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RESEARCH ARTICLE

Acute Effects of Strength and Skill Training on the Cortical and Spinal Circuits of Contralateral Limb

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ABSTRACT. Unilateral strength and skill training increase strength and performance in the contralateral untrained limb, a phenomenon known as cross-education. Recent evidence suggests that similar neural mechanisms might be responsible for the increase in strength and skill observed in the untrained hand after unimanual training. The aims of this study were to: investigate whether a single session of unimanual strength and skill (force-tracking) training increased strength and skill in the opposite hand; measure ipsilateral (untrained) brain (*via* transcranial magnetic stimulation, TMS) and spinal (*via* the monosynaptic reflex) changes in excitability occurring after training; measure ipsilateral (untrained) pathway-specific changes in neural excitability (*via* TMS-conditioning of the monosynaptic reflex) occurring after training. Participants ($N = 13$) completed a session of unimanual strength (ballistic isometric wrist flexions) and skill (force-tracking wrist flexions) training on two separate days. Strength increased after training in the untrained hand ($p = 0.025$) but not in the trained hand ($p = 0.611$). Force-tracking performance increased in both the trained ($p = 0.007$) and untrained ($p = 0.010$) hand. Corticospinal excitability increased after force-tracking and strength training ($p = 0.027$), while spinal excitability was not affected ($p = 0.214$). TMS-conditioned monosynaptic reflex increased after force-tracking ($p = 0.001$) but not strength training ($p = 0.689$), suggesting a possible role of polysynaptic pathways in the increase of cortical excitability observed after training. The results suggest that cross-education of strength and skill at the acute stage is supported by increased excitability of the untrained motor cortex.

New & Noteworthy: A single session of isometric wrist flexion strength and skill straining increased strength and skill in the untrained limb. The excitability of the untrained motor cortex increased after strength and skill training. TMS-conditioned H-reflexes increased after skill but not strength training in the untrained hand, indicating that polysynaptic pathways in the increase of cortical excitability observed after skill training.

Keywords: Cross-education, Transcranial magnetic stimulation, H-reflex, strength training, skill training

Introduction

Unilateral strength training leads to strength increases in the contralateral untrained limb, a phenomenon known as cross-education Scripture et al. (1894). Cross-education is muscle (Davis, 1901) and task (Hellebrandt, 1951) specific, and has been shown to occur across a range of movements such as elbow flexion (Kidgell et al., 2011) and wrist flexion and extension (Kidgell et al., 2015; Lee et al., 2009). Changes in strength and muscle structures are accompanied by neural adaptations in both the trained and untrained hemisphere (Lee & Carroll, 2007). Changes in corticospinal excitability occurring after training can be assessed by stimulating the primary motor cortex *via* transcranial magnetic stimulation (TMS) and measuring the amplitude of the motor-evoked potential (MEP) induced in the muscle of interest (Hallett, 2007). Hortobágyi et al. (2011) measured changes in strength in the untrained hand and excitability of the untrained motor cortex after participants performed submaximal isometric contractions of the right first dorsal interosseus (FDI) over 20 sessions. Increases in maximal voluntary contractions (MVCs) and cortical excitability were observed in the training group but not in a control group not training. The finding that ipsilateral motor cortex excitability increases after unilateral training has since been replicated across multiple muscles (Goodwill et al., 2012; Kidgell et al., 2011), contraction types (Kidgell et al., 2011; Mason et al., 2018) and training conditions (Leung et al., 2018; Zult et al., 2016).

While muscle structural changes are often observed after multiple training sessions, neurophysiological changes occurring in the untrained hemisphere can already be observed at the acute post-training stage (Carroll et al., 2008). Corticospinal excitability of the untrained motor cortex increased after participants completed 300 ballistic (e.g. as fast as possible) right index abductions but not in a control group not performing the movements (Carroll et al., 2008). Similar effects are observed when corticospinal excitability is assessed at multiple time points after the end of training (from 4 to 8 min) and by employing TMS at various stimulation (20% and 70% MEP_{max} intensities) (Poh et al., 2013). It has been suggested that changes in corticospinal excitability observed in the ipsilateral hemisphere after a single session of ballistic training might reflect an early retention process which constitute part of the long-term adaptations observed over multiple sessions (Lee et al., 2010). Lee and colleagues demonstrated that administering low-frequency TMS, which inhibits cortical excitability (Chen

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et al., 1997), to the right untrained M1 immediately after ballistic training (Lee et al., 2010). reduced both corticospinal excitability and the performance gains observed in the untrained hand. Nevertheless, lack of changes in ipsilateral corticospinal excitability after ballistic training have also been reported in the literature (Ruddy et al., 2016). Participants performed 300 ballistic wrist flexion movements while looking at the inactive limb, mirrored visual feedback of the trained limb or in the absence of visual feedback. While ballistic performance increased in the untrained limb after training, no corresponding changes in the excitability of the untrained motor cortex were observed (Ruddy et al., 2016). A recent systematic review suggested that contradictory findings might depend on methodological differences such as the type/level of contraction and the quality of the feedback of performance employed (Colomer-Poveda et al., 2019).

Leung et al. (2015) systematically manipulated conditions of practice by assigning participants to a session of either visuomotor tracking, metronome-paced strength training, self-paced strength training or to a control group not performing movements. Corticospinal excitability increased after visuomotor tracking and metronome-paced strength training but not after the other two trainings in both the trained and untrained arms. The authors speculated that synchronising movements to an external (auditory or visual) stimulus might be critical to modulate neural excitability. This speculation is supported by findings of increased cortical excitability after skill (Mason et al., 2019) and strength (Christiansen et al., 2018; Mason et al., 2019) training timed to external visual stimuli. The results suggest that the increase in ipsilateral cortical excitability might be important in cross-transfer effects and that some of the neurophysiological mechanisms which are responsible for the cross-education phenomenon after multiple training sessions are already occurring at the acute level after a single training session (Leung et al., 2015). However, the authors did not measure behavioural outcomes of the training protocols on the non-trained arm. In the context of ballistic contractions, while some authors suggested that transfer of ballistic and skill training might be mediated by shared mechanisms (Lee et al., 2010; Ruddy & Carson, 2013), to our knowledge the acute effects of the two trained modalities on the untrained limb have never been compared.

