The Journal of Science and Medicine
Vol 2 No 4 (2020): Journal of Science and Medicine, 1-19
Articles

Determining the Effects of Cross-Education on Muscle Strength, Thickness and Cortical Activation Following Limb Immobilization: A Systematic Review and Meta-Analysis: Cross-education and limb immobilization

Madelaine Haggert	Department of Physiotherapy, School of Primary and Allied Health Care, Faculty of Medicine, Nursing and Health Science, Monash University, Melbourne, Australia
Alan Pearce	College of Science, Health and Engineering, La Trobe University, Melbourne, Australia
Ashlyn Frazer	Department of Physiotherapy, School of Primary and Allied Health Care, Faculty of Medicine, Nursing and Health Science, Monash University, Melbourne, Australia
Simin Rahman	Department of Neurology, Institute of Neurosciences, Kolkata, India
Dawson Kidgell	Department of Physiotherapy, School of Primary and Allied Health Care, Faculty of Medicine, Nursing and Health Science, Monash University, Melbourne, Australia
Ummatul Siddique	Department of Neurology, Institute of Neurosciences, Kolkata, India

Purpose:

Cross-education (CE) increases strength of both the trained and untrained limb, with emerging evidence, suggesting CE could be used to attenuate muscle strength and thickness following periods of limb immobilization. This study examined the available evidence for the clinical efficacy of CE to attenuate muscle strength, thickness and neural activation during limb immobilization.

Methods:

We performed a systematic review and meta-analysis on the effects of CE on muscle strength, thickness and activation of an immobilized limb. The evidence from randomized controlled trials (RCTs) were pooled to assess effect estimates for changes in strength, muscle thickness and neural activation of the untrained immobilized limb.

Results:

CE attenuated muscle strength in 5 RCTs (n= 78) which reported a SMD of 1.60 (95% CI 0.62, 2.59; P = 0.001) and muscle thickness, with an SMD of 1.52 (95% CI 0.22, 2.81; P = 0.02) compared to control. There was no difference in muscle activation (SMD of 0.08; 95% CI -0.34, 0.50; P = 0.72), regions of cortical activation (MD 31.8; 95% CI -22.71, 86.31; P = 0.25) or corticospinal excitability (MD 5.2; 95% CI -2.38, 12.78; P = 0.18) compared to control.

Conclusions:

These results show that strength training the free limb via cross-education maintains muscle strength and muscle thickness of the immobilized limb compared to control (immobilization only). Because there was no effect on muscle activation, but a large mean difference in cortical activation, it is likely that the attenuation of muscle strength is due to neural adaptations at a cortical level.

Citation

Haggert M, Pearce A, Frazer A, Rahman S, Kidgell D, Siddique U. (2020). Determining the Effects of Cross-Education on Muscle Strength, Thickness and Cortical Activation Following Limb Immobilization: A Systematic Review and Meta-Analysis. Journal of Science and Medicine; 2(4):1-16. https://doi.org/10.37714/josam.v2i4.54.

Introduction

Immobilization of a limb following injury is common and has well-documented chronic maladaptive effects, particularly a loss in muscle strength and muscle atrophy[1]. Despite such detrimental effects of immobilization, recovery typically requires a period of rehabilitation to regain lost strength and function. In clinical practice, unilateral injuries are extremely common and such injuries can result in immobilization of the affected limb for two to six weeks or longer. Physical rehabilitation is a key element, however, it typically commences following the period of immobilization, which may be too late. In addition, recovery of the strength loss and muscle atrophy experienced following unilateral injury and a period of immobilisation is often hampered by patients and therapists' inability to effectively exercise the involved body part. As a result, final function of the injured limb is often suboptimal, highlighting the critical need to implement new and effective strategies.

An alternative, less labour-intensive rehabilitation approach, is to strength train the non-immobilized limb and improve muscle strength of the immobilized limb by an innovative technique called cross-education[2]. Cross-education is the process whereby strength-training one limb increases muscle strength and function of the opposite untrained limb[3] The cross-education effect is specific to the contralateral muscle, but not restricted to particular muscle groups, ages or genders[4]. Cross-education may have benefits in clinical populations such as stroke [5], anterior cruciate ligament injury (ACL)[6], fracture [7] and limb-immobilization [8-10]. Emerging research has investigated the effects of cross-education in healthy participants undergoing a period of limb immobilisation [8,10,11] (see Table 1). These investigations have typically reported that a cross-education intervention, maintains muscle strength of the immobilized limb [2,9,12]. In addition, some studies have reported that cross-education leads to a sparing effect for muscle size [8-10]. Importantly, cross-education has been used successfully in a clinical population who had suffered a unilateral distal radius fracture [7]. In this particular study, cross-education increased muscle strength and range of motion of the injured wrist 12-weeks post-fracture, providing preliminary evidence of the clinical efficacy of cross-education for immobilized patients. However, at this point, it remains unclear whether there is empirical evidence for the efficacy of cross-education during the early rehabilitation period, to attenuate the loss of muscle strength and atrophy that is associated with immobilization. Theoretically, cross-education could accelerate recovery following immobilization, by enabling patients to maintain a higher level of function in the injured limb prior to remobilisation. This would have the dual benefit of improving functional outcomes in the immediate period post-injury and facilitating the execution of rehabilitation exercises designed to mobilise, reduce atrophy and strengthen the injured limb.

As cross-education studies during limb immobilization are an emerging, but nonetheless a growing area of research, the body of evidence is largely equivocal and, therefore, a systematic review with meta-analysis will serve to clarify the present circumstances regarding the effects of cross-education on attenuating the loss of muscle strength and atrophy. Specifically, as such, conducting a meta-analysis on this topic enables the findings from related studies to be collated resulting in a pooled outcome that has a higher statistical power than any single one of the individual studies. Consequently, the aim of this systematic review and meta-analysis was to examine the effect of cross-education during unilateral limb immobilisation on attenuating the loss of muscle strength, muscle thickness and cortical activation.

Methods

Literature Search Strategy

A standardised search strategy (see supplementary material) used the following electronic databases: Cochrane Library, CINAHL, EMBASE, PsychINFO, PubMed/MEDLINE, Science Direct, SciVerse, SCOPUS, Sport Discus and Web of Science from inception until the last week of September 2020. Medical Subject Headings or keywords and matching synonyms were combined, including “cross-education”, “cross-transfer”, “interlimb transfer, “bilateral transfer”, unilateral strength training”, “resistance training” and “strength training” with “limb immobilization”, “muscle activation” and “muscle thickness”.

The databases were searched from inception until September 28th, 2020. References found from previously published literature were also searched. Figure 1 outlines the flow of studies removed following the application of each criterion according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. While commonly used to report on randomised trials, PRISMA has been used to systematically review quasi-experimental research [14].

