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The ipsilateral corticospinal responses to cross-education are dependent upon the motor-training intervention.

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ABSTRACT:

Purpose: This study aimed to identify the ipsilateral corticospinal responses of the contralateral limb following different types of unilateral motor-training. Three groups performing unilateral slow-paced strength training (SPST), non-paced strength training (NPST) or visuomotor skill training (VT) were compared to a control group. It was hypothesised that four-weeks of unilateral SPST and VT, but not NPST, would increase ipsilateral corticospinal excitability (CSE) and reduce short-intracortical inhibition (SICI), resulting in greater performance gains of the untrained limb. *Results:* Tracking error of the untrained limb reduced by 29% and 41% following two and four-weeks of VT. Strength of the untrained limb increased by 8% and 16% following two and four-weeks of SPST and by 6% and 13% following NPST. There was no difference in cross-education of strength or tracking error. For the trained limb, SPST and NPST increased strength (28% & 26%), and VT improved by 47% and 58%. SPST and VT increased ipsilateral CSE by 89% and 71% at two-weeks. Ipsilateral CSE increased 105% and 81% at four-weeks following SPST and VT. The NPST group and control group showed no changes at two and four-weeks. SPST and VT reduced ipsilateral SICI by 45% and 47% at two-weeks and at four-weeks, SPST and VT reduced SICI by 48% and 38%. *Conclusion:* The ipsilateral corticospinal responses are determined by the type of motor-training. There were no differences in motor performance between SPST, NPST and VT. The data suggests the corticospinal responses to cross-education are different and determined by the type of motor-training.

Key Words: Cross-education; Corticospinal; Cortical inhibition; Skill-training; Strength-training.

Introduction

Cross-education is defined as the improvement in motor performance of an untrained limb following a unilateral motor-training program. The context of cross-education can include the transfer of muscular strength and/or the transfer of motor skills to the untrained homologous muscle (Farthing 2009). Thus, both unilateral motor-skill training and strength training increase motor performance of an untrained limb (Farthing and Zehr 2014; Ruddy and Carson 2013). Interestingly, cross-education is commonly used to describe the magnitude of strength transfer following unilateral strength training, whilst bilateral transfer is used to describe the transfer of motor skills. However there has been no study that has compared the magnitude of transfer following both strength and skill training and they have been studied as separate entities (Criscimagna-Hemminger et al. 2003; Lee et al. 2009; Hinder et al. 2013; Coombs et al. 2016; Mason et al. 2017).

Concurrent activation of both cerebral cortices, a process known as cross-activation or bilateral activation, has been reported during both unilateral skill and strength training (Ruddy and Carson, 2013; Hendy and Kidgell, 2014; Carroll et al. 2008; Lee et al. 2010; Hinder et al. 2011; Hinder et al. 2013; Frazer et al. 2017). Moreover, transcranial magnetic stimulation (TMS) studies have shown increased excitability of the ipsilateral primary motor cortex (iM1) of a resting limb during unilateral voluntary contractions (increased cross-activation) (Muellbacher et al. 2000; Liepert et al. 2001; Hortobágyi et al. 2003; Hendy and Kidgell, 2014; Zult et al. 2016; Frazer et al. 2017; Mason et al. 2017). The elevated activity in the iM1 appears to be associated with the changes in motor function of the untrained limb following unilateral training (Kidgell et al. 2011; Latella et al. 2012; Kidgell et al. 2015; Coombs et al. 2016; Mason et al. 2017; Christiansen et al. 2017). We have recently shown that the improvement in strength of the trained arm following strength training and the improvement in motor-skill performance (e.g., upper limb tracking task) following skill training, are controlled by similar mechanisms that originate within the M1 (Leung et al. 2017). Furthermore, we have previously shown that the acute corticospinal responses to cross-education of strength and bilateral transfer of motor skills are dependent upon the elements within the motor-training task (Leung et al. 2015; Leung et al. 2017). Therefore, it is possible that the cross-education effects of unilateral strength training, are similar to the effects following bilateral transfer of motor skills (Carroll et al. 2008; Hinder et al. 2013) and rather, than relying on separate mechanisms, they may depend on at least partially shared underlying mechanisms.

Because of the clinical potential for cross-education, there is a need to establish new strategies to maximise the benefits of cross-education, in an attempt to increase the magnitude of the contralateral increase in motor function. Acquiring or re-acquiring motor-skill function and increasing muscle strength, due to asymmetric conditions is important to understand, in order to provide targeted guidelines for the prescription of cross-education in the clinical setting. However, the question remains whether the mechanism that provokes cross-education is similar to bilateral transfer of motor skills and if there is a training intervention that augments the extent of cross-education. Presently, there are no studies that have compared the magnitude of cross-education and bilateral transfer or determined the associated corticospinal responses following visuomotor training, slow-paced strength training (SPST) and non-paced strength training (NPST). The purpose of the present study was to determine the effect of different unilateral training interventions of the upper limb on corticospinal excitability (CSE) and short-interval intracortical inhibition (SICI) of the ipsilateral motor pathway and to examine the changes in motor performance of the untrained arm. Given that there

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is evidence that suggests the cerebral responses to cross-education is controlled centrally via the communication between the cerebral hemispheres, through interhemispheric communication and bilateral cortical activity (Hellebrandt 1951), and that a task that is conceived as being more skillful modulates the cross-transfer of motor performance to a greater magnitude (Perez et al. 2007), it was hypothesised that four-weeks of unilateral SPST and VT because of their perceived skill level, but not NPST, would increase ipsilateral CSE and reduce SICI, which would result in greater performance gains of the untrained biceps brachii.