The putative role of the primary motor cortex in the cross-education of strength and skill is largely based on evidence from studies in which MEPs evoked upon cortical stimulation were the primary neurophysiological outcomes (Carson et al., 2016). Importantly, spinal motoneuron excitability is modulated not only by descending (e.g. cortical) inputs but also by a network of intraspinal connections such as the ones mediating reciprocal and presynaptic inhibition (Niemann et al., 2016). It is customary to assess spinal motoneuron excitability by measuring the amplitude of the monosynaptic reflex (H-reflex) evoked upon peripheral nerve stimulation (Palmieri et al., 2004). However, lack of changes in the H-reflex pathway do not necessarily rule out a spinal contribution to the change in the observed MEP, since indirect corticospinal influences to motoneuron excitability cannot be detected with this technique (Palmieri et al., 2004). By conditioning the H-reflex with a cortical pulse delivered at multiple time intervals, it is possible to dissect the relative contribution of early and late corticospinal volleys on motoneuron excitability (Niemann et al., 2016). A possible role of spinal circuits in mediating cross-education is supported by evidence that strong unimanual movements exert an influence over the spinal circuits of the contralateral hand, as indicated by the decrease in the amplitude of the H-reflex evoked in the resting contralateral FCR during wrist flexion (Hortobágyi et al., 2003). The possibility that spinal pathways support the behavioural improvements observed in the untrained limb after a session of strength or skill training remains unknown.

Given the above, the aims of this study are to: (1) measure increases in strength (MVC) and (2) accuracy of force tracking in the trained and untrained limb after a single session of isometric wrist flexion strength/skill training; (3) measure changes in spinal (H-reflex elicited upon median nerve stimulation) and corticospinal (motor-evoked potentials induced by TMS) excitability observed between baseline and after strength and skill training in the untrained hand; (4) measure changes in the excitability of specific ipsilateral neural circuits after strength and skill training by conditioning the H-reflex with cortical stimulation.

Methods

Participants

Thirteen participants (M (SD) = 22.8 ± 4.0; females = 6) volunteered for the study. Participants were included in the study if right-handed, as assessed by the Edinburgh Handedness Questionnaire (Oldfield, 1971). The sample size was chosen according to an a priori power analysis based on effect size estimates (partial eta squared) derived from data given in Leung et al. (2015) (Group*Time interaction, $\eta p^2 = 0.18$). The sample size calculation was determined using the following parameters: $\eta p^2 = 0.18$; number of groups = 2; $\alpha = 0.05$; 1- $\beta = 0.8$; rm.corr = 0.5. The total number of participants required was estimated to be 26 (13 per group/session). All participants completed two sessions separated by at least 7 days to avoid the influence of carry-over effects of stimulating the brain (Nitsche et al., 2008) and scheduled at the same time of the day to control for potential influences of circadian rhythms (Sale et al., 2007). The order of allocation to conditions was counterbalanced across participants. All participants gave written informed consent to experimental procedures approved by the Faculty of Biological Sciences

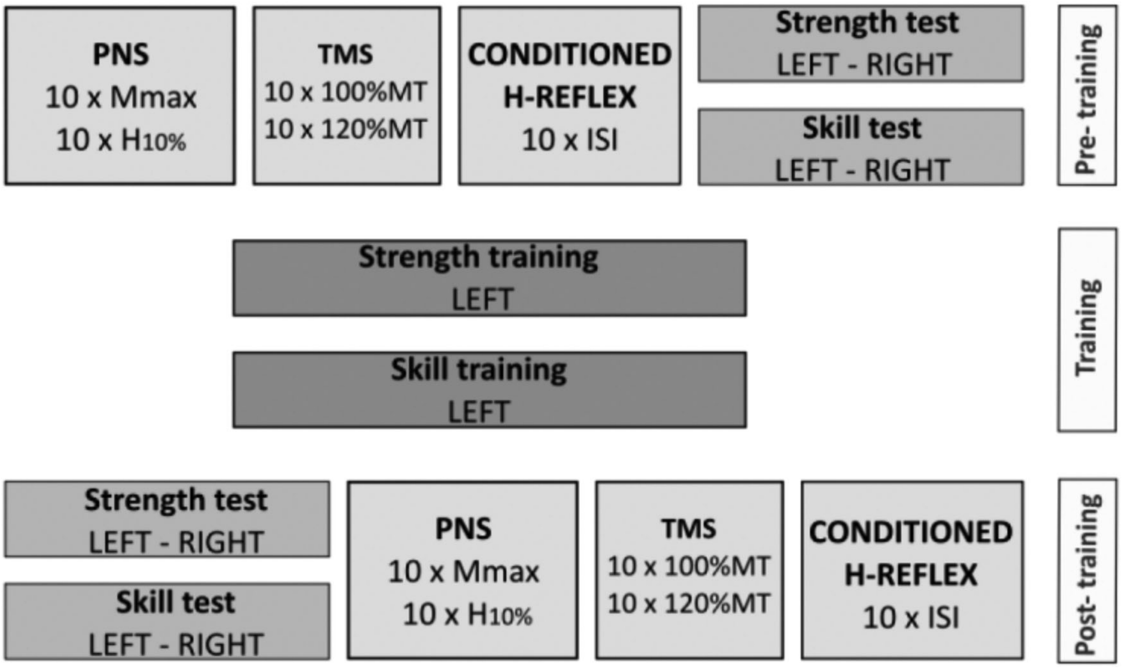

FIGURE 1. Time course of the two experimental sessions. The order of delivery of PNS and TMS was randomised across sessions and participants.

Ethical Review Committee (BIOSCI 19-008) at the University of Leeds, whose principles are based on the Declaration of Helsinki.

