Inter-limb mechanisms and clinical relevance of cross-education in humans

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Chapter 4

Mirror training augments the cross-education of strength and affects inhibitory paths

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Abstract

**Purpose:** Unilateral strength training not only strengthens muscles on the trained side, but also the homologous muscles on the untrained side; however, the magnitude of this interlimb cross-education is modest. We tested the hypothesis that heightened sensory feedback by mirror-viewing the exercising hand would augment cross-education by modulating neuronal excitability. **Methods:** Healthy adults were randomized into a mirror training group (MG, N = 11) and no-mirror training group (NMG, N = 12) and performed 640 shortening muscle contractions of the right wrist flexors at 80% maximal voluntary contraction (MVC) during 15 sessions over three weeks. Maximal strength and specific transcranial magnetic stimulation metrics of neuronal excitability, measured in the mirror and no-mirror setup at rest and during unilateral contractions at 60% MVC, were assessed prior to and following the strength intervention. **Results:** Trained wrist flexor MVC increased 72% across groups while cross-education was higher for the MG (61%) than NMG (34%; P = 0.047). The MG showed a reduction (15-16%) in contralateral silent period duration measured from the contracting left-untrained flexor carpi radialis, while the NMG showed an increase (12%; P ≤ 0.030). Interhemispheric inhibition, measured from the trained to untrained primary motor cortex, increased for the MG (11%) but decreased for the NMG (15%) when measured in the mirror setup at rest (P = 0.048). Other TMS measures did not change. **Conclusion:** Viewing the exercising hand in a mirror can augment the cross-education effect. The use of a mirror in future studies can potentially accelerate functional recovery from unilateral impairment due to stroke or upper limb fracture.

**Keywords:** flexor carpi radialis, inhibition, interlimb transfer, motor cortex, strength training, transcranial magnetic stimulation
4.1 Introduction

It has been known for over 100 years that unilateral resistance training strengthens the actively contracting muscles and also the homologous muscles on the untrained side [1] – a phenomenon called cross-education. This interlimb transfer to produce maximal voluntary force is most likely mediated by neural mechanisms because the force in the untrained muscles increases without changes in muscle size [2]. A growing body of evidence suggests that the transfer is predominantly of cortical origin, but the involvement of subcortical and spinal levels cannot be ruled out [3]. Unilateral forceful contractions result in an increased excitability of the primary motor cortex (M1) contralateral to the movement side. At the same time the ipsilateral M1, modulated by neural interactions between GABAergic intracortical circuits that mediate short-interval intracortical inhibition (SICI) and interhemispheric glutamatergic projections from the contralateral to ipsilateral M1 [4], controls the corticospinal output to the resting hand. Following multiple sessions of unilateral forceful contractions, the interlimb transfer may occur according to one of two models [5]. Firstly, the cross-activation model suggests that bilateral cortical activity observed during unilateral strength training induces task specific changes in the contralateral and ipsilateral cortical motor networks, respectively controlling the trained and untrained contralateral homologous muscles. Secondly, the bilateral access model posits that unilateral strength training creates motor engrams at a locus that is accessible for the motor control of both the trained and contralateral untrained limb. In both models, experimental data assign a key role to the untrained M1 in mediating cross-education. For example, a functional magnetic resonance imaging study showed that the cross-education of strength was accompanied by enlarged neuronal activation of the untrained sensorimotor cortex [2] and transcranial magnetic stimulation (TMS) studies [6-8] have demonstrated that the neuronal excitability from the untrained M1 to the transfer muscles increased following unilateral strength training. Also, the force transfer is associated with reductions in SICI of the untrained M1 [6], contralateral silent period (cSP) duration [9], and interhemispheric inhibition (IHI) from trained to untrained M1 [7]. Collectively, these lines of experimental evidence suggest that cortical and corticospinal paths, possibly modulated via transcallosal connections, mediate the cross-education of strength.

The magnitude of cross-education is modest, ~8% [10]. However, a recent review has proposed the idea that viewing the movements of the exercising hand in a mirror could amplify the magnitude of strength transfer [11]. This expectation is based on the idea that the stationary hand upon which
the mirror image is superimposed is moving and this visual illusion of the muscles contracting activates the mirror-neuron system (MNS). The MNS connects sensory neurons that respond to visual properties of an observed action and motor neurons that depolarize during the execution of a similar action, resulting in altered corticospinal excitability that reflects the pattern of muscle activity of the observed action [12]. Action observation using a mirror might therefore alter the M1 excitability of the inactive hemisphere leading to behavioural performance gains of the untrained hand behind the mirror [13]. An alternative hypothesis is based upon the dominance of vision over proprioception [14], where the mirror-induced increase in attention towards the hand behind the mirror leads to activation of motor networks within the untrained hemisphere. Although the precise neurophysiological mechanisms of mirror training are still poorly understood, it seems that the performance gains following mirror training are a result of the mutual interaction between perceptual and motor activity at a cortical level. Thus, it is possible that elements of the perceptuomotor system, activated by mirror-viewing of the exercising arm, but not activated during unilateral training without a mirror, provide extra input to the untrained M1 and could therefore augment the strength transfer effect. Indeed, as a first step, we recently demonstrated that mirror-viewing of a slow and forceful right wrist flexion contraction reduced SICI in the right-ipsilateral M1 compared with a no-mirror condition [15]. Therefore, we hypothesised that the illusion of the stationary hand moving and its muscles contracting during unilateral strength training modifies the excitability of the untrained M1 and also perceptuomotor circuits with inputs to this M1, thereby magnifying the cross-education effect. We examined this possibility by comparing the effect of unilateral strength training performed with and without a mirror on cross-education and on intracortical and interhemispheric TMS metrics. Because the key element of the stimulus is the illusion of the resting hand to be moving and its muscles contracting, we expected to find a more pronounced modulation of neuronal excitability when tested during muscle contraction when subjects viewed the contracting right hand in the mirror compared with a no-mirror contraction condition and at rest.

4.2 Materials and Methods

4.2.1 Participants and design

Twenty-four right-handed [16] healthy volunteers (19 men, 5 women) participated in the study. A stratified, randomized, matched-pair design was used to control for the confounding effect of baseline strength between groups. Participants with similar maximal dynamic (i.e., shortening) right
wrist flexion strength were grouped into pairs, from which one participant was randomly assigned to the no-mirror training group (NMG, N = 12, age = 29 years ± 9, height = 1.74 m ± 0.07, mass = 75.8 kg ± 14.0, BMI = 25.0 kg/m² ± 3.4) and the other to the mirror training group (MG, N = 12, age = 25 years ± 4, height = 1.78 m ± 0.08, mass = 76.3 kg ± 13.8, BMI = 24.0 kg/m² ± 2.5). One participant from the MG had to withdraw after the pre-test because of illness unrelated to the study. Prior to the start of the study, participants completed a comprehensive questionnaire to determine experimental and medical contraindications to the protocol. All participants provided written informed consent to the experimental procedures, which were approved by the University’s Research Ethics Committee and in accordance with the Declaration of Helsinki.