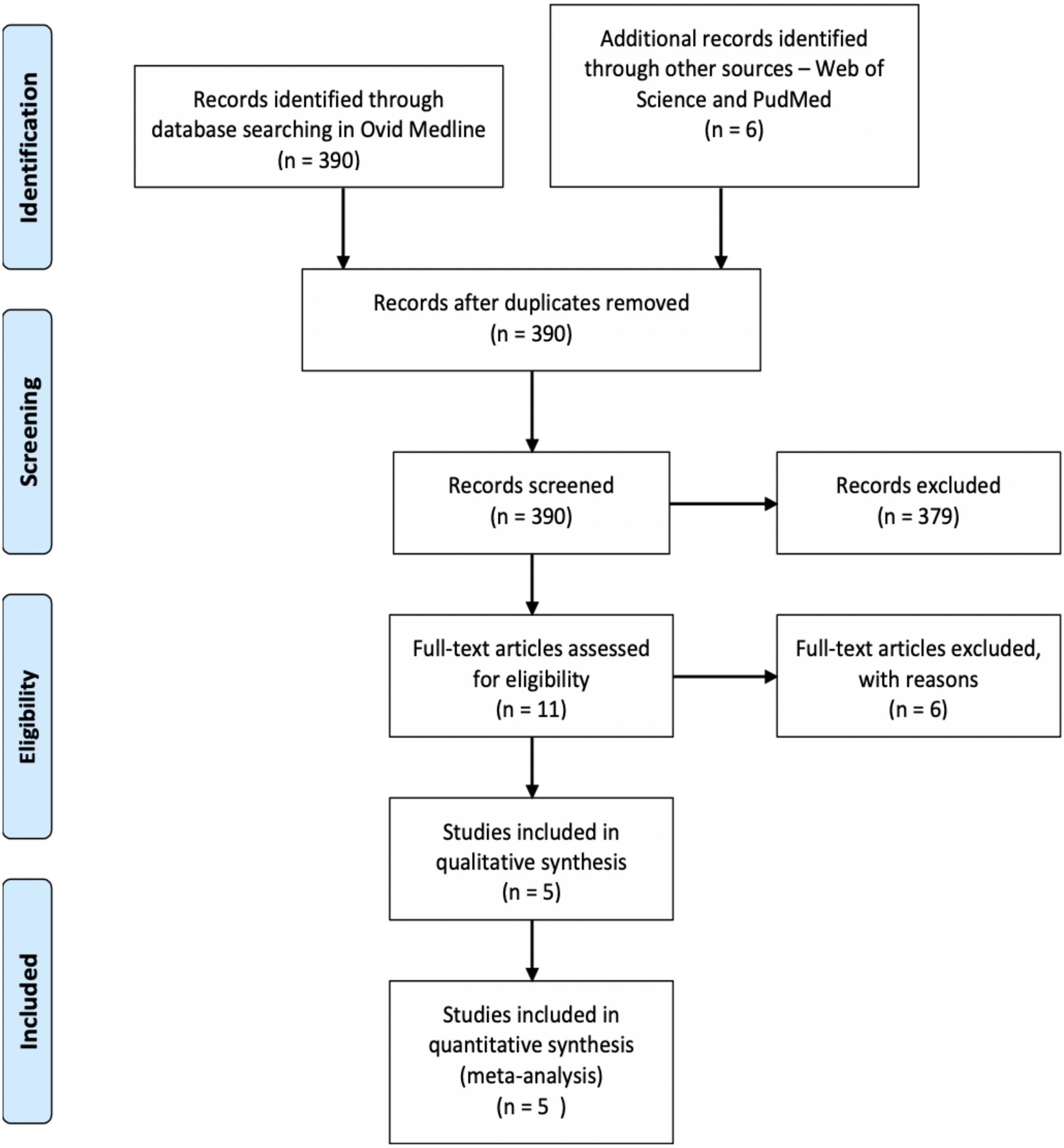

Figure 1. *Yield of articles for the motor cortical responses to strength training literature using the PRISMA guidelines.*

Selection of Studies

The initial search was undertaken by two of the authors (MH and DJK). All titles and corresponding abstracts were retrieved and then screened. Any items that were deemed outside the scope of the present meta-analysis were removed. Following screening of titles and abstracts, one author (AKF) independently selected and reviewed all included articles. At this point, all duplicated studies were removed. Any full-text article that satisfied the inclusion criteria were read and eligible studies were then included in the meta-analysis. In the case of disagreement, both assessors reviewed each study independently, and a third assessor (AJP) graded any discrepancies.

Eligibility Criteria – Exclusion and Inclusion

Studies were considered for review if they met the following criteria: **1)** recreationally trained and untrained healthy young humans of either gender between the ages of 18 and 55 years of age; **2)** training intervention involved two or more weeks of unilateral strength or resistance training of the free non-immobilized limb; **3)** unilateral resistance training involved a training-load that was greater than 50% of the maximal load; **4)** studies must have compared an intervention to a control condition; **5)** muscle strength, thickness and activation of the untrained immobilized were measured for the intervention and control groups. Exclusion criteria included diseased populations, non-English publications, non-peer reviewed proceedings and theses, as well as studies, which employed non-typical resistance training techniques such as superimposed electrical stimulation of the muscle or transcranial direct current stimulation during training, studies were also excluded if there was no comparison between an immobilization plus unilateral resistance training group compared to an immobilization only group (control).

Quality Assessment and Risk of Bias

Quality assessment was conducted for each included study by using the Physiotherapy Evidence Database scale (PEDro scale). The PEDro scale includes 10 criteria for internal validity and studies are awarded a point for each criterion met. The PEDro cut-points are 9-10, excellent; 6-8, good; 4-5, fair; and below 4, poor. Further, the Cochrane Risk of Bias tool [15] for randomised controlled trials rates trial quality on six domains: sequence allocation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting and other sources of bias (Figure 2). A rating of “low” or “high” was assigned if criteria for a low or high risk of bias were met, respectively. The risk of bias was judged “unclear” if inadequate details for the criterion were reported.