Dynamometer Assessment

Participants sat on a dynamometer (Biodex Medical Inc, Shirley, NY, USA) chair, with their right elbow and forearm forming an angle of 140° supported by the dynamometer armrest. Before testing, participants completed 1–2 wrist flexions to ensure that the positions of the handle, chair and armrest were comfortable. During this phase, they also performed wrist flexions at 25%, 50% and 100% of their perceived MVC to ensure participants did not engage additional muscles when performing the tasks. . The refresh rate of the dynamometer screen was 2000 Hz. The study design is depicted in Figure 1.

Strength Session

Three isometric wrist flexion MVCs, each lasting 5 s and with a 1-min interval between them to prevent the onset of fatigue (Gandevia, 2001), were performed with the left and right hand in a randomised order before and after training on the same day (Hortobágyi et al., 2009). Criteria for assessing MVCs included: five familiarisation contractions before testing; standard encouragement from the experimenter; participants were allowed to reject contractions they did not regard as maximal (Gandevia, 2001). When using the left hand, a computer screen instructed participants on when to start the movement and how long to maintain it through a countdown timer. When using the right hand, the researchers instructed participants on when to start the movement and how long to maintain it.

For the training, participants contracted the left wrist as rapidly and as strongly as possible (ballistic strength contraction, BSC) and maintained the contraction for 2 s before relaxing (Selvanayagam et al., 2011). Each contraction was followed by 3 s of rest. Participants completed five familiarisation contractions before training. The training regime was based on the hypothesis that descending drive is greater for contractions nearing muscle failure to compensate for the reduction in muscle efficiency (Muddle et al., 2018) and that strong contralateral MI activity also activates the ipsilateral MI (Lee & Carroll, 2007). The computer monitor showed real-time feedback of the force produced. Four sets of ten contractions, each set lasting 50 s and followed by 3-min rest, were completed.

Force-Tracking Session

Each participant performed three sustained contractions, each lasting 3 s and with 30 s interval between them, at 25% and 50% of their MVC with either the right or the left hand in a randomised order. Before testing, participants completed five familiarisation contractions. When using the left hand, the target force was displayed as a line to be reproduced as closely as possible by contracting the wrist, and actual performance was displayed through another line. Visual feedback was not provided while testing the untrained (right) hand. This feature ensured that participants did not start learning how to better control force during the baseline testing and that corticospinal excitability in the untrained hemisphere was not affected by the movements produced during testing, because practice without feedback does not impact corticospinal excitability (Muellbacher et al., 2001).

For the training, participants were required to produce a force matching 25% or 50% of their left MVC by contracting the left wrist for three seconds. Participants completed five familiarisation contractions before training. Each contraction was followed by 30 s of rest. In front of them, the computer monitor showed the target force as a red line, and the produced force as a purple line. Four sets of ten contractions, each set lasting 50 s and followed by 3-min rest were performed by each participant for each of the 25% and 50% MVC condition.

Electromyography (EMG) Measures

Surface EMG activity was recorded from the right flexor carpi radialis (FCR) *via* a parallel-bar wireless mini sensor (2.5 × 1.2 cm) (Trigno, Delsys Inc., Natick, MA, USA). The optimal location to record activity from the FCR muscle is reported to be at one third of the distance between the medial epicondyle and the radial styloid (Christie et al., 2005). Raw EMG recordings were pre-amplified (gain = 909), recorded with a 20–450 Hz bandwidth and digitised at 2 kHz using data acquisition software (Spike2, Cambridge electronics Design, Cambridge, UK).

M_{max} and H-Reflex

Peripheral nerve stimulation was delivered at a rate of 0.2 Hz through a constant-current stimulator (DS7A, Digitimer Ltd, Welwyn Garden City, UK). Stimuli consisted of square-wave pulses of 1 ms delivered at the cubital fossa level, medial to the tendon of biceps brachii, in parallel with the course of the nerve (Jaberzadeh et al., 2004). In order to facilitate the H-reflex in FCR, participants were trained to maintain a background activation corresponding to 5% of their MVC *via* EMG feedback in this muscle (Bodofsky, 1999). Ten traces were recorded at the intensity at which the motor wave reached its maximal amplitude (M_{max}) (Figure 1). For recording of the H-reflexes (ten traces), the stimulation intensity was set at an intensity which evoked reflexes of about 10–15% of the M_{max} amplitude ($H_{M10\%}$), on the ascending part of the recruitment curve (Capozio et al., 2021b).

Motor-Evoked Potentials (MEPs)

TMS was delivered at a rate of 0.2 Hz to the left primary motor cortex with a figure-8 coil (Magstim Company, Whitland, Dyfed, UK) oriented at ~45° to the sagittal plane to induce currents perpendicular to the central sulcus (Janssen et al., 2015). The optimal coil position to evoke MEPs in FCR was found by moving the coil over the scalp while delivering stimulation and marking the position at which MEPs could be elicited at the lowest stimulation intensity (Capozio et al., 2021a). Participants maintained a background activation of the FCR muscle corresponding to 5% of their MVC during stimulation. The active motor threshold (aMT) was defined as the minimum stimulation intensity, in percentages of maximal stimulator output (MSO), at which MEPs of peak-to-peak amplitudes higher than 100 μV could be elicited in at least 5 out of 10 trials (Turi et al., 2021) (Figure 1). Ten traces were recorded at aMT and 120% aMT intensities to characterise changes in corticospinal excitability between pre and post-training. The two stimulation intensities were chosen as these elicit different patterns of corticospinal activity: at threshold intensity, a single descending volley (I1 wave) is observed while at 120% later descending volleys (I2 and I3), thought to originate from higher cortical areas or repetitive activation of M1 neurons, are observed (Di Lazzaro et al., 2001). Only a sub-group ($n = 10$) of participants received TMS at 120% aMT intensities since the remaining three participants, all naïve to TMS, could not tolerate the higher intensity and were therefore not tested at 120% aMT.