Figure 4.1A outlines the design. Participants visited the laboratory 18 times. Training consisted of 15 strength-training sessions of the right wrist flexors, while the left wrist was at rest. The NMG performed the training with views of both hands blocked, while the MG viewed the mirror image of the exercising right hand, which created the illusion that the left hand was performing the training. One week before the start of the study, participants visited the laboratory for a 30-minute-long familiarization session that involved exposure to peripheral nerve stimulation and to single-pulse TMS. The week before and after the intervention, maximal torque was recorded for the dominant (right) and non-dominant (left) wrist flexor muscles followed by a neurophysiological assessment, using peripheral nerve stimulation and TMS.

4.2.2 Experimental setup
Figure 4.1B illustrates the experimental setup that was used for training and neurophysiological testing. Participants sat comfortably in a chair with both forearms placed in a neutral position on a custom-built table and elbows flexed at 90°. The metacarpophalangeal joint was placed on a plastic covered manipulandum that projected vertically downward toward the table surface and was attached to the lever arm of an isokinetic dynamometer (Biodex, System 4, Medical Systems, Shirley, NY, USA). The thumb was upper most and the fingers extended to avoid passive insufficiency during wrist flexion [17]. For each participant, the distance between the metacarpophalangeal joint position on the manipulandum and the axis of rotation was held at a constant length, but was adjusted between participants to account for anatomical differences. Vision of both forearms was blocked by placing them inside two separate boxes. Because training and testing required a no-mirror and a mirror setup, a cardboard wall or a mirror, respectively, was mounted on the central vertical wall of the left box and was aligned in the sagittal plane in
front of the participant. In the no-mirror setup participants’ view of both forearms was blocked and volunteers were instructed to fix their gaze on a mark placed on the cardboard wall to maintain constant head position. In the mirror setup participants focused on the mirror image of the right forearm which created the illusion of seeing the left forearm. The left arm was placed in the same anatomical position as the right arm. Participants removed jewellery, watches and other adornments to avoid visual or kinaesthetic distractions or inconsistencies between limbs while training and testing.

All the training, and part of the neurophysiological testing, involved dynamic right wrist flexion contractions, which were performed in the transverse plane over the table surface by pressing at the metacarpophalangeal joint against the manipulandum. The shoulder
and forearm were not strapped, but visual inspection ensured that the shoulder and forearm did not contribute to the wrist flexion movement. Contractions started with the wrist at 20° of extension and ended with the wrist at 20° of flexion, resulting in 40° of range of motion. Contractions were performed at 20°/s. Participants received constant verbal feedback from the investigator to ensure the requisite torque was attained; no visual feedback was provided at any point in order to avoid distraction of gaze from the mirror image or cardboard wall.

4.2.3 Maximum voluntary contraction
Dynamic and isometric MVCs for the dominant (right) and non-dominant (left) wrist were measured, using the aforementioned experimental setup but without the two boxes. Torque for the dynamic wrist flexion MVCs was recorded when the wrist past anatomical zero (0°). Isometric wrist flexion MVCs were measured during 5 s-effort at the 0° position. Participants performed three dynamic MVCs followed by three isometric wrist flexion MVCs with the left and right wrist; this was preceded by a warm-up for each wrist (10 dynamic contractions at an estimated 50% of maximal effort). The highest of the three contractions was recorded as the contraction specific MVC. After completion of the pre- and post-test, dynamic MVC torque was measured in a subsample of participants (pre-test: N = 5; post-test: N = 14) to examine the presence of fatigue. During MVCs mean surface EMG was calculated over a 200 ms period.

4.2.4 Surface EMG
Surface EMG was recorded from the left and right flexor carpi radialis (FCR) to quantify voluntary muscle activity and evoked responses from peripheral (maximal M-wave amplitude \([M_{\text{max}}]\)) and cortical (motor-evoked potentials [MEPs]) stimulation. The skin surface was shaved and cleaned, before the electrodes (model 1041PTS; Kendall, Tyco Healthcare Group, Mansfield, MA, USA) were placed on the muscle belly (inter-electrode distance, 2 cm) with the ground electrode fixed on the distal styloid process of the left radius. Surface EMG was band-passed filtered at 20-2,000 Hz, amplified ×1000 (CED 1902, Cambridge Electronic Design, Cambridge, UK Digitimer, Hertfordshire, UK), sampled at 5 kHz (CED Power 1401; Cambridge Electronic Design, Cambridge, UK) and recorded on a personal computer. Surface EMG was calculated as the mean rectified EMG activity, expressed relative to \(M_{\text{max}}\).

4.2.5 Neurophysiological measurements
The neurophysiological assessment was performed according to current methodological [18], safety and ethical [19] guidelines. Corticospinal and motor cortical excitability of both M1s were evaluated using TMS in
the mirror and no-mirror setup at rest and during forceful dynamic and isometric unilateral wrist flexion contractions [15]. Table 4.1 summarizes the TMS measures. To determine the effect of unilateral strength training on the left-trained M1, corticospinal excitability and SICI were examined in the no-mirror setup at rest and recorded from the right FCR. To determine the effect of unilateral strength training on corticospinal excitability and SICI of the right-untrained M1, single and paired pulse TMS were presented in a random order in the mirror and no-mirror setup at rest and during dynamic right wrist flexor contractions at 60% MVC. The muscle contraction phase did not affect the MEP amplitude recorded from the contralateral homologous resting muscle during unilateral dynamic contractions [20]. Therefore, during dynamic contractions, we delivered TMS stimuli to the right-untrained M1 at a standardized position when the right wrist past through 0°. During all conditions where corticospinal excitability and SICI of the untrained-right M1 were measured, MEP amplitudes were recorded from the resting left FCR. The order of the contraction and resting conditions was randomized between participants. The cSP, measured in the no-mirror setup only, was elicited in the left FCR by stimulation of the right-untrained M1 and right FCR by stimulation of the left-trained M1 during either isometric left or right wrist flexion contractions. All unilateral contractions were performed at 60% MVC. During the post-test, contractions were performed at 60% pre-test MVC and 60% post-test MVC (in other words, relative to the post-training MVC). To determine if IHI was further diminished following unilateral strength training with than without the mirror, we measured IHI from left-trained to right-untrained M1 at rest in the mirror and no-mirror setup. Data acquisition was initiated 30 ms before the TMS stimulus was delivered. MEPs were analysed off-line for peak-to-peak amplitude (Signal, v.5.04; Cambridge Electronic Design). The EMG activity arising prior to the stimulus was rectified and computed over a 30 ms period prior to stimulation artefact.