The Journal of Science and Medicine
Vol 2 No 4 (2020): Journal of Science and Medicine, 1-19
Articles

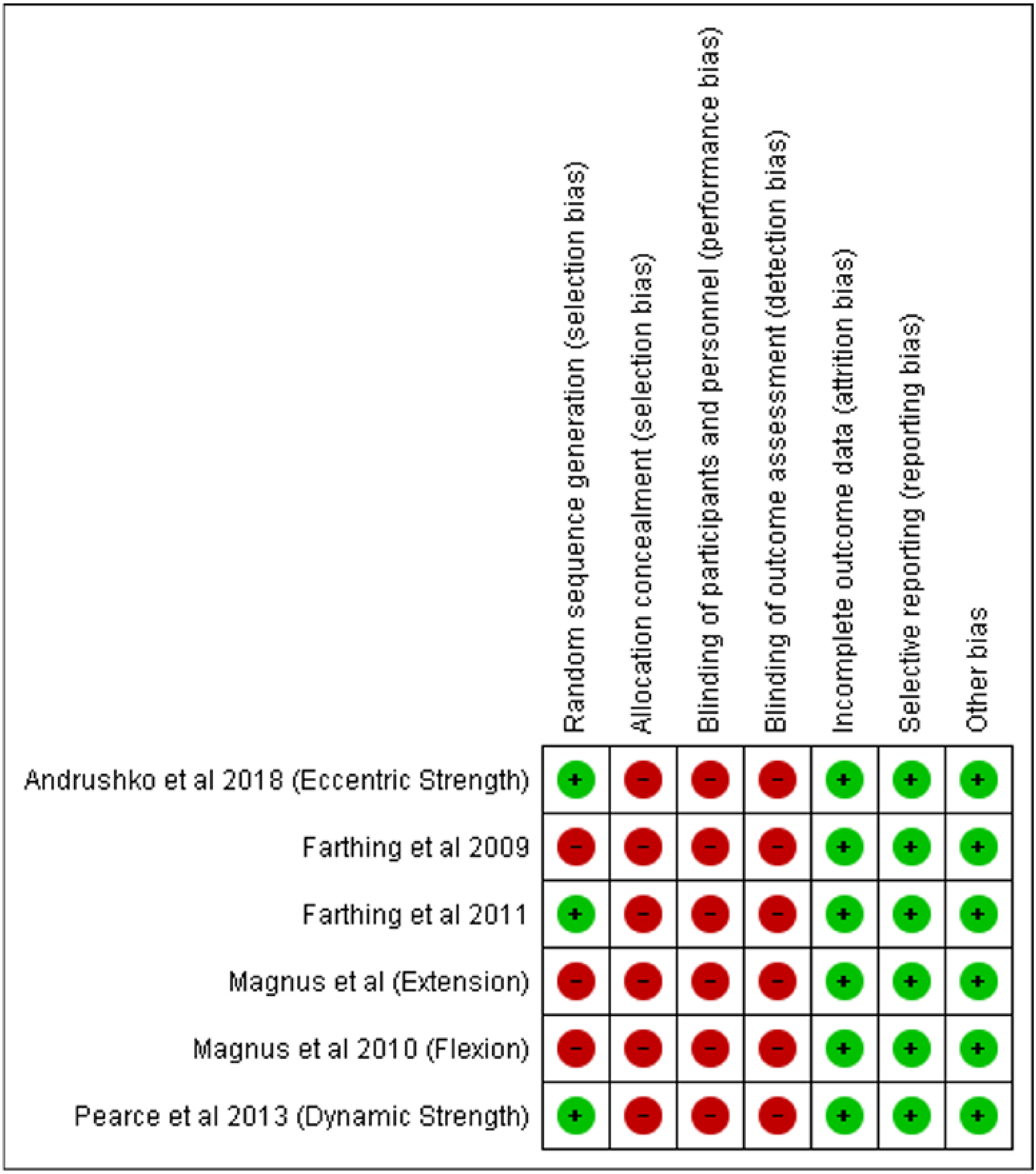

Figure 2. *Cochrane Risk of Bias for included studies.*

Data Extraction and Analyses

For all included articles, data extraction involved the retrieval of study characteristics (author, year, sample size and study design), participant demographic (age, gender), and the unilateral resistance training protocol (isometric, dynamic, eccentric, concentric, isometric, upper body, lower body). In addition, the following outcome measures from included studies were extracted from the available text: Strength, muscle thickness (cm); and muscle activation (mV). Where the reported data were not sufficient for the purposes of this review, the corresponding author of the study was contacted and relevant data were requested. Where mean ± SD or SE values were not provided for post-intervention parameters, the data were extracted from the graphs with Plot Digitizer software [16]. Plot Digitizer is a program for extracting data presented in papers as linear, logarithmic axis scales and scatter plots. After calibration of the image, data values were extracted by clicking on the data points.

Statistical Analysis

The post-unilateral resistance training data from the experimental (immobilization plus unilateral resistance training) and control (immobilization no training) groups for each study were used for the following variables: muscle strength of the immobilized limb, muscle thickness, muscle activation, regions of cortical activation and corticospinal excitability. As systematic influences and random error were predicted to be present between study level effect sizes, a random effects meta-analysis was performed to compare the overall pooled SMDs for the main outcome measures [15]. There is now evidence, to suggest that providing estimates of the size of intervention effects, rather than just the existence of effects with *P* values, is more valuable [17]. SMDs with 95% confidence intervals were used to measure the intervention effect as the included studies presented outcome measures in a variety of ways. Therefore, we used SMDs with 95% confidence intervals to measure the intervention effect. The SMD values of 0.20 ≤ 0.49 indicated small, 0.50 ≤ 0.79 medium, and ≥ 0.80 large effects [18]. In order to maintain consistent reporting, all results are reported with the SMD, followed by their 95% CI and finally the corresponding *P* value. This approach was taken, because information about the size of effects, rather than just the existence of effects (which only *P* values provide), should be encouraged if the mechanisms by which exercise interventions work are to be determined, or the effects of interventions are to be assessed. For outcome measures in studies that were highly homogeneous, employed the same units of measurement, and had consistent methodological procedures for the outcome measures, the mean difference (MD) of the changes along with its SD was used to obtain an absolute estimate of effect. Further, to correct for any bias that was introduced by “double-counting” of subjects in studies that had more than one outcome measure of strength in the same meta-analyses (i.e., flexion and extension strength), but only one control group and experimental, the number of participants in these trials were divided by two. Heterogeneity was measured using the I^2 statistic, which indicates the percentage variance between studies with cut off points corresponding to low (25%), moderate (50%) and high (75%) heterogeneity. In case of heterogeneity exceeding this threshold, a leave-one out sensitivity analysis was performed to check whether our findings were driven by a single study. All statistical analyses were performed in RevMan 5.3 (Review Manager, The Cochrane Collaboration) using an alpha level of $P < 0.05$.

Results

Figure 1 displays the PRISMA flow chart showing the process of study identification, screening and evaluation of the eligibility of included studies. The initial search yielded 396 titles based upon titles and abstracts. Following the removal of duplicates, the abstracts and titles of the remaining 390 records were screened; 379 publications were removed at this point as they did meet the eligibility criteria. Eleven full-text papers were assessed for eligibility with a further 6 of these being removed for a range of reasons, including analysis of a single resistance training session instead of multiple sessions or the use of non-conventional resistance training methods such as vibration training and electrical stimulation. Studies included in the quantitative synthesis was 5.