TMS-Conditioned H-Reflex

PNS and TMS were applied in combination to obtain TMS-conditioned monosynaptic reflexes from the FCR muscle. The intensity of PNS was set to evoke H-reflexes of 10–15% of the respective M_{max} (Capozio et al., 2021b). TMS intensity was given at subthreshold levels of 90% of aMT. TMS was delivered at multiple inter-stimulus intervals (ISIs) based on the intervals at which a conditioning effect has been observed when stimulating the FCR muscle (25, 27) ranging from −5 ms (PNS first) to +5 ms (TMS first) from the delivery of the electrical pulse targeting the median nerve (Niemann et al., 2016). Each ISI was measured 10 to 15 times in a randomised order (Figure 1), and unconditioned H-reflexes and TMS at 90% of aMT were randomly recorded together with the conditioned responses to ensure lack of changes in spinal and cortical excitability during the stimulation (Leukel et al., 2012). The time interval between successive pairs of stimuli was set at 5 s.

Data Analyses

Statistical analyses were performed using SPSS (Version 22.0) software with an a priori significance level of <0.05. For the analysis of strength, the highest muscular force output (MVC, in Nm) produced during the three repetitions was analysed. Paired t-tests were used to compare pre and post-training MVC values in the left and right hand. Whenever the results of the Mauchly's test showed a violation of the sphericity assumption, Greenhouse-Geisser corrected values were reported. For the analysis of skill, the root mean squared error (RMSE) between the target movement and the movement produced was calculated at each contraction level. Since the movements were completed under different conditions (i.e. no concurrent feedback for right hand movements), separate GLM analyses were run for the two hands with Participant included as a random factor and Intensity (25% MVC, 50%MVC) and Time (Pre, Post) included as fixed factor. Data from one participant were removed to meet the assumption of homogeneity of variance (left, $p = 0.221$; right, $p = 0.606$) but removal did not affect the significance of the results.

The mean amplitude of the 10 (for M_{max}, $H_{M10\%}$, aMT and 120% aMT) or 10–15 (TMS-conditioned reflexes) recordings was analysed for each session. Separate GLM analyses were run with Participant included as a random factor and Condition (Skill, Strength) and Time (Pre, Post) included as fixed factors for each of the parameter recorded from the right FCR muscle (aMT, 120% aMT, M_{max}, $H_{M10\%}$). The Levene's test showed no violation of the assumption of homogeneity of variance for any of the parameters (aMT, $p = 0.853$; 120% aMT, $p = 0.500$; M_{max}, $p = 0.754$; $H_{M10\%}$, $p = 0.643$). For the analysis of TMS-conditioned monosynaptic reflexes, the mean amplitude value calculated at each ISI for each participant was first divided by the mean of the individual unconditioned reflex value (Leukel et al., 2012) to account for the differences in the amplitude of the H-reflex at baseline. The first interval at which facilitation could be observed (EF) was estimated as the first interval for which conditioned H-reflex amplitudes significantly increased from the unconditioned amplitude values as shown by uncorrected Student's paired *t*-tests (Niemann et al., 2016). Conditioning test-intervals following EF were aligned to it (e.g. EF + 2) across participants and sessions (Capozio et al., 2021b). The rationale for assessing each interval independently relies on the assumption that the early facilitation (EF) represent the fastest corticospinal volley while later occurring ones (EF + 2, EF + 4, EF + 6) represent increasingly longer polysynaptic volleys into spinal motoneurons (Leukel et al., 2012). Separate GLM analyses were run for the two conditions with Participant included as a random factor and Interval (EF, EF + 2, EF + 4, EF + 6) and Time (Pre, Post) included as fixed factor. Bonferroni-corrected paired *t*-tests were used to follow-up analyses for significant effects. The Levene's test showed no violation of the assumption of homogeneity of variance (strength, $p = 0.906$; skill, $p = 0.816$).

To further characterise the relationship between changes in strength/skill and changes in the neurophysiological measures employed, we first calculated percentage differences from pre to for each participant [(post/pre × 100) − 100] and then ran linear regression analyses between changes in skill/strength and changes in neurophysiological measures which significantly differed from pre to post (Leung et al., 2018).

Results

Strength and Force-Tracking

Group means and standard deviations of the behavioural data collected are reported in Table 1. From the strength data, no violations of the normality assumption could be inferred from the Shapiro-Wilk test. Paired t-tests revealed a significant difference between MVCs collected before and after strength training in the right hand ($t(12) = 2.562$, $p = 0.025$, $d = 0.71$) but not in the left hand ($t(12) = 0.522$, $p = 0.611$, $d = 0.71$). From the skill data, results from the GLM analysis revealed that the interaction between Intensity and Time was not significant ($F_{1,33} = 0.059$, $p = 0.810$, $\eta^2 = 0.001$) and the main effects of Intensity ($F_{1,33} = 9.848$, $p = 0.004$, $\eta^2 = 0.23$) and Time ($F_{1,33} = 8.184$, $p = 0.007$, $\eta^2 = 0.20$) were significant for the left hand. Similarly, the interaction between Intensity and Time was not significant ($F_{1,33} = 0.447$, $p = 0.508$, $\eta^2 = 0.01$) and the main effect of Time ($F_{1,33} = 7.408$, $p = 0.010$, $\eta^2 = 0.18$) was significant for the right hand . The main effect of Intensity ($F_{1,33} = 1.296$, $p = 0.263$, $\eta^2 = 0.04$) was not significant. No violation of normality of the distribution of residuals could be inferred from the results (left, $p = 0.606$; right, $p = 0.606$).

M_{max} and H-Reflex

Group means and standard deviations of the neurophysiological data collected are reported in Table 2. For M_{max}, the interaction between Condition and Time was not significant ($F_{1,33} = 0.079$, $p = 0.781$, $\eta^2 = 0.001$) and the main effects of Condition ($F_{1,33} = 0.715$, $p = 0.404$, $\eta^2 = 0.02$) and Time ($F_{1,33} = 0.159$, $p = 0.693$, $\eta^2 = 0.001$) were not significant (Figure 2). No violation of normality of the distribution of residuals could be inferred from the results ($p = 0.324$). For $H_{M10\%}$, two outliers (2/52, 4% of data) were removed to meet the assumption of normality of the distribution of residuals ($p = 0.102$), but removal did not affect the significance of the results of the GLM analysis. There was no significant interaction between Condition and Time ($F_{1,33} = 0.010$, $p = 0.920$, $\eta^2 = 0.001$) nor significant effect of Condition ($F_{1,33} = 0.666$, $p = 0.420$, $\eta^2 = 0.01$) and Time ($F_{1,33} = 1.605$, $p = 0.214$ $\eta^2 = 0.05$) (Figure 2).