EXPERIMENTAL PROCEDURES

The present results are from a study undertaken to examine the effects of different motor-training interventions on CSE, SICI and the cross-transfer of motor function. We have reported the trained arm and corticospinal responses in Leung et al. (2017), and the previously unreported cross-education and cross-transfer effects are reported in the present report. In accordance, some of the experimental procedures have previously been reported in Leung et al. (2017). A full account of the methods employed is presented (including the procedures we have reported previously) in the present paper to make this report self-contained.

Participants and sample size calculations

Forty-three participants (age 26.4 ± 6.9 years; 21 males and 22 females) volunteered to participate in the study and were randomised into four groups (control $n = 10$; MPST $n = 11$; visuomotor skill training [VT] $n = 11$; and SPST $n = 11$). There was one left-hand dominant participant in each group. All participants provided written consent prior to participation in the study and were screened for neurological and musculoskeletal disease or injury and hand dominance was measured by the Edinburgh handedness inventory (Oldfield 1971). All participants were stratified for gender and handedness and pseudo-randomly allocated to receive either VT, SPST, NPST or be part of a control group. Participants had little or no history of strength training, but were recreationally active based upon reporting to be involved in recreational team activity one day per week. None of the participants reported that they had been completing regular strength training of the upper or lower limbs in the previous three months prior to data collection. Irrespective of training history, all participants were instructed not to perform any strength training exercise in the 48 hours prior to the experiment. All participants were naïve to the strength testing procedures used this study.

Sample size calculations were established on the average effect sizes for changes in the magnitude of strength transfer following a short-term unilateral strength training program and VT. Using previous cross-education data in healthy untrained adults (Mason et al. 2017), we estimated that 10 participants in each group would provide at least 80% power (95% confidence interval) to detect a 18% cross-transfer of strength and 16% transfer of VT performance using a repeated measures design (G*Power 3.1.7 software).

The study was approved by Deakin University Human Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki. No participants reported discomfort or ill effects during or after the study.

Experimental approach

Recruited participants first attended a familiarisation session that involved a single trial of all training tasks and were screened for eligibility. Following a two-week washout period, baseline measures of CSE of the iM1 were obtained with TMS prior to the first training session. Participants in the VT, SPST and NPST groups trained with their dominant arm, and all physiological and performance measures were taken from the contralateral untrained arm. Participants allocated to the strength training and motor-skill training groups, undertook a supervised strength training and motor-skill training program three times per week for four-weeks. TMS and performance measures were taken at two-weeks (mid-intervention) and four-weeks (post-intervention) within the iM1. Post-testing was performed 48 hours following the 12th (last) training session at week-four. Figure 1 provides a summary of the neurological tests and outcome measures taken at each testing point.

Insert Figure 1.

Voluntary strength testing

To obtain the participant's maximum voluntary dynamic strength of the untrained elbow flexors, a one-repetition maximum test (1-RM) was employed (Kidgell et al. 2010). Firstly, participants performed a light warm-up with a two-kilogram dumbbell, and then performed two sets of eight repetitions of the untrained arm. The initial weight lifted was taken from the participant's estimation of their own strength. Participants performed the 1-RM test standing, holding a dumbbell in the untrained limb, the elbow in full extension and the forearm supinated with their back pressed against the wall in order to maintain an upright posture. Participants were encouraged to flex their untrained arm and lift the dumbbell as they would during a standard biceps curl. If the participant completed the trial, the weight of the dumbbell was increased by 0.25 - 0.5 kg and the 1-RM trial was repeated following a three-minute recovery period. This was done until failure and the heaviest weight lifted was recorded as the participant's 1-RM strength. Participants completed on average three trials to achieve their 1-RM strength. The same procedure was conducted for the trained limb, which was used to determine the training intensity for the strength-training interventions.

Following a 5-minute rest period, maximal voluntary isometric contraction force (MVIC) was obtained via a brake test to determine the maximum voluntary strength not specific to the training task, but utilising the same muscle group of the untrained arm (Leung et al. 2017). Participants stood with their arm held at 90° and a dumbbell was placed in the participant's hand for the duration of three seconds. The weight of the dumbbell was progressively increased by 0.25 - 0.5 kg and the MVIC trial was repeated following a three-minute recovery period. The weight increased until the participant was unable to hold the weight for three seconds at 90° elbow flexion. To allow for optimal performance, a three-minute rest period separated each contraction. On average, participants' completed three trials to achieve their MVIC strength. This procedure was followed for pre testing, mid and post testing for both the 1-RM and brake test to ensure consistency across testing time points.

Motor-Skill testing

The outcome measure for motor-skill performance was obtained by calculating the sum of errors during a visuomotor tracking task. Participants stood with their back straight against the wall with their forearm supinated. This position was similar to the strength training protocol and only elbow flexion and extension movements of the untrained arm were permitted. For motor-skill testing, participants performed three sets of 10 seconds of visuomotor tracking on a purpose built computer program (Jgcode V2.0, Australia). The three sets of visuomotor tracking had a range of motion from 30° to 140°, and the animated arm moved at 0.2 Hz, 0.8 Hz and 1.3 Hz, respectively. The tracking task required the participants to move their untrained arm in response to the movement patterns of an animated arm displayed on a computer screen (Leung et al. 2015; Leung et al. 2017). The position and movement of the elbow joint was tracked by a wireless electromagnetic goniometer (Biometrics Ltd. SG110 twin axis elbow goniometer). Participants were provided with a percentage score of time spent in the correct tracking position whilst performing the tracking task.