Quality Assessment

The quality assessment, according to the PEDro scale is presented in Table 1. This revealed that studies meeting the inclusion criteria ranged between 5 and 6 points (out of a possible 10 points),

The Journal of Science and Medicine
Vol 2 No 4 (2020): Journal of Science and Medicine, 1-19
Articles

with a mean score of 4.4 ± 1.5. This indicated that the quality of the studies were fair. Most studies lost points for blinding, allocation concealment, and randomisation. There was a high risk of bias across all studies with most publications being exposed to high risk of bias for participant selection, performance, detection, attrition, and reporting biases (Figure 2).

Changes in muscular strength

Complete strength data were extracted from 5 studies (n = 45) that measured maximum strength post-unilateral resistance training of the immobilized limb compared to control (n =45). The pooled data indicated that following unilateral resistance training, cross-education attenuated the loss of muscular strength (SMD 1.60, 95% CI 0.62, 2.598, P = 0.001) in the immobilized limb compared to the immobilized limb of the control group, with the heterogeneity of results between the studies being moderate (I^2 = 70%; Fig. 3).

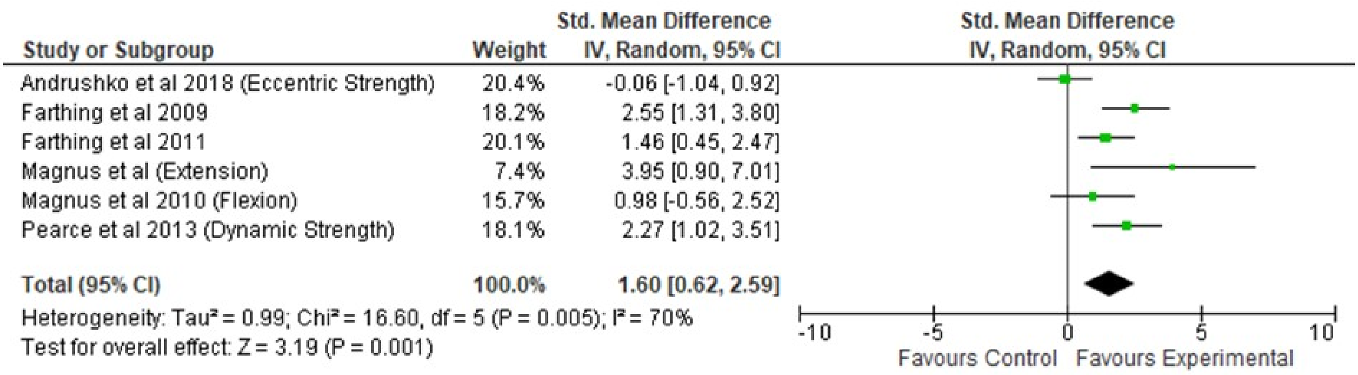

Figure 3. *Forest plots for muscle strength following short-term limb immobilization following cross-education compared to control (no training and immobilization). Pooled effect size for horizontal line = 95% confidence interval. CI: confidence interval, IV: inverse variance.*

Changes in muscle thickness

Changes in muscle thickness of the immobilized limb were extracted from 5 studies (n = 57) that assessed muscle thickness in cm post-unilateral resistance training compared to control (n =47). The pooled data indicated that following unilateral resistance training, cross-education attenuated the loss of muscle thickness (SMD 1.52, 95% CI 0.22, 2.81, P = 0.02) in the immobilized limb compared to the immobilized limb of the control group. The heterogeneity of results between the studies being high (I^2 = 86%; Fig. 4).

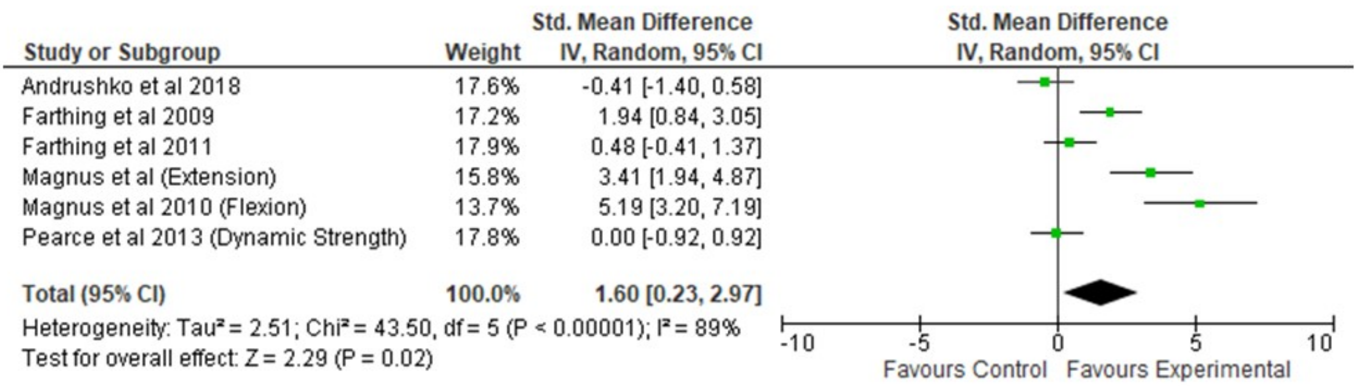

Figure 4. *Forest plots for muscle thickness following short-term limb immobilization following cross-education compared to control (no training and immobilization). Pooled effect size for horizontal line = 95% confidence interval. CI: confidence interval, IV: inverse variance.*

The Journal of Science and Medicine
Vol 2 No 4 (2020): Journal of Science and Medicine, 1-19
Articles

Changes in muscle activation

Changes in muscle activation were extracted from 5 studies (n = 50) that assessed the electromyographic activity post-unilateral resistance training compared to control (n = 42). The pooled data indicated that unilateral resistance training had no effect on muscle activation (SMD 0.08, 95% CI -0.34, 0.50, P = 0.72) of the untrained immobilized limb, with the heterogeneity of results between the studies being low (I^2 = 0%; Fig. 5).