TABLE 1. Means and standard deviations of the parameters measured during strength and skill testing.

Parameter	Hand	MEAN ± SD (PRE)	MEAN ± SD (POST)
MVC (N)	LEFT	12.83 ± 5.11	13.05 ± 4.50
MVC (N)	RIGHT	14.35 ± 3.96	15.4 ± 4.50
RMSE _25% (N)	LEFT	1.44 ± 0.75	1.05 ± 0.59
RMSE_25% (N)	RIGHT	2.49 ± 1.25	1.60 ± 0.94
RMSE_50% (N)	LEFT	1.93 ± 0.84	1.48 ± 0.67
RMSE_50% (N)	RIGHT	2.61 ± 1.19	2.08 ± 1.18

TABLE 2. Means and standard deviations (in mV) of the parameters recorded across time and conditions.

Condition	Parameter	MEAN ± SD (PRE)	MEAN ± SD (POST)
STRENGTH	aMT	0.116 ± 0.036	0.151 ± 0.069
	120% aMT	0.273 ± 0.123	0.271 ± 0.142
	M_{max}	4.374 ± 1.885 11.9533	4.236 ± 1.602
	$H_{M10\%}$	0.568 ± 0.366	0.557 ± 0.461
SKILL	aMT	0.115 ± 0.035	0.150 ± 0.068
	120% aMT	0.318 ± 0.205	0.316 ± 0.208
	M_{max}	4.489 ± 1.893	4.465 ± 2.051
	$H_{M10\%}$	0.480 ± 0.277	0.439 ± 0.274

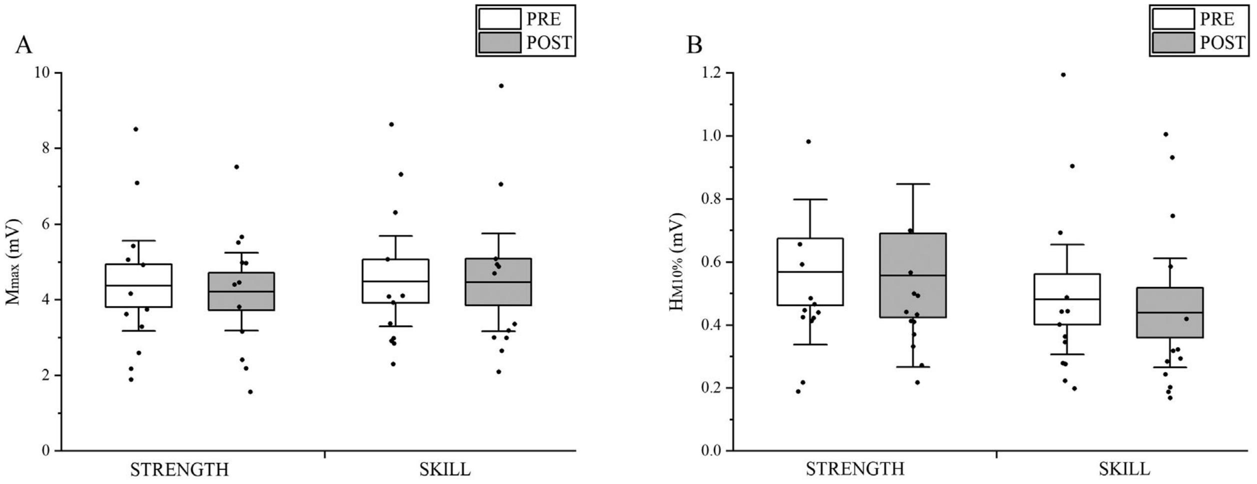

FIGURE 2. Results from peripheral nerve stimulation. *(A)* M_{max} ($n = 12$) and *(B)* $H_{M10\%}$ ($n = 13$) mean amplitudes recorded before (PRE) and after (POST) strength and skill training. Boxes represent the associated standard error (SE) and whiskers represent the associated 95% confidence interval.

MEPs

Mean and standard deviations of the MT values across all participants were 55 ± 5% MSO. For the MEPs recorded at aMT intensity, the interaction between Condition and Time was not significant ($F_{1,36} = 0.001$, $p = 0.982$, $\eta^2 = 0.001$), the main effects of Condition ($F_{1,36} = 0.007$, $p = 0.932$, $\eta^2 = 0.001$) was not significant and the main effect of Time ($F_{1,36} = 5.306$, $p = 0.027$, $\eta^2 = 0.14$) was significant (Figure 3). No violation of normality of the distribution of residuals could be inferred from the results ($p = 0.131$). For the MEPs recorded at 120% aMT intensity, the interaction between