Strength training protocols

Participants allocated to the SPST group completed four sets of six-eight repetitions of a standard biceps curl exercise with their dominant limb using a dumbbell paced to a metronome. The movement of the arm through the eccentric and concentric phases was performed in synchrony to a metronome with the timing set for three seconds during the concentric phase (bending the elbow joint) and four seconds during the eccentric phase (straightening the elbow joint). There was a three-minute recovery period between sets, and verbal encouragement was provided throughout the training. The weight of the dumbbell was adjusted to ensure that the participant could complete six-eight repetitions per set at 80% of 1-RM. Throughout the training intervention, the weight was progressively increased by 0.25-0.5 kg increments when the participant could complete eight repetitions per set. Participants allocated to the NPST group performed a similar procedure to the SPST group; however, the pace of the training task was determined by the participant. In this regard, given the heavy load nature (80% 1-RM), the preferred pace on average was two seconds for the concentric phase and two seconds for the eccentric phase. Participants were required to perform four sets of six-eight repetitions of the biceps curl exercise at 80% of their 1-RM. The weight of the dumbbell was adjusted to ensure that the participant could complete six-eight repetitions per set at 80% of their 1-RM. A three-minute recovery period was provided between sets, with verbal encouragement provided throughout the training period.

Visuomotor skill-training protocol

For skill training, participants performed four sets of 56 seconds of visuomotor tracking on a custom-built computer program (Jgcode V2.0, Australia) of their dominant arm only. The position and movement of the elbow joint was tracked by a wireless electromagnetic goniometer (Biometrics Ltd. SG110 twin axis elbow goniometer). On the monitor, participants observed two animated arms, one automated and the other controlled by the participant to track the movement of the automated arm. Participants were provided with a report of a percentage score of time spent in the correct position whilst performing the tracking task. The visuomotor tracking task has been previously reported (Leung et al. 2015; Leung et al. 2017). The tracking task had a range of motion from 30° to 140° and the animated arm moved within a 0.2–1.3 Hz range. This position was similar to the strength training protocol, and only elbow flexion and extension movements were permitted (similar to a biceps curl). The difficulty of the tracking task was adjusted by randomising the speed of the task throughout the four-week training period. The tracking task was also matched to the duration of the strength training task and each set consisted of 56 seconds of visuomotor tracking. A three-minute recovery period separated each set.

Control group

Participants allocated to the control group were required to maintain their current levels of physical activity throughout the four-week period. Participants completed a baseline TMS session and functional testing measures. Following two and four-weeks, participants returned to complete post-TMS and functional testing measures (i.e., motor-skill testing and voluntary strength testing).

Surface electromyography

The area of electrode placement was shaven to remove fine hair, rubbed with an abrasive skin gel to remove dead skin and then cleaned with 70% isopropyl alcohol. Surface EMG (sEMG) was recorded from the untrained biceps brachii muscle using unipolar Ag–AgCl electrodes. For the untrained biceps brachii, the site of measurement was determined by marking the skin two-thirds of the distance between the acromion and the lateral epicondyle while the participant stood relaxed in the anatomical position. This mark was then extended to the most anterior point of the muscle bulk where the electrode was placed over the mid-belly of the biceps brachii, with a ground electrode secured to the lateral epicondyle of the humerus. sEMG signals were amplified ($\times$ 1000), band-pass filtered (20–1 kHz), digitised online at 2 kHz, recorded (1 s) and analysed using Power Lab 4/35 (AD Instruments, Bella Vista, Australia).

Transcranial magnetic stimulation

TMS was delivered using two Magstim 200^2 stimulators (Magstim Co., UK) to produce motor evoked potentials (MEPs) in the untrained active biceps brachii. The motor hot spot for the untrained biceps brachii (with posterior- to anterior-induced current flow in the cortex) was determined, and active motor threshold (AMT) was established as the intensity at which at least five of ten stimuli produced MEP amplitudes of greater than 200 μV (Hendy and Kidgell 2014). Following the training intervention, AMT was re-tested and adjusted if required. To ensure all stimuli were delivered to the optimal motor hot spot 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 untrained biceps brachii. Participants were required to maintain an elbow joint angle of 90° elbow flexion. Joint angle was measured with an electromagnetic goniometer (ADInstruments, Bella Vista, Australia), with visual feedback provided on a screen visible to both the participant and the researcher (Hendy and Kidgell 2014). Holding the lower arm in this joint position equated to $5 \pm 1\%$ of the maximal root-mean squared electromyography (rmsEMG). Because this position resulted in a low level of muscle activity, and to ensure that background muscle activity was consistent between TMS stimuli, rmsEMG was recorded 100 ms before the delivery of each TMS pulse. During the TMS trials, visual feedback was presented to the volunteer to display an upper limit of 5% rmsEMG; participants were instructed to maintain their muscle activation levels below this upper limit. The stimulus delivery software (LabChart 8 software, ADInstruments, Bella Vista, NSW, Australia) was set so that stimuli were not delivered if the rmsEMG value, 100 ms immediately prior to the stimulus, exceeded $5 \pm 1\%$ (Table 1). In order to establish CSE of the iM1, ten stimuli were applied at 130% of each individuals AMT during low-level voluntary contraction. In addition, single-pulse TMS was used to determine the stimulator intensity required to elicit an MEP amplitude response equating to an average of 1 mV over 10 stimuli which was subsequently used for paired-pulse TMS to examine SICI. For establishing SICI, the conditioning stimulus was set at 80% AMT; the test stimulus was set at the stimulator output that elicited MEPs of 1 mV and the interstimulus interval was set to 3 ms.