The influence of associated activity (i.e., the EMG activity of the contralateral resting muscles during a right-unilateral muscle contraction) on cortical and corticospinal excitability remains unclear. Therefore 60% MVC was used as the contraction intensity because participants were less able to prevent associated EMG activity at higher force levels [21]. During the experimental conditions, participants were frequently reminded to relax the non-exercising arm when performing wrist flexion contractions. Trials (N = 43 of a total of N = 2760; ~1.5%) in which associated FCR activity exceeded the background noise level of 25 μV were excluded from the analyses [4].
<table>
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<td>No-mirror, at rest</td>
<td>Left</td>
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<td>X (conditioning pulse) ——</td>
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<td>Mirror, at rest</td>
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<td>X (test pulse) ——</td>
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<td>No-mirror, dynamic right wrist contractions at 60% MVC&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Mirror, dynamic right wrist contractions at 60% MVC&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>No-mirror, isometric left wrist contractions at 60% MVC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Right</td>
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X, denotes that a measurement was administered; ——, denotes that a measurement was not administered.
cSP, contralateral silent period; IHI, interhemispheric inhibition measured from the left-trained to the right-untrained M1; MVC, maximal voluntary contraction; SICI, short-interval intracortical inhibition.
<sup>a</sup> measured at 60% pre-test MVC during the pre-test and measured at 60% pre- and post-test MVC during the post-test.
4.2.6 Transcranial magnetic stimulation of the primary motor cortex

To assess corticospinal excitability, SICI and the cSP, TMS was delivered from a magnetic stimulator (Magstim 200²; Magstim Company Ltd, Carmarthenshire, UK) through a figure-of-eight coil (loop diameter 90 mm; Magstim, Spring Gardens, Wales, UK) with a monophasic current waveform. With the addition of a second Magstim 200² stimulator, equipped with a BiStim² timing module, paired pulses were delivered through the same figure-of-eight coil. The coil was moved in 0.5-cm steps over the M1 to identify the optimal scalp position, i.e., hotspot, for activation of the left FCR overlying right M1 and the right FCR overlying left M1. The handle of the coil was pointing backwards and was held approximately 45° away from the midline so the direction of the current induced in the M1 was from posterior to anterior. Initially the ‘hotspot’ was located on each participant. The hotspot was defined as the lowest threshold capable of evoking the biggest potential in the targeted muscle [22]. A marker pen was used to mark this optimal position of the coil on the scalp to ensure constant positioning of the coil throughout the experiment. After the hotspot had been identified, resting motor threshold (rMT) was determined as the lowest stimulator intensity to produce a peak-to-peak MEP amplitude ≥ 50 µV in 5 out of 10 trials [22]. Corticospinal excitability was measured as part of the SICI measurement, by a single TMS pulse delivered at an intensity of 120% rMT. For measuring SICI, a conditioning pulse at 80% rMT preceded the test pulse of 120% rMT with an interstimulus interval of 2 ms to create inhibition that is normally deeper than the inhibition created at neighbouring interstimulus intervals [23]. A total of 20 MEPs were evoked in each condition, 10 MEPs for measuring SICI and 10 MEPs for measuring corticospinal excitability, with an interval of ~5 s between stimuli. For determining SICI the conditioned MEPs were expressed relative to the MEPs from the unconditioned test pulse.

To evoke a cSP, a single TMS pulse was applied at an intensity of 160% rMT. The cSP was determined by using a previously described method [24]. Briefly, the duration of the cSP was calculated in eight single EMG trials from the stimulus onset to the end of the cSP, which was defined as the point where the first burst of EMG activity was seen following the period of EMG silence. In the same trials, active amplitudes recorded from the contracting FCR were defined as the peak-to-peak amplitude of the MEPs evoked by the single TMS pulse. Participants were constantly reminded to ‘push through’ the silent period. All data processing was completed by the same investigator.
Mirror training augments cross-education

IHI from the left-trained to right-untrained M1 was determined by using an established method [25]. Two custom-built figure-of-eight coils (loop diameter 60 mm, model D60 mm; Magstim, Spring Gardens, Wales, UK) were positioned at the optimal scalp position for eliciting MEPs in the left and right FCR, respectively. The handles of the two coils pointed ~45° backwards away from the midline with a posterior to anterior current direction [7]. The rMT for each hemisphere was determined using the aforementioned method and the intensity used for the IHI conditioning and test stimulus was 120% rMT. To evoke inhibition, the conditioning stimulus was delivered to the left M1 10 ms before the test stimulus was given to the right M1 [25]. Ten test stimuli and 10 conditioned-test stimuli were presented in random order with ~5.5 s between each trial; MEPs were recorded from the left FCR. For determining IHI the conditioned MEPs were expressed relative to the MEPs elicited by the test stimulus alone.

In four participants (two from the NMG; two from the MG) it was not possible to measure IHI because the two coils could not be positioned without causing interference of optimal coil placement or the magnetic field. Additionally, in three participants (two from the NMG; one from the MG) we were not able to elicit MEPs during the post-test assessment; therefore IHI was reported for 16 participants (eight from each group).

4.2.7 Peripheral nerve stimulation
The $M_{\text{max}}$ of the left and right FCR was determined by delivering a 1-ms, rectangular pulse, percutaneous electrical stimulation (model DS7A, Digitimer, Welwyn Garden City, UK) at the medial aspect of the elbow over the median nerve. The electrode was moved systematically to find the optimal stimulation position to elicit the M-wave, while both forearms were rested on a custom-built table with the hands in a supinated position. Stimulation intensity was increased incrementally until there was no further increase in M-wave size. The maximal M-wave amplitude (i.e., $M_{\text{max}}$) was used to standardize corticospinal excitability and mean surface EMG data over different test sessions.

