensity (% Max Output)
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Stimulus Intensity (% Max Output)
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Silent Period (ms)
Stimulus Intensity (% Max Output)
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