Maximum compound muscle action potential

Direct muscle responses were obtained from the untrained biceps brachii muscle by supramaximal electrical stimulation (pulse width, 200 μs) of the brachial plexus at Erb's point (DS7A; Digitimer, Hertfordshire, UK). The stimuli were delivered while the participant sat in an upright position, with the elbow at 90° elbow flexion holding 5% ± 1% of maximal rmsEMG. This low level of muscle activity was used to match the conditions under which TMS was delivered (Frazer et al. 2017). An increase in current strength was applied to Erb's point until there was no further increase observed in the amplitude of the sEMG response (M_{MAX}).

Ultrasonography

A SonoSite ultrasound (Springfield, NJ, USA) was used to measure muscle thickness of the untrained biceps brachii. Ultrasound was taken at the beginning of every testing session to ensure that muscle growth was not different between training paradigms and did not confound the measurements (Pearce et al. 2013). The site of measurement was determined by measuring half the distance from the acromion and the lateral epicondyle while the participants rested their arm on a bench in a resting state (180°). The ultrasound transducer was placed onto the most anterior point of the muscle belly. To verify the accuracy of the measurements, the distance between the markings and the coronoid fossa was recorded and anatomical landmarks on the ultrasound image were noted. A 6–8 Hz transducer probe was lubricated with transmission gel and pressed lightly against the marked area of the biceps brachii. The pressure of the probe was reduced when a clear image was displayed on the ultrasound screen; this was to ensure that there was minimal compression of the musculature. The image was captured and the distance between the humerus and the most superficial point of the muscle fascia was noted; this measurement represented the thickness of the muscle (in mm). Five measurements were taken from the untrained arm and averaged to determine the thickness of the biceps brachii muscle.

2.12 Contralateral Strength Transfer.

The contralateral transfer of strength and motor-skill performance was calculated to determine the difference in change in the mean strength and tracking error of the untrained non-dominant elbow flexors in the control and trained groups following the training period (Carroll et al. 2006). The calculation was as follows:

$$\left(\frac{EPost - EPre}{EPre} - \frac{CPost - CPre}{CPre} \right)$$

where EPost refers to mean post-training values for 1-RM strength and visuomotor tracking error for the trained groups' untrained elbow flexors, EPre refers to mean pre-training values for the trained groups' untrained elbow flexors, CPost refers to mean post-training values for the controls' untrained (non-dominant) elbow flexors, and CPre refers to mean pre-training values for the control groups' untrained (non-dominant) elbow flexors.

Data analysis

Pre-stimulus rmsEMG activity was determined in the untrained biceps brachii 100 ms prior to each TMS stimulus during pre- and post-testing. The range of rmsEMG was accepted at 5%–1% of maximal rmsEMG activity. The peak-to-peak amplitude of MEPs evoked as a result of stimulation was measured in the untrained biceps brachii contralateral to the cortex being stimulated in the period 10–50 ms after stimulation. 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, averaged and normalized to the M_{MAX}, and multiplied by 100. SICI was quantified by dividing the average paired-pulse MEP by the average single-pulse MEP (test intensity set to produce MEPs of 1 mV) and multiplying by 100. Therefore, when SICI percentage change increased following training, this signified a decrease in cortical inhibition; when SICI percentage change decreased following training, this signified an increase in cortical inhibition.

Statistical analysis

All data were screened for normality using Mauchly's test of sphericity, specifically looking at Greenhouse-Geisser and Huynh-Feldt corrections to test the equality of variance. To screen for normal distribution, Shapiro-Wilk and Kolmogorov-Smirnov tests were used. A one-way analysis of variance (ANOVA) was used for all dependent variables (1-RM elbow flexion/MVIC/ visuomotor skill-training performance, rmsEMG, muscle thickness, CSE, and SICI) to ensure that there were no significant differences between groups at baseline. A 4 (GROUP) x 3 (TIME) multivariate analysis was used to determine any difference between groups for the variables rmsEMG, CSE, SICI, ultrasonography, voluntary strength and visuomotor tracking error. If significant main effects were found, a Tukey's test was used to analyse the percentage change comparing group interaction (control, MPST, SPST and visuomotor skill-training) by time (pre, two-weeks and four-weeks) for each dependent variable. 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. Linear regression analysis was also used to examine any potential association between changes in muscle strength ((pooled post-strength/pre-strength $\times$ 100) – 100), and tracking error ((pooled post-error/pre-error $\times$ 100) – 100), changes in MEP amplitude after training ((pooled MEP amplitude post-training/pre-training $\times$ 100) – 100), and changes in SICI after training ((pooled SICI post-training/pre-training $\times$ 100) – 100) for the untrained homologous muscle. To ascertain the differences in the magnitude of cross-transfer between training interventions (visuomotor skill training, MPST and SPST), a one-way ANOVA was performed on the pooled (two and four-week) percentage improvement using the formula described by Carroll et al. (2006). Graphpad Prism version 7.00 (GraphPad Software, La Jolla, California, USA) was used for all statistical analyses and the level of significance was set at $P < 0.05$. Data are presented as mean (±SE) in text and figures and as mean (±SD) in tables.