4.2.8 Strength training
Participants attended 15, 20-min-long training sessions during a 3-week period (5 sessions/week) and performed dynamic wrist flexions with the dominant (right) wrist at 80% maximal voluntary contraction (MVC). The NMG used the no-mirror setup for training while the MG used the mirror setup where mirror-viewing of the right exercising hand created the illusion that the left hand was exercising. Each week, dynamic right wrist flexor MVC was measured to re-establish the 80% MVC training intensity
for that week. During every training session, participants performed one set of 10 repetitions at 50% MVC as a warm-up followed by six sets of eight repetitions, separated by 60 s of rest. The training program was based on a previous study showing cross-education and was progressive in nature; beginning with three sets of eight repetitions and increasing the volume by one additional set each training day, up to a maximal training volume of six sets [26]. We used 80% instead of 100% MVC exercise intensity to prevent the participants from getting too fatigued; in addition, during the exercise participants were frequently reminded to completely relax the left arm. All training sessions were supervised and coached, whereby the participants received verbal feedback from the investigator to reach the target torque. All participants completed the 15 training sessions successfully, apart from one participant from the MG who completed 14 training sessions. In two participants from each group, EMG activity of the left and right FCR was recorded during the 5th, 10th and 15th training session to examine if the left hand was at rest and if the mirror had an effect on EMG activity. The mean surface EMG was calculated over a 200 ms period during the main contraction phase of the right FCR.

4.2.9 Statistical analysis
Data in the text and figures are presented as mean ± SD. Each variable was checked for normality prior to the analysis. Corticospinal excitability, SICI and pre-stimulus EMG were log transformed to correct for non-normally distributed data. The main analysis, used for analysing each outcome measure (MVCs, M_max, rMT, corticospinal excitability, SICI, cSP, IHI, pre-stimulus EMG activity), was a group (MG, NMG) x time (pre, post) repeated measures ANOVA. Where appropriate, interaction effects were subjected to a Tukey HSD post hoc pairwise comparison. Partial eta squared (η²_P) and Cohen’s d were calculated as measures of effect size. Cutoffs for η²_p are ≥ 0.01 (small), ≥ 0.06 (medium), and ≥ 0.14 (large) [27]. Between groups equality at baseline was tested by an independent samples t-test for all variables. A paired-samples t-test was used 1) to examine differences in maximal torque at the start and end of the pre- and post-test to verify that fatigue did not affect the results, 2) to test if the produced torque during the TMS measurements was equal to the target torque. A Friedman’s ANOVA was performed to test if EMG activity in a population sub-set (N = 4) of the left and right FCR was different between the 5th, 10th and 15th training session. SPSS version 22 was used for the statistical analysis and significance was accepted as P < 0.05.
4.3 Results

4.3.1 MVC torque and EMG right-trained wrist
Individual and group data for changes in MVC torque in the right-trained wrist are presented in Fig. 4.2A and 4.2B. The two groups did not differ in dynamic ($t_{(21)} = 0.2$, $P = 0.878$) and isometric MVC torque ($t_{(21)} = 0.7$, $P = 0.501$) at baseline. There was no group–time interaction for dynamic ($F_{1,21} < 0.1$, $P = 0.961$) or isometric MVC torque ($F_{1,21} < 0.1$, $P = 0.867$), suggesting that strength gains after training were not different between groups. The time main effects was observed for both dynamic ($F_{1,21} = 110.5$, $P < 0.001$, $\eta^2_p = 0.840$) and isometric MVC torque ($F_{1,21} = 73.2$, $P < 0.001$, $\eta^2_p = 0.777$); dynamic training increased dynamic MVC torque by 72% across groups (pre-test $13.3 \pm 3.8$ Nm, post-test $22.9 \pm 6.1$ Nm) and isometric MVC torque by 66% across groups (pre-test $18.8 \pm 4.0$ Nm, post-test $27.6 \pm 6.7$ Nm. The $M_{max}$-normalized EMG activity measured during these MVC torque tests revealed no group–time interactions and time main effects under dynamic and static conditions (all $P \geq 0.174$, $\eta^2_p \leq 0.086$).

![Dynamic MVCs and Isometric MVCs](image)

**Figure 4.2** | Change in maximal voluntary force in the right-trained wrist flexor muscles (A: training specific dynamic contraction, B: isometric contraction) and left-untrained wrist flexor muscles (C: training specific dynamic contraction, D: isometric contraction). The black solid lines represent the individual torque changes. †, group–time interaction ($P < 0.05$).
4.3.2 MVC torque and EMG left-untrained wrist

Figures 4.2C and 4.2D show the individual and group data for changes in MVC torque in the left-untrained wrist. With the two groups being not different in dynamic ($t_{(21)} = -0.3$, $P = 0.740$) and isometric MVC torque ($t_{(21)} = 0.1$, $P = 0.916$) at baseline. There was a group–time interaction for dynamic ($F_{1,21} = 4.5$, $P = 0.047$, $\eta^2 = 0.176$) but not for static MVC torque ($F_{1,21} = 1.3$, $P = 0.268$, $\eta^2 = 0.058$). Dynamic MVC torque increased 61% for the MG (pre-test 9.0 ± 3.0 Nm, post-test 14.4 ± 2.5 Nm) and 34% for the NMG (pre-test 9.5 ± 3.7 Nm, post-test 12.7 ± 4.4 Nm). Post-hoc analysis revealed that dynamic post-test MVC torque was 13% higher in the MG than the NMG ($P < 0.05$, $d = 0.50$), suggesting that viewing the exercising hand in the mirror increased the training-specific torque in the untrained wrist. Likewise, there was a time main effect for dynamic ($F_{1,21} = 47.4$, $P < 0.001$, $\eta^2 = 0.693$) and isometric MVC torque ($F_{1,21} = 52.5$, $P < 0.001$, $\eta^2 = 0.714$), respectively increasing 48% and 42% across groups. The $M_{max}$-normalized EMG activity recorded during these MVC torque test showed no interaction under dynamic and static conditions (all $P \geq 0.820$, $\eta^2 \leq 0.003$). There was a time main effect for the EMG activity measured during dynamic ($F_{1,21} = 10.3$, $P = 0.004$, $\eta^2 = 0.330$) and isometric MVC torque ($F_{1,21} = 10.9$, $P = 0.003$, $\eta^2 = 0.342$), respectively increasing 36% across groups (pre-test 4.0 ± 2.0% $M_{max}$, post-test 5.5 ± 1.8% $M_{max}$) and 38% across groups (pre-test 3.6 ± 2.1% $M_{max}$, post-test 4.9 ± 1.4% $M_{max}$). Dynamic wrist flexion MVC was not different before and after assessments prior to, or following the training intervention ($P \geq 0.124$), indicating that the testing protocol did not induce fatigue.