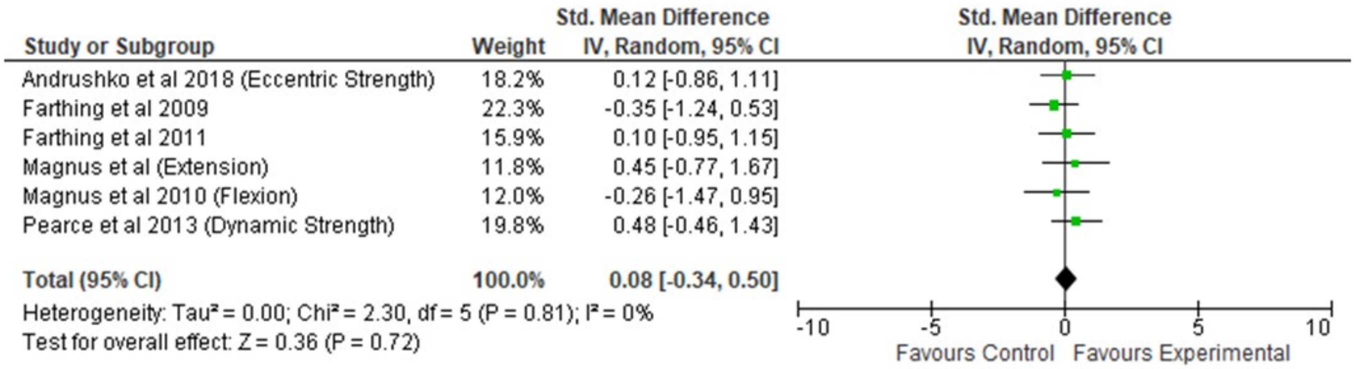

Figure 5. *Forest plots for muscle activation following short-term limb immobilization following cross-education compared to control (no training and immobilization). Pooled effect size for horizontal line = 95% confidence interval. CI: confidence interval, IV: inverse variance.*

Changes in cortical activation

Changes in regions of cortical activation as assessed by functional magnetic resonance imaging was extracted from one study (n = 10) that assessed the BOLD response post-unilateral resistance training compared to control (n = 10). The pooled data indicated that unilateral resistance training had no statistical effect on cortical activation, however, the pooled estimate was large (MD 31.8, n = 20; Fig 6) of the untrained immobilized limb.

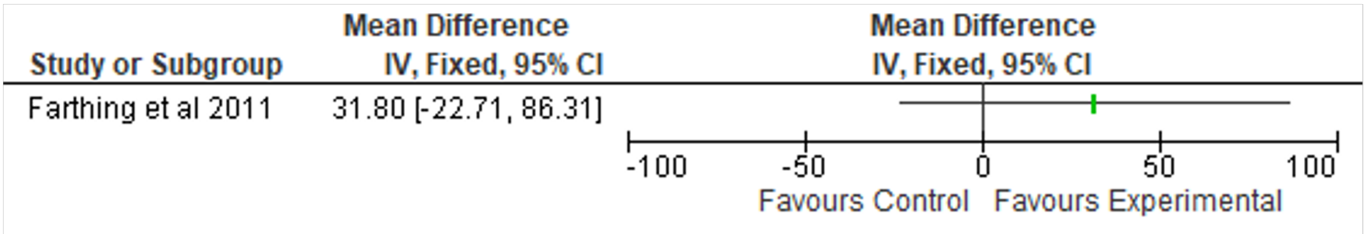

Figure 6. *Forest plots for regions of cortical activity following short-term limb immobilization following cross-education compared to control (no training and immobilization). Pooled effect size for horizontal line = 95% confidence interval. CI: confidence interval, IV: inverse variance.*

Changes in corticospinal activity

Changes in corticospinal excitability assessed by transcranial magnetic stimulation (TMS) was extracted from one study (n = 9) that assessed the amplitude of TMS induced motor-evoked potentials post-unilateral resistance training compared to control (n = 10). The results showed that MEPs of the untrained limb remained unchanged following cross-education, despite a large mean difference in favour of the experimental group (MD 5.20, n = 19; Fig 7).

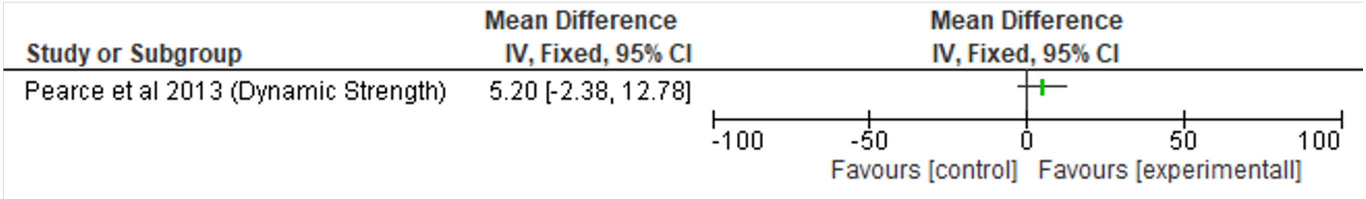

Figure 7. *Forest plots for regions of corticospinal exctability following short-term limb immobilization following cross-education compared to control (no training and immobilization). Pooled effect size for horizontal line = 95% confidence interval. CI: confidence interval, IV: inverse variance.*

Discussion

This meta-analysis revealed that cross-education is a viable form of resistance training that attenuates the loss of muscle strength following short-term limb immobilization when compared to usual care. Specifically, unilateral resistance training of the non-immobilized limb produced a large effect for strength and muscle thickness maintenance, but had no effect on muscle activation. Interestingly, moderate to large differences were observed between the experimental and control groups, for cross-education to attenuate the loss of neural drive to the immobilized limb. It may be that resistance training of the free limb, maintains strength of the immobilized limb via supraspinal mechanisms, such as bilateral corticospinal activity and reduced interhemispheric inhibition (IHI) associated with the cross-education of muscular strength [2,19,20].

Resistance training of the free limb prevents strength loss of the immobilized limb

The main finding of the present study was that strength training the non-immobilized limb provided a beneficial effect for strength in the immobilized limb after short-term immobilization. The overall pooled effect shows that there is clinical efficacy in the cross-education effect following unilateral resistance training [2]. The present study also found that cross-education had no effect on maximal voluntary activation or the amplitude of muscle activation following unilateral resistance training of the free limb. In support of previous research, cross-education attenuated the loss of muscle thickness of the immobilized limb, suggesting it may prevent muscle atrophy. Collectively, these finding suggest that there is a cross-education effect following limb immobilization that is likely to be mediated by neural mechanisms that are known to underlie the cross-education and counteract the negative effects that immobilization has on the central nervous system (CNS) [19]. Certainly, the current results show that there is preliminary data to support that changes in the cerebral cortex, likely contributes to the maintenance of strength following short-term immobilization (For review, see Manca 2018[20] and Frazer 2018[2]).

Immobilization following transient musculoskeletal injury is known to have significant detrimental effects on the functional capacity of skeletal muscle, resulting in the loss of both muscle strength and muscle mass [12]. The loss in maximal force production is rapid even during periods of immobilization as short as one week [21], whilst the changes in muscle mass occurs at a much slower rate [12]. Given the rate in which strength is lost during limb immobilization, it is likely such decreases are due to changes in the CNS. For example, several studies using surface electromyography (sEMG) have reported reduced muscle activation following immobilization [22]. Outside of sEMG studies, several lines of evidence show that the excitability of the alpha-motoneuron pool is reduced following immobilization, with the H-reflex, F-wave and M-wave amplitudes significantly reduced [23,24]. More recently, non-invasive brain stimulation techniques such as TMS have been used to determine the detrimental effects of immobilization on the excitability of the primary motor cortex [1,10,25]. Overall, it seems that immobilization leads to a reduction in neural excitability to the musculature of the immobilized limb. However, similar to the mechanism associated with cross-education [20], it seems resistance training of the free limb also attenuates the loss in corticospinal excitability [10]. However, a caveat to this interpretation is that the current systematic review was only able to include one TMS study and one fMRI study, thus there are not enough studies to draw any firm conclusions on CNS sparing effects of cross-education. However, the mean difference reported for corticospinal excitability and regions of cortical activation, provide preliminary support for a supraspinal mechanism attenuating the loss of neural drive to an immobilized limb.