Results

Changes in muscle strength and visuomotor tracking performance

Changes in maximal 1-RM strength

Mean (±SE) changes in 1-RM strength for the untrained biceps brachii at baseline, two and four-weeks are displayed in Figure 2, whilst the raw data are displayed in Table 1. There were no differences in 1-RM strength at baseline between groups [($F_{3, 39} = 1.69$; $P = 0.18$)], however a main effect for TIME [($F_{2, 78} = 56.03$; $P < 0.001$)] and a GROUP x TIME interaction [($F_{6, 78} = 9.36$; $P < 0.0001$)] were detected. At two weeks, the SPST group demonstrated a greater increase in 1-RM strength of the untrained left arm (8%, $P < 0.0001$; 95% CI -12.18 to -4.285, $d=4.8$) than the VT group. There were no differences in the change in 1-RM strength between NPST, VT and the control group ($P > 0.05$). At four-weeks, the increase in 1-RM strength of the untrained limb was significantly greater in the SPST group (16%, 95% CI, 20.1 to 12.2, $d=8.2$) and the NPST (13%, 95% CI, -17.5 to -9.59, $d=7.0$) compared to the VT group (1% increase) and the control group (3% increase).

There was a significant positive correlation between the percentage of strength gained in the trained elbow flexors (18%) and the percentage of the contralateral transfer of strength to the untrained elbow flexors (16%) following SPST ($r^2 = 0.4084$; $P < 0.01$; Figure 3). Unilateral strength training of the elbow flexors resulted in a 14.5% strength-transfer to the contralateral untrained elbow flexor. Interestingly, there was no correlation between the percentage of strength gained in the trained elbow flexors (26%) and the percentage of the contralateral transfer of strength to the untrained elbow flexors following NPST ($r^2 = 0.1278$; $P = 0.70$; Figure 3). In light of this, unilateral strength training of the elbows flexors did result in a 12% strength-transfer to the contralateral untrained elbow flexors.

Insert Figure 2 and 3

Changes in visuomotor tracking performance

Pooled mean (±SE) changes in visuomotor tracking error of the untrained arm (0.2 Hz, 0.8 Hz, 1.3 Hz) at baseline, two and four-weeks are displayed in Figure 4. There were no differences in visuomotor tracking error at baseline between groups [($F_{3, 36} = 0.16$; $P > 0.05$)]. Main effects were observed for TIME [($F_{2, 72} = 27.69$; $P < 0.0001$)] and GROUP x TIME interactions [($F_{6, 72} = 3.41$; $P = 0.005$)]. At two weeks, the VT group demonstrated a greater decrease in tracking error of the untrained arm (29%, 95% CI, 14.73 to 41.28, $d=3.8$) than the SPST group (7%), NPST group (4%), and control group (9%). Similar results were found at four weeks with the VT group demonstrating a greater decrease in tracking error (17%, 95% CI, 4.54 to 31.1, $d=2.6$) than the SPST group (12%), NPST group (17%), and control group (13%).

Linear regression revealed that there was no significant correlation between the percentage decrease in visuomotor tracking error in the trained limb (41%) and the percentage improvement (12.5%) for the untrained limb for the visuomotor skill-training group ($r^2 = 0.0004$, $P > 0.05$).

Insert Figure 4

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Magnitude of cross-education

In order to determine if the cross-transfer of motor function (i.e. strength and tracking error) was greater following different types of motor training, a one-way ANOVA performed on the pooled data using the formula by Carroll et al. (2006); revealed that there was no significant difference in the magnitude of cross-transfer between the visuomotor tracking group (12.4 ± 2.3% improvement), SPST group (14.4 ± 3.8% 1-RM increase) or the NPST group (11.9 ± 4.5% 1-RM increase) ($P > 0.05$).

Maximum voluntary isometric contractions and ultrasonography

Table 1 displays the raw values for MVIC and ultrasonography. One-way ANOVA showed no significant difference in MVIC between conditions at baseline, while repeated measures multivariate analysis showed no main effects for TIME or GROUP x TIME interactions for the untrained left arm ($P > 0.05$). There were no significant differences in ultrasonography between conditions at baseline and no main effects for TIME or GROUP x TIME interactions ($P > 0.05$).

Electrophysiological mesaures

Table 2 displays the raw values for stimulator output for AMT, MEP amplitude (mV), SICI as a percentage of the test response and maximal compound waves (mV). A one-way ANOVA showed no significant differences in MEP amplitude or SICI for the untrained arm at baseline ($P > 0.05$), while repeated measures multivariate analysis showed main effects for TIME and GROUP x TIME interactions ($P < 0.05$). There were no significant differences in M_{MAX} between conditions at baseline and no main effects for TIME or GROUP x TIME interactions ($P > 0.05$).

Insert Table 1 and Table 2

Changes in ipsilateral corticospinal excitability

CSE was obtained at baseline, two-weeks and four-weeks post the training interventions (see Figure 5 and Table 2). CSE was similar between conditions at baseline across all groups ($P > 0.05$). Following the training interventions, there was a main effect for TIME [($F_{2, 78} = 11.28$; $P < 0.0001$)] and GROUP x TIME interactions [($F_{6, 78} = 3.87$; $P = 0.001$)]. At two-weeks, the increase in CSE was significantly greater in the SPST (89%, 95% CI, -140.8 to -37.87, $d=4.4$), and the VT group (71%, 95% CI, -122.9 to -19.92, $d=4.9$) compared to the NPST (22%) and control group (3%). At four-weeks, the increase in CSE was significantly greater in the SPST group (106%, 95% CI, 40.62 to 169.1, $d=4.1$) and VT group (82%, 95% CI, -133.1 to -30.13, $d=3.5$) compared to the NPST group (1% increase) and control the group (15% decrease). There were no differences in the change in CSE between the SPST and VT group and between the NPST group and control group (both $P > 0.05$).