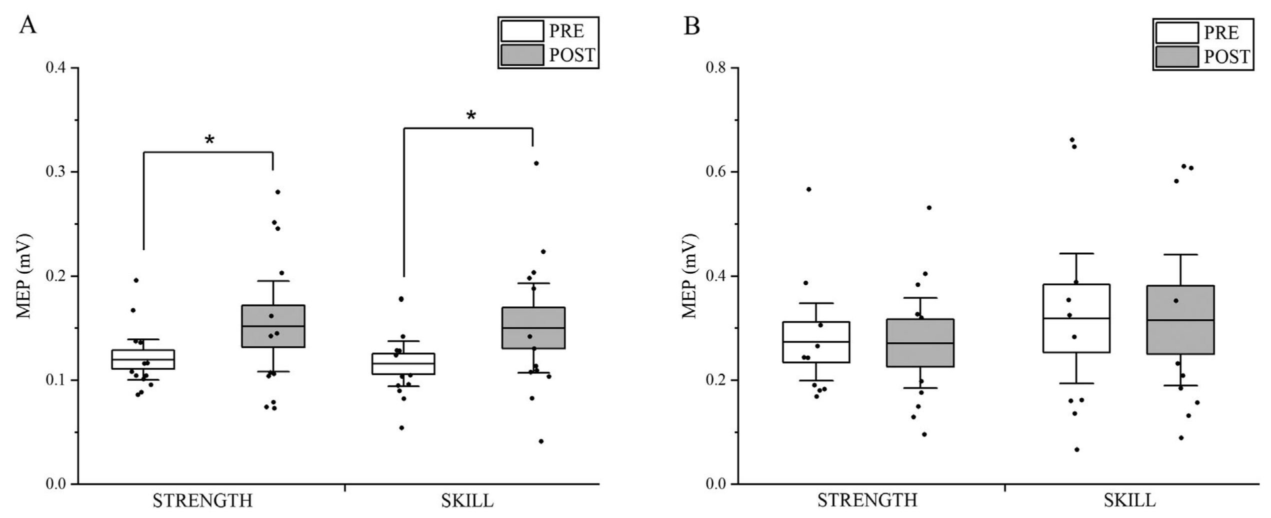

FIGURE 3. Results from TMS. *(A)* aMT ($n = 13$) and *(B)* 120% aMT ($n = 10$) mean amplitudes recorded before (PRE) and after (POST) strength and skill training. Boxes represent the associated standard error (SE) and whiskers represent the associated 95% confidence interval. The asterisks represent the significant effect of Time.

Condition and Time was not significant ($F_{1,27} = 0.000$, $p = 0.990$, $\eta^2 = 0.001$), the main effects of Condition ($F_{1,27} = 1.304$, $p = 0.263$, $\eta^2 = 0.04$) and Time ($F_{1,27} = 0.004$, $p = 0.951$, $\eta^2 = 0.001$) were not significant (Table 2). No violation of normality of the distribution of residuals could be inferred from the results ($p = 0.515$). We did not observe any significant associations between the individual change in MEP amplitudes and the individual changes in strength ($r^2 = 0.02$, $p = 0.96$) and skill (${}^{r2} = 0.15$, $p = 0.47$).

TMS-Conditioned H-Reflex

The four intervals of facilitation analysed were interpreted as corresponding to the fastest (EF) and increasingly slower (e.g. polysynaptic) (EF + 2, EF + 4, EF + 6) descending volleys to spinal motoneurons (Capozio et al., 2021b). Four outliers (4/94, 4% of data) were removed to meet the assumption of normality of the distribution of residuals ($p = 0.052$) from the TMS-conditioned H-reflexes of the strength condition, but removal did not affect the significance of the results of the GLM analysis. The results revealed a non-significant interaction between Time and Interval ($F_{3,\ 74} = 0.200$, $p = 0.896$, $\eta^2 = 0.01$) and non-significant main effects of Interval ($F_{3,\ 74} = 1.171$, $p = 0.327$, $\eta^2 = 0.05$) and Time ($F_{1,74} = 0.161$, $p = 0.689$, $\eta^2 = 0.001$) (Figure 4). Three outliers (3/95, 3% of data) were removed to meet the assumption of normality of the distribution of residuals ($p = 0.142$) from TMS-conditioned H-reflexes of the skill condition, but removal did not affect the significance of the results of the GLM analysis. The results revealed a non-significant interaction between Time and Interval ($F_{3,\ 75} = 0.288$, $p = 0.834$, $\eta^2 = 0.01$) and significant main effects of Interval ($F_{3,\ 76} = 3.751$, $p = 0.014$, $\eta^2 = 0.13$), and Time ($F_{1,75} = 12.372$, $p = 0.001$, $\eta^2 = 0.33$) (Figure 4).

Discussion

This study was designed to investigate the effects of a single session of unimanual strength training and skill training on performance and on the neural excitability of the contralateral hand. Aims of the study were to: (1) measure increases in strength (MVC); (2) measure increases in accuracy of force tracking; (3) measure changes in spinal and corticospinal neural excitability; (4) measure changes in the excitability of specific ipsilateral neural circuits observed between baseline and after strength and skill training in the untrained hand.

Strength and Force-Tracking

Acute changes in strength between the baseline pre-training phase and the post-training phase were assessed by measuring the peak torque produced during three MVCs. The training protocol was successful in increasing strength in the untrained hand. This finding partially contradicts the lack of cross-education of strengths effects observed by Alibazi and colleagues (Alibazi et al., 2021) after a single session of submaximal grip training. Similarly, cross-education of strength was not observed after 4 sets wrist extensions at 70% RM (repetition maximum) (Hendy & Kidgell, 2014) nor elbow

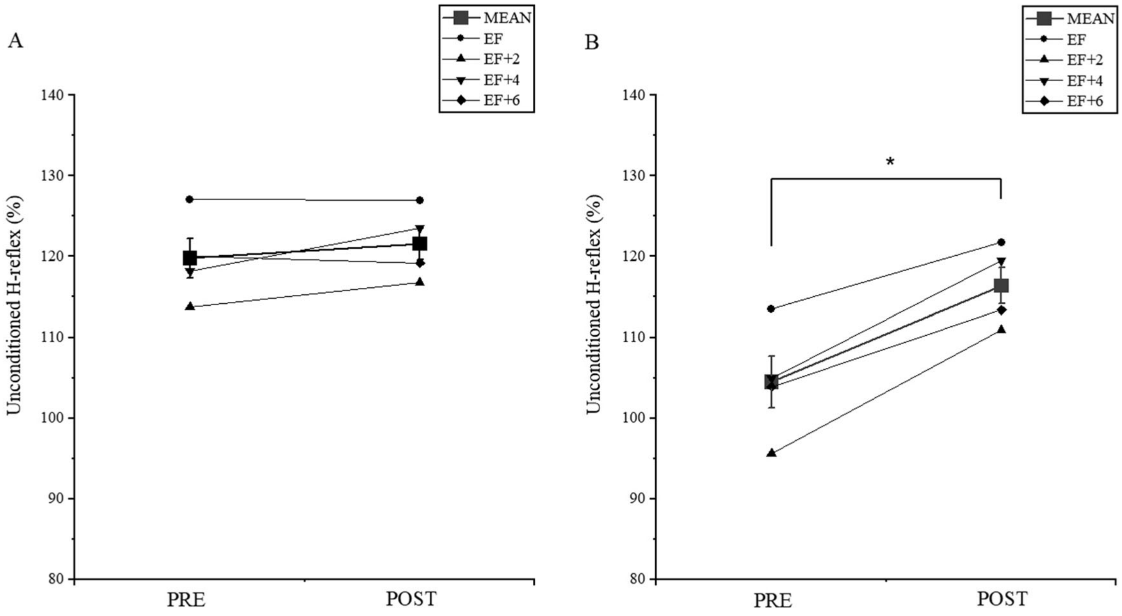

FIGURE 4. Mean conditioned H-reflex values (± SE) of all intervals across time for the *(A)* strength and *(B)* skill conditions as percentages of the unconditioned H-reflex). The asterisk represents a significant main effect of Time ($p < 0.05$).