Implications for cross-education during limb immobilization

Cross-education is the phenomenon that describes the increase in muscle strength in one limb following unilateral resistance training of the opposite limb [2,19]. First observed in 1894, there are now many published reports that have confirmed that the cross-education of muscle strength is a real effect [4,26] and the changes in strength of the untrained limb are due to neural adaptations (for review see Manca 2017[4] and Frazer 2018[2]). These adaptations include both structural and functional changes within cortical motor and non-motor regions and involve subtle changes along the entire neuroaxis (from the brain to the spinal cord) which include increased corticospinal excitability, reduced cortical inhibition, reduced interhemispheric inhibition, increased cortical voluntary activation and new regions of cortical activation as detected from neuroimaging techniques [2,20]. If neural adaptations are indeed responsible for the early reduction in muscle strength following immobilization, it is likely that cross-education may provide a means to reduce these detrimental effects by maintaining function of the CNS innervating the musculature of the immobilized limb. The findings of the current study support this hypothesis. The successful maintenance of strength in healthy immobilized tissue provides a promising outlook for reducing the negative impact of immobilization and enhancing recovery. Certainly, the current findings support a role for cross-education during periods of immobilization.

Cross-education attenuates the loss of muscle thickness but not muscle activation

Although cross-education induces neural plasticity in neural circuits that are involved in the force generating capacity of a muscle, currently there is very little evidence showing the effects of cross-education at the skeletal muscle level. This is interesting, because skeletal muscle is also a plastic tissue that can also rapidly modify its structure and function based upon both internal and external demands. Despite this, there is data available to suggest that cross-education during periods of limb immobilization may prevent muscle atrophy. For example, studies by Farthing et al. 2009 [27] and Magnus et al. 2010 [11], reported that cross-education prevented a loss in muscle thickness of the immobilized. Interestingly, in both studies, the immobilization only group had a significant reduction in muscle thickness. Similarly, Pearce et al. 2013 [10] reported similar findings. Despite only a small number of studies, when we pooled these effects together, our meta-analysis showed that there was a large effect for cross-education to attenuate the loss of muscle thickness. The mechanism underpinning this is not clear, but could be related to adaptive changes within the muscle fiber, as well as systemic and hormonal factors that may accompany neural drive induced by the unilateral resistance training [28]. However, a major limitation is that all included studies used ultrasonography for indirectly measuring cross-sectional area via muscle thickness. At a minimum, ultrasound is not the gold standard technique to detect changes in muscle cross-sectional area and thus there is a need to use more objective assessment techniques to determine the true effect of cross-education on attenuating the loss of muscle mass.

Although changes in muscle activation quantified by the amplitude of the sEMG signal is inferred as a measure of motor-unit recruitment and firing rate (rate coding), with increases in sEMG amplitude and rate coding being an indication of neural adaptation to resistance training of a trained limb, it is unlikely such changes would occur in an untrained limb, following cross-education. Although some studies have reported increased sEMG amplitude in the untrained limb following cross-education, a recent systematic review reported that the overall pooled effect was not significant [20]. To date, studies have failed to identify significant peripheral muscle adaptations in the contralateral untrained limb [29]. However, it is likely such changes have not been observed because of the inherent limitations associated with sEMG [30], thus any change in sEMG should not be inferred as a proxy measure for changes in the CNS.

Limitations

There are several limitations to this meta-analysis that should be taken into consideration when interpreting the current findings. Because of the high level of bias and lower quality assessment score of the included studies, the analysis might have led to an overestimation of the pooled effect for changes in strength. Further, most of the outcome measures displayed a high level of heterogeneity, suggesting that there is a need to standardise the methods of assessing muscle strength, muscle thickness and neural activation. By standardising testing protocols, the results of individual studies should become more homogenous making conclusions more robust, especially for muscle thickness. There is also a need to determine the time-course motor cortical response of cross-education during limb immobilization, as understanding the physiological mechanisms underpinning the current results, will enable targeted and effective guidelines for exercise prescription.

The large estimate for cross-education to attenuate the loss of strength and muscle thickness n should be considered preliminary due to the small number of studies that entered the meta-analysis. Further, because we employed a random effects model, due to different methodologies employed (i.e., type of resistance training employed in the cross-education intervention, the type of immobilization and type of muscle immobilized, different unit of measurement for same variable, etc.), we most likely underestimated some discrepancies amongst the included studies.

Conclusion

The evidence for cross-education to increase strength of an untrained limb is well supported and has now been translated into a clinical model. Based upon the current available data, cross-education during periods of limb immobilization maintains strength and muscle thickness of an immobilized limb, suggesting that there is a cross-education effect. Because cross-education is mediated by changes in the CNS [4], a finding partially supported by this review, it seems that cross-education acts to reduce and even eliminate the detrimental effects that immobilization has on the CNS. Although cross-education had no effect on preventing muscle activation, there is a need to use more objective measurement techniques to determine the potential for cross-education to alter or maintain muscle mass of the immobilized limb.

Reference	**Country**	**Study Design**	**Muscle Group**	**Participants**	**Intervention**	**DV**	**Measures**	**% change in 1RM**	**% change in isometric force**	**% change in muscle thickness**	**% change in corticospinal excitability**	**PEDro Score**
	Australia	RCT	Left elbow flexors	n = 28(immob. + train = 9, immob. = 9, control = 10) Age: 25.2 +/- 7.4 Gender: 13 males 15	Concentric strength training (80% 1RM) on R elbow flexors 6-8 reps x 3s flexion and 4s extension 4 sets with 3	Dynamic and isometric strength L elbow flexors Muscle thickness BB muscle Corticospinal activity	1RM Handheld dynamometry Ultrasound guided measurement MEP using TMS	Control = 0% (+/- 1.9) Immob. = -19.87% (+/- 2.1) Immob. + train = -0.56 %(+/- 3.1)	Control = 0.10% (+/- 7.85) Immob. = -5.66% (+/- 9.05) Immob. + train = 2.69% (+/- 10.35)	Control = 0.37% (+/- 2.7) Immob. = -5.98 %(+/- 1.4) Immob. + train = 0%(+/- 2.95)	At AMT: Control = 0.22% (+/- 2.3) Immob. = 1.84% (+/- 2.85)Immob. + train = 2.84% (+/- 2.9) MEP/Mmax at AMT:Control =	5/10