4.3.3 rMT and $M_{max}$

The rMT and $M_{max}$ data were not different between groups at baseline and showed no interaction or time effect (all $P \geq 0.081$). The rMT of the left-trained M1 was on average 53 ± 10% of maximal stimulator output and the rMT of the right-untrained M1 was on average 59 ± 9% of maximal stimulator output. The $M_{max}$ was on average 5.64 ± 1.96 mV for the right-trained FCR and 5.02 ± 1.46 mV for the left-untrained FCR.

4.3.4 Pre-stimulus EMG

For corticospinal excitability, SICI and IHI, pre-stimulus EMG activity upon which the MEPs were evoked, was not different between groups at baseline and showed no interaction (all $P > 0.05$). A time main effect in pre-stimulus EMG activity of the left FCR was observed for corticospinal excitability and SICI in the mirror and no-mirror setup when right wrist flexion contractions were performed at 60% post-test MVC ($P < 0.001$). Although pre-stimulus EMG recorded from the left FCR was higher at the post-test than the pre-test ($\sim 0.15$ vs. $\sim 0.05%$ $M_{max}$), it is unlikely that
these small differences in pre-stimulus EMG have affected corticospinal excitability or SICI. For the cSP, pre-stimulus EMG recorded from the isometrically contracting FCR showed no between group differences at baseline and no interaction (all $P \geq 0.264$). A time main effect was caused by the 35% higher pre-stimulus EMG activity observed during contractions at 60% post-test MVC compared with 60% pre-test MVC (2.8 vs. 2.1% $M_{max}$; $P \leq 0.021$), but the difference in EMG activity did not affect cSP duration or MEP amplitude.

### 4.3.5 Target torque
Not all produced torques during the TMS measurements were equal to the target torque of 60% MVC. The mean maximal torque offset of the contractions that were different from the target torque was 0.64 Nm, which was less than 7% of the target torque. It is therefore unlikely that such a small torque offset would have had an effect on TMS outcomes.

### 4.3.6 Corticospinal excitability left-trained M1
Corticospinal excitability of the left-trained M1, recorded from the right FCR in the no-mirror setup at rest, was not different between groups at baseline and showed no group–time interaction or time main effect (all $P \geq 0.262$).

### 4.3.7 Corticospinal excitability right-untrained M1
Table 4.2 shows the corticospinal excitability of the right-untrained M1, recorded from the resting left FCR in the no-mirror and mirror setup at rest and during dynamic right wrist flexion contractions. Corticospinal excitability of the right-untrained M1 was not different between groups at baseline in all setups ($t_{(21)} = \text{range} -0.8 - 0.1$, $P \geq 0.446$). No interaction was observed in any of the setups ($P \geq 0.167$) and there was only a time main effect when corticospinal excitability of the right-untrained M1 was measured in the no-mirror ($F_{1,21} = 4.4$, $P = 0.049$, $\eta^2_p = 0.172$) and mirror setup ($F_{1,21} = 9.5$, $P = 0.006$, $\eta^2_p = 0.312$) during right wrist flexion contractions performed at 60% post-test MVC; right M1 corticospinal excitability increased following unilateral strength training, 49% across groups when measured in the no-mirror setup and 55% across groups when measured in the mirror setup.

### 4.3.8 SICI left-trained M1
SICI of the left-trained M1, recorded from the right-trained FCR in the no-mirror setup at rest, was not different between groups at baseline and showed no interaction or time main effect (all $P \geq 0.262$).
### Table 4.2 | Descriptive data for corticospinal excitability and SICI of the right-untrained M1 (mean ± SD)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group</th>
<th>Corticospinal excitability (% $M_{max}$)</th>
<th>SICI (% test alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-test</td>
<td>Post-test</td>
</tr>
<tr>
<td>No-mirror setup, rest</td>
<td>Mirror</td>
<td>3.7 ± 3.7</td>
<td>3.7 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>No-mirror</td>
<td>4.1 ± 2.6</td>
<td>5.3 ± 4.6</td>
</tr>
<tr>
<td>Mirror setup, rest</td>
<td>Mirror</td>
<td>3.9 ± 2.7</td>
<td>3.7 ± 2.6</td>
</tr>
<tr>
<td></td>
<td>No-mirror</td>
<td>4.5 ± 2.7</td>
<td>5.3 ± 4.6</td>
</tr>
<tr>
<td>No-mirror setup, 60% pre-test MVC</td>
<td>Mirror</td>
<td>8.1 ± 3.2</td>
<td>8.5 ± 6.1</td>
</tr>
<tr>
<td>right-trained wrist</td>
<td>No-mirror</td>
<td>8.6 ± 5.8</td>
<td>12.1 ± 7.3</td>
</tr>
<tr>
<td>Mirror setup, 60% pre-test MVC</td>
<td>Mirror</td>
<td>7.7 ± 5.0</td>
<td>8.4 ± 5.8</td>
</tr>
<tr>
<td>right-trained wrist</td>
<td>No-mirror</td>
<td>8.0 ± 4.6</td>
<td>10.4 ± 6.2</td>
</tr>
<tr>
<td>No-mirror setup, 60% post-test MVC</td>
<td>Mirror</td>
<td>8.1 ± 3.2</td>
<td>11.9 ± 7.9*</td>
</tr>
<tr>
<td>right-trained wrist*</td>
<td>No-mirror</td>
<td>8.6 ± 5.8</td>
<td>12.9 ± 6.5*</td>
</tr>
<tr>
<td>Mirror setup, 60% post-test MVC</td>
<td>Mirror</td>
<td>7.7 ± 5.0</td>
<td>9.7 ± 5.8*</td>
</tr>
<tr>
<td>right-trained wrist*</td>
<td>No-mirror</td>
<td>8.0 ± 4.6</td>
<td>14.5 ± 6.9*</td>
</tr>
</tbody>
</table>

$M_{max}$ maximal M-wave amplitude; MVC, maximal voluntary contraction

* at the pre-test contractions are performed at 60% pre-test MVC and at the post-test contractions are performed at 60% post-test MVC

*, Significant time main effect (P < 0.05)
4.3.9 SICI right-untrained M1
Table 4.2 shows SICI of the right-untrained M1 recorded from the left FCR in the no-mirror and mirror setup at rest and during dynamic right wrist flexion contractions. SICI of the right M1 was not different between groups at baseline in all setups (t_{(21)} = range -0.1 – 0.7, P ≥ 0.483). No group–time interaction was observed in any of the setups (P ≥ 0.078) and only a time main effect was observed when SICI of the right-untrained M1 was measured in the no-mirror (F_{1,21} = 10.6, P < 0.004, η²_p = 0.335) and mirror setup (F_{1,21} = 10.0, P = 0.005, η²_p = 0.322) during right wrist flexion contractions performed at 60% post-test MVC. The time main effect showed that SICI of the right M1 was diminished following unilateral strength training, 45% across groups when measured in the no-mirror setup and 28% across groups when measured in the mirror setup.