flexions at 80% RM (Frazer et al., 2017). A possible explanation for the discrepancy between studies is the different nature of the strength training employed. Indeed, it has been suggested that the ballistic component employed in the current study is crucial in inducing the cross-education effect. Nevertheless, in the current study training did not increase maximal strength in the trained hand. Increases in peak acceleration of the trained hand have been observed after 300 movements ballistic finger abduction training (Carroll, 2008; Lee, 2010). A possible explanation for the lack of effect observed in the current study is that the total number of repetitions produced during training was too small to induce lasting effects (Selvanayagam et al., 2011). Another possibility is that fatigue confounded the effects of training on maximal strength in the trained limb (Nuzzo et al., 2016). However, MEP amplitudes collected after fatigue-inducing isometric contractions were shown to be significantly decreased compared to pre-contraction values (Kotan et al., 2015), a phenomenon which is not consistent with the increase of cortical excitability observed in the current study. In addition, we did not observe decreases in the amplitude of the monosynaptic reflex evoked upon median nerve stimulation, characteristics of fatigue-inducing contraction (Duchateau & Hainaut, 1993). To note, while the strength increase observed in the untrained limb satisfy our definition of cross-education (“the increase in muscle strength and/or motor skills in the opposite, untrained limb following a period of unilateral exercise training”, Manca et al. (2021), the lack of strength increases in the trained limb evidence that interlimb transfer of strength did not occur since the attained increase in strength did not transfer from the trained to the untrained limb. Force tracking performance significantly increased in both limbs after training, as evidenced by smaller RMSE. This finding indicates that the trained skill (force-tracking) transferred to the contralateral untrained limb. The task used in this study required participants to produce and maintain a specific amount of force for a given time. In addition, participants received visual feedback of the outcome of their movement online while training and learned to modify future behaviour accordingly (Hurley & Lee, 2006). Multiple studies have shown that externally triggered movements induce changes in excitability in motor areas (Perez et al., 2006). For example, Leung et al. (2015) showed that metronome-paced strength training and skill training both successfully increased the excitability of the untrained motor cortex, while self-paced strength training did not. The current study augments their findings by showing that tracking performance increased in both hands after a single session of training. Similar findings were reported in a study in which participants learned to reproduce a specified (35% MVC) pinch force output (Goodall et al., 2013). Errors in force production were reduced after training in the untrained hand, indicating that the skill learned (force tracking) transferred to the contralateral hand.

M_{max}/H10%

The role of spinal circuits in mediating the cross-education phenomenon is largely unknown (Carroll et al., 2006). In the current study, neither the amplitude of the M_{max}, which was used to normalise H-reflex values before training, nor the amplitude of the monosynaptic reflex were significantly increased by strength or skill training (see Figure 2). This is largely supported by other previously published work. For example, while Lagerquist and colleagues (Lagerquist et al., 2006) observed increases in the amplitudes of the H-reflex recorded in the trained soleus muscle after maximal isometric plantar flexions, they did not observe corresponding changes in the excitability of the untrained spinal circuits (Lagerquist et al., 2006). Changes in spinal excitability of the trained muscle after acute strength training are observed even when the spinal cord is stimulated at the spinal segment level, suggesting that adaptations are occurring at the motoneuronal level (Ansdell et al., 2020).

With respect to skill training, Tinazzi and Zanette (1998) reported no change in the excitability of the H-reflex pathway while participant produced finger tapping movements with the other hand. Taken together, these findings and the present study suggest that a single session of unilateral strength or skill training does not induce changes in the excitability of monosynaptic reflex pathway in lower and upper limbs.

MEPs

Results from the MEPs analyses support the hypothesis that unilateral skill and strength training modulated the excitability of the ipsilateral hemisphere to a similar extent (see Figure 3). Our findings are partially at odds with the ones reported by Ruddy et al. (2016), who did not observe any increase in corticospinal excitability after 300 ballistic wrist flexion movements completed while looking at the inactive limb, mirrored visual feedback of the trained limb or while fixating upon a white cross. Nevertheless, there are a number of methodological difference between the two studies which can explain this discrepancy: Ruddy et al. (2016) assessed excitability by stimulating at multiple intensities and measuring the area under the recruitment curve (AURC); TMS was delivered with the limb in a resting state; participants completed isotonic rather than isometric contractions; all contractions were self-paced and no online knowledge of results was given to the participants. Regarding the last point, Leung and colleagues (Leung et al., 2015) specifically tested whether the conditions of training could modulate ipsilateral cortical excitability. The authors found increased MEP amplitudes in the untrained hemisphere after visuomotor tracking and metronome-paced strength training but not in the self-paced strength training. It has been suggested that visual feedback could be necessary to induce excitability changes after visuomotor tracking (Jensen et al., 2005). Our results support the hypothesis that practice of tasks which make use of acoustic or visual cues affects ipsilateral corticospinal excitability. Our behavioural and neural findings are consistent with the "cross-activation" model, which posits that unilateral training produces neural adaptations in both hemispheres (Lee et al., 2010). Nevertheless, the lack of significant correlations between changes in strength/skill and changes in MEP amplitudes raises the question on whether the increased corticospinal excitability is a determinant factor in inducing cross-education. Similar conclusions on the association between behavioural and neurophysiological parameters were drawn from two literature reviews on cross-education of skill (Berghuis et al., 2017) and strength (Colomer-Poveda et al., 2019). However, each parameter only provide a restricted index of ipsilateral activation (Calvert & Carson, 2022), and therefore further studies employing additional TMS or neuroimaging-based parameters are needed to support the hypothesis that ipsilateral MI has a role on modulating cross-education of skill and strength.