				females	min recovery b/n sets 3 sessions per week 3-week duration Left arm immobilised						-2.20% (+/- 6.1) Immob. = -23.73%(+/- 4.9)Immob. + train = 7.29%(+/- 6.75) % Above AMT:Control = -0.17% (+/- 8.86)Immob. = -20.97% (+/- 9.19)Immob. + train = 0.40% (+/- 9.38)	
Reference	**Country**	**Study Design**	**Muscle group**	**Participants**	**Intervention**	**DV**	**Measures**	**% change peak torque**	**% change in muscle thickness**	**% change activation amplitude**	**% change in activation frequency**	**PEDro Score**
	Canada	RCT with a between within mixed design	Left wrist flexors	n = 30 (immob. + train = 10, immob. = 10, control = 10) Age: 22.8 +/- 2.7 Gender: 8 males 22 females	Isometric ulnar deviation of R wrist 8 reps x 3s hold Initially 3 sets, progressed to 6 sets 5 sessions per week 3-week duration	Muscle thickness of FCU and FDS Isometric ulnar deviation Maximal isometric muscle activation	B-mode ultrasound Isokinetic dynamometer EMG	Control = -5.53% (+/- 1.81) Immob. = -14.81% (+/- 0.99) Immob. + train = 2.30% (+/- 1.35)	Control = -1.13 (+/- 0.23) Immob. = -4.32% (+/- 0.17) Immob. + train = -1.38% (+/- 0.15)	Control = 8.70% (+/- 0.03) Immob. = 6.67% (+/- 0.06) Immob. + train = 20% (+/- 0.04)	Control = 6.00% (+/- 7.40) Immob. = -12.07% (+/- 8.30) Immob. + train = -6.10% (+/- 10.28)	5/10
Reference	**Country**	**Study Design**	**Muscle group**	**Participants**	**Intervention**	**DV**	**Measures**	**% change isometric strength**	**% change in muscle thickness**	**% change activation (via twitch)**	**% change activation (via EMG)**	**PEDro Score**
	Canada	RCT with between within mixed design	Left elbow flexors and extensors	n = 25(immob. + train = 8, immob. = 8, control = 9) Age:22.03 +/- 3.37 Gender: 8 males17 females	Maximal isometric elbow flexion and extension training 3 sec contraction, 3 sec rest, 1 min rest between sets Initially,	Isometric strength Muscle thickness (BB and TB) Maximal voluntary activation	Dynamometer B-mode ultrasound Interpolated twitch and EMG	Elbow flexionControl = 5.65% (+/- 4.02) Immob. = 3.99% (+/- 3.62) Immob. + train = 7.71% (+/- 2.99)	BBControl = -0.20% (+/- 0.74) Immob. = -2.81% (+/- 1.07) Immob. + train = 2.28% (+/- 0.65) TB	Elbow flexionControl = -3.00% (+/- 5.8) Immob. = -1.97% (+/- 6.85) Immob. + train = 1.00% (+/- 7.7) Elbow e	Elbow flexion Control = -4% (+/- 0.004) Immob. = -5.88% (+/- 0.013) Immob. + train = 7.14% (+/-	5/10

					3 sets of 8 flexion, and 8 extension contractions, progressed to 6 sets 3 sessions per week 4-week duration			Elbow extension Control = 0% (+/- 3.79) Immob. = -5.59% (+/- 7.81) Immob. + train = 32.20% (9.00)	Control = -0.87% (+/- 0.77) Immob. = -5.17% (+/- 2.76) Immob. + train = 3.36% (+/- 2.12)	xtension Control = 0.69% (+/- 10.25) Immob. = 3.79% (+/- 7.65) Immob. + train = -1.42% (+/- 7.70)	0.0075) Elbow extension Control = 22.72% (+/- 0.009) Immob. = 4.17% (+/- 0.011) Immob. + train = -37.5% (+/- 0.021)	
Reference	**Country**	**Study Design**	**Muscle group**	**Participants**	**Intervention**	**DV**	**Measures**	**% change pooled strength**	**% change in muscle thickness**	**% change EMG activation**	**% change EMG activation**	**PEDro Score**
	Canada	RCT with between within mixed design	Left wrist flexors	n = 16 (immob. + train = 8, immob. control = 8) Age:21.5 (+/- 3.5) Gender:3 males13 females	ECC, CON and ISO isokinetic wrist action (flexion and extension) 2 sets of 8 reps, progressed to 6 sets, 1min rest between sets 3 sessions per week 4-week duration	Strength changes in L wrist flexors Muscle thickness /CSA Muscle activation	Peak torque US EMG Maximal electrically evoked contraction	Control = -19.44% (+/- 3.1) Immob. + train = -5.32% (+/- 3.1)	Control = -2.27% (+/- 7.68) Immob. + train = 1.35% (+/- 6.91)	Elbow flexionControl = -23.88% (+/- 0.09) Immob. + train = -24.07% (+/- 0.12)	Elbow extension Control = -29.31% (+/- 0.07) Immob. + train = -10.48% (+/- 0.04)	6/10
Reference	**Country**	**Study Design**	**Muscle group**	**Participants**	**Intervention**	**DV**	**Measures**	**% change peak force**	**% change in muscle thickness**	**% change activation amplitude (via EMG)**	**% change activation contralateral motor cortex**	**PEDro Score**
Farthing et al., 2011	Canada	RCT with a between within mixed design	Left wrist flexors andextensors	n = 14(immob. + train = 7, immob. control = 7) Age: 21.65 (+/- 2.9) Gender: 2 males12 females	Isometric handgrip contractions 3 sec contraction (cadenced with metronome) 3 sets, 8 reps, progresses	Muscle thickness (FCU and FDS) Isometric handgrip force Maximal isometric muscle activation	B-mode ultrasound Hand grip dynamometer EMG, FMRI	Control = -10.96% (+/- 2.67) Immob. + train = 1.16% (+/- 2.68)	NS (table or graphs)	Control (immob.) = -9.88% (+/- 0.087) Immob. + train = 17.41% (+/- 0.072)	Control (immob.) = -8.14% (+/- 51.12) Immob. + train = 5.46% (+/- 36.85)	5/10

					up to 6 sets 5 sessions per week 3-week duration							

Table 1.