4.3.10 cSP right-trained FCR
Figure 4.3A and 4.3B show the cSP duration recorded from the isometrically contracting right-trained FCR after stimulation of the left-trained M1. The cSP duration was not different between groups at baseline (t_{(21)} = -0.5, P = 0.650) and no group–time interaction or time main effect was observed for contractions performed at 60% pre-test MVC and 60% post-test MVC (all P ≥ 0.508).

4.3.11 cSP left-untrained FCR
Figure 4.3C illustrates a representative cSP trace for a single participant illustrating the cSP duration recorded from the isometrically contracting left FCR following stimulation of the right-untrained M1. Figure 4.3D and 4.3E show the cSP duration group data recorded from the left-untrained FCR. The cSP did not differ between groups at baseline (t_{(21)} = 0.9, P = 0.355) and a group–time interaction was observed for contractions performed at 60% pre-test MVC (F_{1,21} = 8.5, P = 0.008, η²_p = 0.289) and 60% post-test MVC (F_{1,21} = 5.4, P = 0.030, η²_p = 0.206). Follow up analysis revealed that the post-test cSP duration differed for the MG compared to the NMG when measured upon left wrist flexion contractions at 60% pre-test MVC (P < 0.05, d = -0.83) and 60% post-test MVC (P < 0.05, d = -0.56). Thereby, the cSP duration measured upon contractions at 60% pre-test MVC became 16% shorter for the MG and 12% longer for the NMG following unilateral strength training (P < 0.05). When the cSP was measured upon left wrist flexion contractions at 60% post-test MVC, then the cSP duration decreased 15% for the MG (P < 0.05) but remained unchanged for the NMG (P > 0.10). There was no time main effect (P ≥ 0.423)
Figure 4.3 | Group data of the cSP duration measured during isometric contractions of the right-trained wrist at 60% pre-test MVC (A) and at 60% post-test MVC (B). Panel C shows representative traces of the cSP of a single participant recorded from the isometrically contracting left-untrained FCR. Each trace comprises one trial. Note that the participant in the mirror group exhibits a shortening while the participant in the no-mirror group reveals a lengthening of the cSP, results also born out by the group data in panel D (contractions performed at 60% pre-test MVC) and panel E (contractions performed at 60% post-test MVC). †, group–time interaction (P < 0.05).
4.3.12 MEPs recorded from the contracting FCR
MEPs recorded from the isometrically contracting right-trained and left-untrained FCR were not different for both groups at baseline and no group–time interaction or time main effect was observed for contractions performed at 60% pre-test MVC and 60% post-test MVC (all P ≥ 0.161). MEPs evoked upon the contracting right FCR had an average amplitude of 40.6 ± 17.0% $M_{max}$ and MEPs evoked upon the contracting left FCR had an average amplitude of 40.5 ± 14.3% $M_{max}$.

![Figure 4.4](image)

**Figure 4.4** | IHI from left-trained to right-untrained M1 measured at rest and recorded from the left-untrained FCR. A: representative MEP waveforms of a single participant. **Dotted lines** are single trials and the **thick solid line** represents the average of the ten single trials. The conditioned MEP size is ~75% of test alone. B: group data of IHI measured in the no-mirror setup at rest. C: group data of IHI measured in the mirror setup at rest. A higher value means less IHI. The **horizontal dashed line** at 100% represents the control value, i.e., absence of inhibition and facilitation. *, time main effect (P < 0.05); †, group–time interaction (P < 0.05).
4.3.13 IHI
Figure 4.4 shows IHI from left-trained to right-untrained M1, recorded from the left-untrained FCR, measured in the no-mirror and mirror setup at rest. IHI was not different between groups at baseline. IHI measured in the no-mirror setup showed no group–time interaction ($F_{1,14} = 1.5, P = 0.235$), but there was a time main effect ($F_{1,14} = 11.1, P = 0.007, \eta^2_p = 0.418$); training increased IHI by 26% across groups. An interaction ($F_{1,14} = 4.7, P = 0.048, \eta^2_p = 0.251$), but no time main effect ($F_{1,14} = 0.2, P = 0.634$) was observed for IHI measured in the mirror setup; IHI of the MG increased by 11%, while IHI of the NMG decreased by 15% following the strength intervention.

The size of the test pulse, which was used as a control value for determining IHI, was not different for both groups at baseline and no interaction or time main effect was observed (all $P \geq 0.227$). The size of the test pulse was $\sim 0.3$ mV in the MG and NMG and was stable across test sessions. Also, the one-sample t-tests showed that IHI was significantly different from 100% during all IHI measurements (all $P < 0.01$).

4.3.14 EMG activity during training
EMG activity of the contracting right FCR and resting left FCR was measured during the 5th, 10th and 15th training session in two participants from each training group. Overall, mean EMG activity did not increase over time for the right FCR (session 5: $4.5 \pm 1.5\% M_{max}$, session 10: $5.3 \pm 2.2\% M_{max}$, session 15: $6.9 \pm 6.5\% M_{max}$, $\chi^2 (2) = 0.5, P = 0.779$) and left FCR (session 5: $0.3 \pm 0.1\% M_{max}$, session 10: $0.5 \pm 0.3\% M_{max}$, session 15: $0.6 \pm 0.3\% M_{max}$, $\chi^2(2) = 4.5, P = 0.105$). Because of the small sample size, we were not able to calculate between group comparisons.

4.4 Discussion
In line with our expectations, three weeks of unilateral strength training using a mirror produced greater cross-education from the trained to untrained wrist flexor muscles (61%) compared to training without a mirror (34%) where no visual feedback was provided. This increased cross-education was accompanied by an increase in IHI from the trained to untrained M1 measured at rest and by a decrease in cSP duration of the left-untrained FCR, measured during contraction. Mirror-viewing did not further increase the strength gains in the trained hand. These results provide the first evidence that unilateral strength training with a mirror can augment the magnitude of cross-education.
4.4.1 Behavioural changes
Viewing the mirror did not affect the magnitude of strength gains in the trained wrist but caused greater cross-education. The 72% strength gain observed in the trained wrist after 640 wrist flexion contractions over 15 training sessions is higher than the 45% increase previously reported using a wrist task [2]. However, the aforementioned studies used isometric wrist contractions whereas subjects in the present study performed dynamic contractions, suggesting that motor practice with dynamic contractions could provide a stimulus for greater strength gains. A lack of mirror effect in the trained hand is compatible with the idea that looking at the illusionary motion of the untrained hand does not provide an additional training stimulus relative to the main training stimulus provided by muscle contraction.