Insert Figure 5

Changes in corticospinal excitability, muscle strength and visuomotor tracking

Using linear regression of data from individual subjects, we examined whether the training-related change in the pooled MEP amplitude of the untrained biceps brachii (averaged over the four-week training period) was associated with any change in muscle strength or visuomotor tracking error. There was no association between the change in biceps brachii MEP amplitude and the change in maximum strength of untrained biceps brachii following SPST ($r^2 = 0.007$, $P = 0.719$), SPST ($r^2 = 0.075$, $P = 0.2168$) or VT training ($r^2 = 0.0184$, $P = 0.547$). There was no association between the change in biceps brachii MEP amplitude and the change in tracking error of the untrained biceps brachii following SPST ($r^2 = 0.0141$, $P = 0.617$), SPST ($r^2 = 0.037$, $P = 0.413$) or VT training ($r^2 = 0.0017$, $P = 0.862$).

Changes in short-interval cortical inhibition

Figure 6 displays the mean (±SE) changes in SICI at baseline, two and four-weeks following the training interventions, whilst Table 2 displays the raw data. There were no differences in SICI at baseline between groups ($P = 0.24$); however, there was a main effect for TIME [($F_{2, 78} = 10.39$; $P = 0.0001$)] and GROUP x TIME interactions [($F_{6, 78} = 2.51$; $P = 0.028$)]. At two-weeks, the reduction in SICI was significantly greater in the VT group (47%, 95% CI, 9.917 to 85.49, d=2.6), and the SPST group (37%, 95% CI, 0.00837 to 75.58, d=2.9) compared to the NPST (13% increase) and control group (7% decrease). There were no differences in the change in SICI between the VT and SPST groups ($P > 0.05$). At four-weeks, the decrease in SICI was significantly greater in the SPST group (47%, 95% CI, 3.017 to 78.58, d=4.1) and VT group (44%, 95% CI, 0.09221 to 75.66, d=3.5) compared to the NPST group (11% decrease) and control the group (6% decrease). There were no differences in the change in SICI between the SPST and VT group and between the NPST group and control group (both $P > 0.05$).

Insert Figure 6

Changes in SICI, muscle strength and visuomotor tracking

Using linear regression of data from individual subjects, we also examined whether the training-related change in the pooled SICI changes of the untrained biceps brachii (averaged over the four-week training period) was associated with any change in muscle strength or visuomotor tracking error. There was no association between the change SICI and the change in maximum strength of the untrained biceps brachii following SPST ($r^2 = 0.0382$, $P = 0.383$), NPST ($r^2 = 0.013$, $P = 0.607$) or VT training ($r^2 = 0.0035$, $P = 0.808$). There were no associations between the change in SICI and the change in tracking error of the untrained biceps brachii following SPST ($r^2 = 0.026$, $P = 0.489$), NPST ($r^2 = 0.033$, $P = 0.436$) or VT training ($r^2 = 0.0006$, $P = 0.913$).

Discussion

 The main findings show that different types of strength training of the elbows flexors increased voluntary strength for both the trained and untrained limbs, and visuomotor training improved tracking error of the untrained limb following unilateral skill training. These findings show that the performance benefits of cross-education are not different following visuomotor training, paced strength training and non-paced strength training. Interestingly, the corticospinal responses are dependent upon the type of motor training; ipsilateral CSE increased and SICI decreased following visuomotor training and SPST, but not following NPST. This evidence suggests that the ipsilateral corticospinal responses following cross-education are different and influenced by the type of constraints of the training task. However, from a behavioural perspective, the cross-education effect was not associated with the changes in CSE and SICI, suggesting that regions outside of the ipsilateral M1 may be involved (Ruddy et al. 2017; Farthing et al. 2007).

Cross-education of motor function is not different between training tasks

 The cross-education of motor function has been extensively reported following both acute (Carroll et al. 2008; Hinder et al. 2013; Hendy and Kidgell 2014; Frazer et al. 2017) and chronic training paradigms (Kidgell et al. 2011; Latella et al. 2012; Manca et al. 2015; Manca et al. 2016; Christiansen et al. 2016). However, there have been no reports within the literature that have examined the extent of the cross-education effect following strength or visuomotor training. We have shown that there is no difference in the magnitude of cross-education of strength or tracking error following two and four-weeks of visuomotor training and different types of strength training. Regardless whether the training intervention was visuomotor training or strength training, using the cross-transfer calculation proposed by Carroll et al. (2006), the range of cross-education was 12-14%, with SPST and VT yielding the largest transfer effects. It is important to highlight that very few skill-training studies have assessed the cross-transfer effects following four-weeks of training (Christiansen et al. 2016). Unlike the cross-education of strength literature, where studies are consistently in the range of 2-4 weeks (Kidgell et al. 2011; Latella et al. 2012; Kidgell et al. 2015; Hendy et al. 2015), the cross-education of motor skills is usually examined following an acute training session (Carroll et al. 2008; Lee et al. 2010; Hinder et al. 2013; Leung et al. 2015). The magnitude of cross-education following both unilateral strength training and visuomotor training is consistent with a recent systematic review that reported the pooled estimate for 31 cross-education studies being 11.9% (Manca et al 2017). Interestingly, sub-analysis revealed the pooled estimate for upper limb cross-education was 9.4% (Manca et al. 2017). To our knowledge, the present study is the first to report that chronic unilateral visuomotor training also results in significant cross-education effects that are similar to the cross-education of muscular strength. When calculating the magnitude cross-education following visuomotor training, whereby the performance gain of the untrained limb was compared to the performance of the untrained limb in the control group, visuomotor tracking error improved tracking performance by 12.4%. This improvement is larger than the pooled estimate for the cross-education of muscular strength for the upper limb (Manca et al. 2017).