References

1. Andrushko Justin W., Lanovaz Joel L., Björkman Kelsey M., Kontulainen Saija A., Farthing Jonathan P.. Unilateral strength training leads to muscle-specific sparing effects during opposite homologous limb immobilization. *Journal of Applied Physiology.* 2018; 124(4)DOI
2. Borenstein Michael, Hedges Larry V., Higgins Julian P.T., Rothstein Hannah R.. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods.* 2010; 1(2)DOI
3. Clark Brian C., Issac Lailah C., Lane Jason L., Damron Leatha A., Hoffman Richard L.. Neuromuscular plasticity during and following 3 wk of human forearm cast immobilization. *Journal of Applied Physiology.* 2008; 105(3)DOI
4. Cohen J. Statistical power analysis for the behavioral sciences. L. Erlbaum Associates: Hillsdale, N.J; 1988.
5. Downs S. H., Black N.. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology & Community Health.* 1998; 52(6)DOI
6. Dragert Katie, Zehr E. Paul. High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke. *Experimental Brain Research.* 2012; 225(1)DOI
7. Farina Dario, Merletti Roberto, Enoka Roger M.. The extraction of neural strategies from the surface EMG: an update. *Journal of Applied Physiology.* 2014; 117(11)DOI
8. Farthing Jonathan P., Krentz Joel R., Magnus Charlene R. A.. Strength training the free limb attenuates strength loss during unilateral immobilization. *Journal of Applied Physiology.* 2009; 106(3)DOI
9. FARTHING JONATHAN P., KRENTZ JOEL R., MAGNUS CHARLENE R. A., BARSS TREVOR S., LANOVAZ JOEL L., CUMMINE JACQUELINE, ESOPENKO CARRIE, SARTY GORDON E., BOROWSKY RON. Changes in Functional Magnetic Resonance Imaging Cortical Activation with Cross Education to an Immobilized Limb. *Medicine & Science in Sports & Exercise.* 2011; 43(8)DOI
10. Frazer Ashlyn K., Pearce Alan J., Howatson Glyn, Thomas Kevin, Goodall Stuart, Kidgell Dawson J.. Determining the potential sites of neural adaptation to cross-education: implications for the cross-education of muscle strength. *European Journal of Applied Physiology.* 2018; 118(9)DOI
11. Hendy Ashlee M., Lamon Séverine. The Cross-Education Phenomenon: Brain and Beyond. *Frontiers in Physiology.* 2017; 8DOI
12. Hortobágyi T., Dempsey L., Fraser D., Zheng D., Hamilton G., Lambert J., Dohm L.. Changes in muscle strength, muscle fibre size and myofibrillar gene expression after immobilization and retraining in humans. *The Journal of Physiology.* 2000; 524(1)DOI
13. Hortobagyi T., Hill J. P., Houmard J. A., Fraser D. D., Lambert N. J., Israel R. G.. Adaptive responses to muscle lengthening and shortening in humans. *Journal of Applied Physiology.* 1996; 80(3)DOI
14. Huwaldt Joseph A. *Plot Digitizer.*
15. Kawakami Yasuo, Akima Hiroshi, Kubo Keitaro, Muraoka Yoshiho, Hasegawa Hiroshi, Kouzaki Motoki, Imai Morihiro, Suzuki Yoji, Gunji Atsuaki, Kanehisa Hiroaki, Fukunaga Tetsuo. Changes in muscle size, architecture, and neural activation after 20 days of bed rest with and without resistance exercise. *European Journal of Applied Physiology.* 2001;

84(1-2)DOI
16. Lee Michael, Carroll Timothy J. Cross Education. *Sports Medicine.* 2007; 37(1)DOI
17. Leung Michael, Rantalainen Timo, Teo Wei-Peng, Kidgell Dawson. The ipsilateral corticospinal responses to cross-education are dependent upon the motor-training intervention. *Experimental Brain Research.* 2018; 236(5)DOI
18. Liberati Alessandro, Altman Douglas G., Tetzlaff Jennifer, Mulrow Cynthia, Gøtzsche Peter C., Ioannidis John P.A., Clarke Mike, Devereaux P.J., Kleijnen Jos, Moher David. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology.* 2009; 62(10)DOI
19. Liepert J., Tegenthoff M., Malin J.-P.. Changes of cortical motor area size during immobilization. *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control.* 1995; 97(6)DOI
20. Lundbye-Jensen Jesper, Nielsen Jens Bo. Central nervous adaptations following 1 wk of wrist and hand immobilization. *Journal of Applied Physiology.* 2008; 105(1)DOI
21. Magnus Charlene R.A., Arnold Cathy M., Johnston Geoffrey, Dal-Bello Haas Vanina, Basran Jenny, Krentz Joel R., Farthing Jonathan P.. Cross-Education for Improving Strength and Mobility After Distal Radius Fractures: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation.* 2013; 94(7)DOI
22. Magnus Charlene R. A., Barss Trevor S., Lanovaz Joel L., Farthing Jonathan P.. Effects of cross-education on the muscle after a period of unilateral limb immobilization using a shoulder sling and swathe. *Journal of Applied Physiology.* 2010; 109(6)DOI
23. Manca Andrea, Hortobágyi Tibor, Rothwell John, Deriu Franca. Neurophysiological adaptations in the untrained side in conjunction with cross-education of muscle strength: a systematic review and meta-analysis. *Journal of Applied Physiology.* 2018; 124(6)DOI
24. Manca A., Hortobágyi T., Carroll T. J., Enoka R. M., Farthing J. P., Gandevia S. C., Kidgell D. J., Taylor J. L., Deriu F.. Contralateral Effects of Unilateral Strength and Skill Training: Modified Delphi Consensus to Establish Key Aspects of Cross-Education. *Sports Medicine.* 2020. DOI
25. Opie George M., Evans Alexandra, Ridding Michael C., Semmler John G.. Short-term immobilization influences use-dependent cortical plasticity and fine motor performance. *Neuroscience.* 2016; 330DOI
26. Pearce A. J., Hendy A., Bowen W. A., Kidgell D. J.. Corticospinal adaptations and strength maintenance in the immobilized arm following 3 weeks unilateral strength training. *Scandinavian Journal of Medicine & Science in Sports.* 2012; 23(6)DOI
27. Zanette Giampietro, Tinazzi Michele, Bonato Claudio, di Summa Alfonsina, Manganotti Paolo, Polo Alberto, Fiaschi Antonio. Reversible changes of motor cortical outputs following immobilization of the upper limb. *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control.* 1997; 105(4)DOI
28. Zult Tjerk, Gokeler Alli, van Raay Jos J. A. M., Brouwer Reinoud W., Zijdewind Inge, Farthing Jonathan P., Hortobágyi Tibor. Cross-education does not improve early and late-phase rehabilitation outcomes after ACL reconstruction: a randomized controlled clinical trial. *Knee Surgery, Sports Traumatology, Arthroscopy.* 2018; 27(2)DOI
29. Manca A., Dragone D., Dvir Z., Deriu Franca. Cross-education of muscular strength following unilateral resistance training: a meta-analysis. *European Journal of Applied Physiology.* 2017; 117(11)DOI
30. Herbert Rob. Research Note: Significance testing and hypothesis testing: meaningless, misleading and mostly unnecessary. *Journal of Physiotherapy.* 2019; 65(3)DOI