According to our prediction, unilateral training with the mirror produced greater cross-education than training without the mirror, which equated to 27% or 2.2 Nm more transfer. This preferential increase in strength occurred only when the effect was tested by dynamic but not isometric contractions. Thus, in line with our expectations, the illusionary movement of the stationary hand was likely a critical element in the mirror-magnifying effect of cross-education. The magnitude of cross-education in the present study was 61% with the mirror and 34% without the mirror, which exceeds the values of -3 to 22% reported previously [10]; importantly >50% of the studies included in these meta-analyses used isometric instead of dynamic training. The greater cross-education observed in the current compared with previous studies was not inconceivably caused by the dynamic muscle contraction, as there also was 47% increase in strength following 12 dynamic wrist flexion-training sessions without the use of a mirror [28]. Most likely the novelty and unusual nature of the wrist flexion task, could therefore provide a greater scope for performance improvement; an observation that was also suggested in a previous cross-education study that used an ulnar deviation training task [2]. The strength improvement in the untrained wrist flexors was accompanied by 36% increase in surface EMG activity (during the MVC), suggesting that an increase in neural drive contributed to the cross-education effect. However, the increase in surface EMG was similar in the mirror and no-mirror training group, despite the mirror training group showing greater cross-education; therefore other neural adaptations not captured by surface EMG might also contribute to the greater cross-education effect produced by the mirror.

4.4.2 Corticospinal and motor cortical excitability: trained M1
Changes in corticospinal excitability are thought to reflect neuronal
adaptations in long-term-potentiation-like mechanisms [29]. A human study suggested that skill training comprising low-force, but highly variable movements (as opposed to strength training, using high force, monotonic movements), would preferentially cause plasticity as measured by increases in corticospinal excitability [30]. While corticospinal excitability remained unchanged after strength training of the finger [31], wrist (present study), and leg [9], strength training of a leg muscle, in the context of cross-education, increased the peak height of the recruitment curve by 53% [6]. Notwithstanding, a lack of changes in corticospinal excitability in the trained M1 seems to imply the involvement of the untrained hemisphere in cross-education. Our results add to the evidence that motor practice with high-force, monotonic movements does not change corticospinal excitability and causes little or no plastic changes in the corticospinal path, however, these findings require further verification [32].

To quantify the potential role of intracortical circuits, we measured SICI in the trained M1. GABA_\text{A} receptors are thought to mediate SICI [23]. Increases in GABA_\text{A} receptor function tend to diminish motor learning by blocking the induction of long-term-potentiation [29]. Previous strength studies reported no change [33] or a decrease [34] in SICI. Our data add to the prevailing view that GABA_\text{A} mediated long-term-potentiation-like mechanisms probably play little or no role in strength gains produced by strength training. The absence of changes in SICI points to the involvement of the untrained hemisphere in evoking cross-education.

The cSP is the interruption of ongoing EMG activity by TMS discharged over the contralateral M1. While ~50 ms of the initial part of the cSP is due to spinal inhibition [35], the latter part of the cSP, as suggested by direct cortical [36], transcranial electrical and magnetic stimulation [37], is of motor cortical origin mediated by GABA_\text{B} receptors [38]. Our cSP of 135 ms at baseline is well within the 90 to 190 ms range reported in healthy humans arm muscles [39]. Previously, finger and leg strength training studies reported 3 to 26% reductions in cSP duration at stimulation intensities of 5 to 20% above active motor threshold in the presence of 21 to 34% strength gains [9,31], but we observed no changes in cSP. To increase the specificity of the recording conditions and capture changes in inhibition by referencing it to the training stimulus, we measured the cSP at a background contraction of 60% MVC, an intensity much higher than previously. However, this difference in contraction intensity is unlikely to account for a lack of change in our cSP because contractions above 20% MVC tend not to further increase cSP duration [39].
4.4.3 Corticospinal and motor cortical excitability: untrained M1

In line with the cross-activation model [5], studies reported increases in corticospinal excitability measured in the untrained M1 at rest [7] and during weak muscle contractions (10% MVC) of the untrained upper [8] and untrained lower [6] extremities. There is a tendency for smaller changes (6%) when measured at rest compared with contractions of the trained hand (10 and 64% at 20 and 80% MVC, respectively) [7], assigning specificity and functionality of these neuronal changes to cross-education. Our data concur with previous data as we observed no changes in corticospinal excitability at rest, but found 49 and 55% increases in the mirror and no-mirror condition during dynamic contractions of the trained wrist at 60% post-test MVC. Our data also support the notion that strength training of one hand increases the neural drive from the untrained M1 to the untrained wrist muscles and this increase in excitability contributes to cross-education. These results however, must be interpreted with caution because corticospinal excitability did not increase when subjects performed the contractions of the trained wrist at 60% pre-test MVC. Thus, the mechanism for the increased neural drive to the untrained wrist is due to the test being conducted at a higher relative contraction intensity at the post-test (60% post-test MVC vs. 60% pre-test MVC) [4]. Importantly, our data show that the increase in excitability occurred independent of mirror use. That is, mirror-augmented cross-education of strength is caused by mechanisms other than corticospinal excitability.