 Our data support the idea that the cross-education of muscular strength bears some similarity to the cross-education of motor skills. It is possible that unilateral strength training enables the untrained limb to learn from the

training limb and this process is similar to how one limb can learn from the other limb during unilateral motor-skill training. Whilst not directly determined, there is emerging evidence that the mirror neuron system (MNS) may augment the cross-education of motor skills (Howatson et al. 2013). The MNS is a complex network of neurons dispersed over several regions of the cerebral cortex and provides an important neuroanatomical foundation for the development and acquisition of motor skills (Zult et al. 2014). There are several lines of evidence that show that motor skills can be learned and facilitated by observing motor actions (Rizzolatti et al. 1999; Rizzolatti and Craighero 2004; Iacoboni 2005) and, critically, the MNS is activated during self-observation of a motor task and by motor execution itself, both of which occur during unilateral motor training (Heyes 2010; Ray and Heyes 2011). Interestingly, performing movements with mirror illusions engages the MNS and increases ipsilateral CSE (Garry et al. 2005), thus, it is was surprising that the magnitude of cross-education following visuomotor skill training was no greater, considering the training to a degree, employed a mirror-like paradigm whereby the participants' limb was displayed on a computer screen. It seems that the level of activation of the MNS across the motor-training tasks is not different, which may in part support why there were no differences in the magnitude of cross-education across the training modalities. However, a caveat to this interpretation is that we did not directly assess the neurophysiological aspects of the MNS. In light of the above, critically, the change in motor function (i.e. strength and tracking error) was not associated with the change in CSE or SICI. This suggests that the effects of cross-education may extend beyond the region of the iM1. There is emerging evidence that suggests regions outside, but functionally connected to the M1 may influence the neural control of force production following cross-education (Farthing et al. 2007; Ruddy et al. 2017). For example, during unilateral movements, there are larger increases in the BOLD response within the pre-motor cortex (Koeneke et al. 2004), supplementary motor area (Grafton et al. 2002) and cingulate motor area (Kermadi 2000). Structural connectivity reveals that dorsal premotor cortex; supplementary motor area and cingulate motor area have dense structural white matter connections within the homologous zone in the opposite cerebral hemisphere (Ruddy et al. 2017). Thus, there seems to be a pressing need to measure other regions of the cerebral cortex following cross-education, in order to increase the understanding of potential physiological mechanism mediating cross-education.

The cortical adaptations to cross-education are dependent upon the motor-training intervention

It is well accepted that motor learning is associated with functional changes (i.e., plasticity) within several regions of the cerebral cortex, including pre-motor areas and M1 (Fu et al. 1995; Butefisch et al. 2000; Hardwick et al. 2013; Doyon and Benali 2005). There is a growing body of literature that suggests plasticity within the M1 is the most likely cortical adaptation following cross-education, simply because of the important role that the M1 plays in the early phases of motor learning (Muellbacher et al. 2002; Pruitt et al. 2016). In the context of cross-education and bilateral transfer, several acute studies that have used TMS have shown increased CSE (Muellbacher et al. 2000; Hortobágyi et al. 2003; Perez and Cohen 2008; Howatson et al. 2011; Frazer et al. 2017), decreased SICI (Perez and Cohen 2008; Leung et al. 2015), and decreased interhemispheric inhibition (IHI) (Perez and Cohen 2008; Howatson et al. 2011) in the iM1. While some structural changes occur within several motor areas (Ruddy et al. 2017; Pruitt et al. 2016), experimental findings from chronic cross-education studies support a mixture of increased CSE (Hendy et

al. 2015; Kidgell et al. 2011; Kidgell et al. 2015) and a decrease in cortical inhibition (SICI, IHI and silent period duration) (Hortobágyi et al. 2011; Hendy et al. 2012; Kidgell et al. 2015; Coombs et al. 2016; Mason et al. 2017) in the neural structures innervating the untrained limb.

Intriguingly, non-paced strength training had no effect on CSE or SICI. This finding is consistent with previous studies, whereby skilled motor training leads to the functional reorganization of movement representation maps in contralateral M1 and the ipsilateral M1 (Pruitt et al. 2016), but is absent following repetitive unskilled motor training (Kleim et al. 1998; Plautz et al. 2000; Carroll et al. 2002). Therefore, the ipsilateral corticospinal adaptations to unilateral visuomotor training and slow-paced strength training are distinct to that of non-paced strength training, despite no differences in the extent of the cross-education effect. The increase in ipsilateral CSE following both visuomotor training and slow-paced strength training is consistent with previous cross-education of muscular strength studies (Kidgell et al. 2011; Kidgell et al. 2015). The increase in ipsilateral CSE following unilateral visuomotor training is also consistent with previous acute studies (Perez and Cohen 2008; Leung et al. 2015), but here we add new knowledge showing persistent increases in CSE following visuomotor training. It is likely that both forms of unilateral motor training lead to specific modulation of IHI between the ipsilateral and the contralateral M1 following the training intervention, whereas non-paced strength training does not (Leung et al. 2015; Latella et al. 2012).