In contrast with previous findings (e.g. Lee et al., 2010), the amplitude of MEPs evoked at 120% of MT did not change after either of the training protocols. Importantly, Lee et al. (2010) recorded responses at rest rather than during baseline contractions, a state which yields substantially smaller responses compared to the ones hereby reported, and EMG was recorded from hand muscles rather than forearm muscles. Since recruitment curves recorded from FCR show a plateau at relatively small intensities (around 130% MT, Suzuki et al., 2012), it is possible that 120% aMT stimulation at baseline was already capable of activating the neural populations which would become more excitable after training. Supporting our findings, Alibazi et al. (2021) did not report any changes in the amplitudes of MEPs recorded from FCR at 120% of aMT after submaximal grip strength training.

TMS-Conditioned H-Reflex

Monosynaptic reflexes evoked in the FCR muscle were conditioned by TMS delivered at multiple stimulus intervals, a method which permits to differentiate the monosynaptic component of the descending drive to motoneurons from other polysynaptic pathways contributing to the monosynaptic reflex (Leukel et al., 2012). Results showed that the conditioning effect of TMS on the monosynaptic reflex elicited in the untrained FCR did not change after contralateral strength training (see Figure 4). Since the subthreshold cortical stimulus evokes descending activity along the corticospinal tract (Niemann et al., 2016), the lack of changes in excitability of the TMS-conditioned H-reflexes seems to contradict the finding of increased cortical excitability after training. Importantly, the subthreshold stimulus does not elicit direct descending waves, corresponding to the monosynaptic pathway from MI to spinal motoneurons (Lazzaro et al., 2001). Therefore, both findings are consistent with an increase in the excitability of the monosynaptic component of the corticospinal tract after training.

TMS-conditioned monosynaptic reflexes increased after skill training in the untrained limb (see Figure 4). The overall significant effect of Time suggests that the increases of ipsilateral corticospinal excitability observed after skill training are mediated by M1 intracortical networks or by projections of higher-order motor areas into M1 (Ruddy & Carson, 2013). Another possibility is that unilateral movements modulate the ipsilateral descending drive to the homologous muscle *via* presynaptic inhibition of the afferents (Carson et al., 2004). During rhythmic unilateral wrist flexion, MEPs evoked from the ipsilateral M1 are increased and the afferent volley evoked by electrical stimulation of the median nerve is inhibited, but the excitability of the spinal motoneurons remains unchanged (Carson et al., 2004), suggesting that skill training might elicit neural changes in the circuit mediating presynaptic inhibition of Ia afferents of the untrained arm.

Limitations

A limitation of the current study is the lack of a control condition in which participants did not perform movements after the baseline phase. This experimental limit, commonly observed in studies assessing brain excitability after acute training (Muellbacher et al., 2001; Selvanayagam, 2011), might lead to an erroneous attribution of the changes in strength to training when these could in fact depend on task familiarisation during the testing (e.g. baseline) procedures (Carroll. 2006). In the current study, participants had the opportunity to familiarise themselves with the training environment before the start of the baseline training session. Visual feedback was also removed during the baseline force-tracking testing to ensure that participants did not learn to better control their force already at this stage. Nevertheless, we cannot exclude the possibility that learning is already occurring during testing. Future studies might address this limitation by employing a familiarisation session and adding a control group to ensure lack of learning effects due to familiarisation. We believe that this limitation does not impact the main finding of the study that single sessions of skill and strength training modulate ipsilateral cortical excitability to a similar extent.

A further limitation of the current study is the lack of spinal/cortical excitability assessment in the trained limb. This choice was dictated by the evidence that the effects of motor training on cortical excitability resolve rapidly after the end of the training (Bologna et al., 2015) and that unilateral testing including MEPs, H-reflexes and conditioned H-reflexes can take up to 40 min. For the same reason, we employed a limited range of stimulations rather than characterising fully the input-output properties of the corticospinal system by building recruitment curves (Carson et al., 2021). By using this approach in the future, further studies would shed light on the role of higher-order motor areas and/or intraspinal circuits, thought to contribute to MEPs collected at higher stimulation intensities (Di Lazzaro et al., 2012), in mediating changes in excitability. Finally, the technique of TMS-conditioning of the H-reflex does not permit us to attribute the changes observed after skill training to specific neural populations (Niemann et al., 2018). Manipulating the amplitude of the conditioning stimulus from subthreshold to above-threshold values and the orientation of the coil would reveal pattern-specific changes in excitability after skill training.

Conclusions

This study was designed to assess the effects of a single session of unimanual skill training or strength training on movements performed with the trained and untrained hands and on the motor circuits of the untrained hand. First, the finding that unilateral skill training acutely increases both performance in the contralateral hand and neural excitability in the untrained motor cortex was replicated. The novel finding of the present study was that a single session of ballistic strength training increased peak force in the untrained but not the trained hand. In addition, MEP amplitudes recorded from the untrained FCR muscle increased after a single session of skill and strength training. Nevertheless, the lack of association between changes in strength/skill and changes in ipsilateral corticospinal excitability from pre to post caution against a role of the ipsilateral motor cortex in determining the cross-education effect. It was argued that conditions of practice (visual feedback during training) are important determinant of the effects of training on ipsilateral cortical excitability. The amplitudes of TMS-conditioned H-reflexes increased after skill training, which indicates a possible role of intracortical circuits and/or the circuits mediating presynaptic inhibition of Ia afferents in modulating the increase of cortical excitability observed after skill training.

Author Contributions

A.C., S.C. and S.A. conceived and designed research; A.C. performed experiments; A.C. analysed data; A.C.

prepared manuscript; A.C. and S.A. interpreted results of experiments;

A.C., S.C. and S.A. edited and revised manuscript; A.C., S.C. and S.A. approved final version of manuscript.

Disclosure statement

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