The size of SICI becomes smaller in the ipsilateral M1 when healthy subjects perform a forceful voluntary contraction with vs. without a mirror [15]. However, training did not further decrease SICI. In the context of the cross-education of strength, SICI in the untrained M1 measured at rest remained unchanged following eight weeks of index finger strength training [7]. Past and present data collectively suggest that SICI in relation to unilateral strength training is not sensitive to changes when measured at rest. However, when measured during 10% MVC of the untrained rectus femoris, SICI decreased by 21% in the untrained M1 following three weeks of unilateral leg strength training [6] and decreased further (32%) when measured at a 40% MVC contraction of the untrained wrist flexors [28]. We also observed a reduction in SICI (45% in the no-mirror setup, 28% in the mirror setup) in the right-untrained ipsilateral M1 when measured during a 60% dynamic MVC of the trained-right hand. Together, GABA<sub>A</sub> mediated intracortical inhibitory circuits become especially sensitive to the effects of unilateral strength training when tested during a muscle contraction but this effect, similar to corticospinal excitability, is independent of training with or without a mirror.
Modulation of cSP arguably provides the strongest evidence to support the mirror training effects in the present study. The cSP duration in the left-untrained FCR, measured at 60% pre-test MVC, decreased by 16% for the MG and increased by 12% for the NMG following the intervention; a pattern replicated for the MG when measured at 60% post-test MVC (15% decrease for the MG vs. no-change for the NMG, Fig. 4.3D and 4.3E). A reduction in cSP duration has been previously linked to cross-education without a mirror [9] and a recent study showed that the 19% extra cross-education produced by eccentric vs. concentric strength training was accompanied by a 27% reduction in cSP duration [28]. These results and our data strengthen the potential importance of this inhibitory path in cross-education. We employed the use of cSP as a surrogate measure of GABA_B mediated inhibition, but acknowledge that the observed reduction in cSP duration could be of either cortical, spinal origin, or both. It is less likely that spinal mechanisms play a role in evoking cross-education [40], therefore we speculate that the reduction in cSP duration is likely due to a mirror-training induced reduction in GABA_B mediated intracortical inhibition.

4.4.4 Interhemispheric inhibition from trained to untrained M1

The IHI measured from the trained to the untrained M1 provides information on interhemispheric glutaminergic connectivity that arises from the trained M1 and projects on to local GABAergic inhibitory interneurons located in the untrained M1 [25]. Eight weeks of isometric index finger strength training without a mirror resulted in 28% cross-education accompanied by a reduction in IHI from the trained to untrained M1 [7]. In contrast, IHI increased in both the MG and NMG in the present study when measured in the no-mirror setup at rest and increased for the MG; however was decreased for the NMG when recorded in the mirror setup at rest. These IHI data tentatively suggest (N = 8 per group) that interhemispheric plasticity contributes to cross-education and that the nature of the interhemispheric communication is altered in a training-specific manner. The functional interpretation of these data is complex. First, the IHI data were obtained at rest and the small sample size restricted us from calculating correlations between the changes in IHI at rest and the magnitude of cross-education. Second, cross-sectional studies showed that IHI, SICI, and their interaction contribute to the control of corticospinal output to the resting hand during the execution of forceful unilateral wrist flexion contractions [4]. However, we found no such effect, as both corticospinal excitability and SICI, but not IHI measured at rest, were unchanged following unilateral strength training. While we did not measure directly the effects of IHI on CSE and SICI before and after the intervention, changes in IHI without changes in CSE
Mirror training augments cross-education and SICI might suggest that IHI effects were isolated. Thus, any of its effects did not become manifested in cross-education through CSE and SICI, instead through the modifications of interhemispheric connections. Such changes may have some functional effects especially for the MG, as there is evidence that anterior callosal regions, associated with IHI, contribute to the integration of perception and action within a subcortico-cortical network promoting a unified experience of how we perceive the visual world and prepare our actions [41]. It is suggested that stimulus driven activity in one hemisphere suppresses activity in the opposite hemisphere by increasing the amount of interhemispheric inhibition, which is compatible with the increased IHI in our MG [42]. Therefore, three weeks of unilateral strength training while mirror-viewing the moving right hand induces a shift in attention to the untrained M1 associated with the mirror image by increasing inhibition from the trained to the untrained M1. Future research should elucidate the role of IHI in unilateral strength training using a mirror, specifically in stroke patients where modulation of IHI seems to be an important factor for improving motor function of the paretic side.

4.4.5 Associated EMG activity
Many participants showed associated EMG activity in the homologous resting muscles during unilateral contractions, confirming previous work [21,43]. This activity is thought to represent the increased activity of task-specific brain areas during and following motor practice and hence contributes to the improved motor control and strength of the untrained homologous muscles [11]. It is possible that the use of the mirror increased associated activity, which in turn augmented cross-education. We expected that the associated activity during training would be higher for the MG than the NMG but the data from a few subjects suggested no such effect. Because of the magnitude of associated activity in strong muscle contractions, future studies will clarify this activity in cross-education. Such work is needed because weak muscle contractions, corresponding to forces predicted by associated activity, can increase maximal voluntary muscle strength [44].

4.4.6 Limitations
During unilateral motor practice subjects tend to direct their attention to the moving limb. A limitation of the present study is that without an active-vision group we cannot exclude the possibility that viewing the moving limb per se could have also augmented cross-education. However, mirror training augmented cross-education of fine motor skills more than direct viewing of the practicing limb [45]. Thus, it is the mirror illusion instead of the view of the hand moving that was the likely factor
augmenting cross-education in the present study.

The observed changes in IHI and cSP duration following mirror training suggest that probably $\text{GABA}_B$ mediated circuits are involved in the augmented cross-education of strength. Two other circuits that are believed to be dependent on $\text{GABA}_B$ mediated neurotransmission are long-interval intracortical inhibition (LICI) and long-latency IHI (LIHI), both infrequently if at all measured in relation to cross-education. Thus, future studies should also focus on $\text{GABA}_B$ mediated LICI and LIHI to disentangle the cortical mechanisms that are involved in cross-education.

In addition to cortical mechanisms, involvement of subcortical and spinal circuits should not be excluded [3]. Increased spinal reflex excitability, expressed as an increase in H-reflex amplitude, contributed to the strength improvement of the trained limb but not the strength improvement of the contralateral untrained limb [40]. Although an increased H-reflex excitability might contribute to the cross-education of strength, either by increasing motoneuronal excitability or reducing presynaptic inhibition, unequivocal evidence for the involvement of spinal mechanisms is still needed.

### 4.4.7 Conclusions

The present study provides initial evidence that the use of a mirror can augment strength in a cross-education paradigm. The neurophysiological basis for the augmented cross-education seems to be related to altered inhibition as measured by cSP and IHI. Additional candidate areas other than M1 include somatosensory areas and elements of the MNS, which we, by TMS, could not measure. The present data warrant further studies that involve connectivity analyses using TMS, EEG, and imaging to help determine the brain areas and mechanism that underpin how viewing one’s own hand in a mirror can facilitate cross-education of strength. In summary, this study provides important information that viewing the exercising hand in a mirror can augment the cross-education effect and potentially accelerate functional recovery from unilateral impairment. Regardless of the underlying mechanisms, there is now accumulating evidence that patients with unilateral orthopaedic [46] and neurological [47] impairments can benefit from the cross-education of strength, a phenomenon that mirror-viewing could further augment.

Acknowledgements and conflicts of interest

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The authors report that no conflicts of interest have occurred that are associated with the current study. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

References