At present, we are unable to explain why there were no changes in ipsilateral CSE following unilateral non-paced strength training. One hypothesis could be related to the training adaptations that occur in the contralateral trained M1. Previous research has shown that the neural adaptations to strength training likely reside at the level of the spinal cord (Kleim et al. 1998; Carroll et al. 2002; Adkins et al. 2005). The role of specific patterns of plasticity in spinal cord circuits following cross-education remains debated, with only two studies showing no change in H-reflexes (Lagerquist et al. 2006; Fimland et al. 2009) and only one study reporting increased V-wave amplitude (Fimland et al. 2009). On the other hand, both acute and chronic skilled motor tasks consistently increase CSE showing the important role of the M1 in skilled movements, whereas unskilled or self-paced movements may require other regions of the cortex to be involved, such as the supplementary motor area and the pre-motor area (Gerloff et al. 1998b; Thaut et al. 2002; Ackerley et al. 2011; Plow and Carey 2012). Alternatively, the lack of cortical-mediated plasticity following NPST could simply be due to the training task itself. Conceivably, NPST could be perceived as requiring less skill compared to SPST and visuomotor training. Certainly, evidence suggests that the TMS responses to simple and complex movements are distinct (Tinazzi and Zanette 1998; Gerloff et al. 1998a); paced movements increase cortical excitability, but self-paced movements do not. However, a caveat to this interpretation is that there have been no cross-education studies that have examined the effect of paced versus self-paced training on the magnitude of cross-education.

SICI is a standard method used to estimate the excitability of cortico-cortical circuits within the M1 that uses $GABA_A$ neurotransmission (Rothwell et al. 2009). Many plasticity-inducing interventions, such as motor-skill training (Liepert et al.1998) and strength training (Weier et al. 2012; Leung et al. 2017), show that the removal of SICI is an important mechanism for optimal motor-skill learning (Christiansen et al. 2017). Cross-education of motor performance studies, including acute (Perez and Cohen 2008; Howatson et al. 2011) and chronic studies (Goodwill et al. 2012; Kidgell et al. 2015) that have examined SICI, have reported reduced SICI in the M1 ipsilateral to the training

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limb. Here we show that both unilateral visuomotor training and SPST reduce SICI in the iM1, suggesting that unilateral SPST and visuomotor training affect the synaptic efficacy of GABA$_A$ receptors of neurons that form cortico-cortical connections within the iM1. This finding supports a behavioural connection between the cross-education of muscular strength and the cross-education of motor-skills (Goodwill et al. 2012; Kidgell et al. 2015).

It is unclear why unilateral NPST had no effect on the excitability of cortico-cortical circuits within the iM1. Increases in CSE can be modulated by changes in SICI (Kidgell et al. 2013); however, given that NPST had no effect on ipsilateral CSE, it is not surprising that there were no changes in SICI. In addition, it has recently been shown that motor training that is progressively challenging, such as visuomotor tracking and SPST, leads to greater levels of cortical plasticity when compared to non-progressive motor-skill training (Christiansen et al. 2017). In this current study, both the visuomotor training and SPST protocol involved progressive overload compared to NPST and a greater number of sensory cues (visual and auditory), and these factors alone may account for the changes in CSE. At a minimum, unilateral visuomotor training and SPST appear to target neurons that use GABA$_A$ which, in turn, reduce the synaptic efficacy of their synapses onto corticospinal neurons. Because we have shown no changes in SICI following unilateral NPST, it would seem that unilateral SPST does not affect the functional properties of the intra-cortical inhibitory circuits within the iM1. Irrespective of this, it seems that the type of motor training is important in modulating cortico-cortical circuits.

Limitations

Although we have reported that the corticospinal responses following different types of unilateral motor training affect the cortical circuitry of the iM1, we cannot ignore the possibility of task-specific plasticity at the level of the spinal cord. Although visuomotor training and SPST modified the ipsilateral cortical circuits, suggesting a task-specific effect, it is well accepted that MEP amplitude can be affected by changes in pre-synaptic inhibition (e.g., reduced) and this cannot be ignored. In addition, although the facilitated TMS responses suggest an increase in CSE, the specific site of neuronal adaptation cannot be ascertained via TMS. As we did not record cervicomedullary motor-evoked potentials (cMEPS), which is a robust measure of the corticospinal-motoneuronal synapse, it is thus unclear how cMEPS change following strength training (Nuzzo et al. 2017), making conclusions about the effect of potential changes at a spinal level difficult. The lack of any spinal cord measures is a limitation and the data should be interpreted with some caution. Finally, as the MEP amplitude reflects the excitability of the corticospinal system along with the inputs to the cortex, any change in CSE could simply be due to tonic input as a result of increased attention and motivation required during the visuomotor training and SPST intervention (Bestmann and Krakauer 2015). In addition, this study was unable to discriminate whether the tone, the rhythm, or both that caused the changes in CSE and SICI in the SPST group compared to the NPST group.

Lastly, in contrast to all of the other findings, NPST improved visuomotor tracking performance more than SPST or the control group. Taking all of the data of the present study, and the findings reported in the literature into account, this appears to be a spurious finding and therefore requires further testing with a similar paradigm to confirm whether this is an actual phenomenon or not. Presently, we are unable to explain this finding. Further, the corticospinal responses observed could simply be due to the difference in training volume between the SPST group and the NPST.

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Thus, a limitation to the present study is that we are unable to determine the corticospinal responses following paced strength training. One potential approach would be to include a second metronome group, whereby the pacing could be set at four seconds. It is likely that paced strength training results in different levels of concentration and this could be the defining point between paced ad non-paced strength training. However, this remains to be tested.

Conclusion

The present findings show that the cross-education of muscular strength and the bilateral transfer of motor skills lead to specific patterns of CSE and inhibition of the ipsilateral motor pathway. Critically, the corticospinal responses are modulated by the type of motor training, with visuomotor training and SPST showing the greatest corticospinal responses following unilateral training. This finding suggests that SPST can be seen as a form of motor-skill training. However, there seem to be no differences in the behavioural aspects of unilateral training between different types of motor-training interventions. Overall, the data indicate that the corticospinal adaptations that mediate the cross-transfer of motor function are different and training specific.

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