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RESEARCH REPORT

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Corticospinal and intracortical responses from both motor cortices following unilateral concentric versus eccentric contractions

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Abstract

Cross-education is the phenomenon where training of one limb can cause neuromuscular adaptations in the opposite untrained limb. This effect has been reported to be greater after eccentric (ECC) than concentric (CON) strength training; however, the underpinning neurophysiological mechanisms remain unclear. Thus, we compared responses to transcranial magnetic stimulation (TMS) in both motor cortices following single sessions of unilateral ECC and CON exercise of the elbow flexors. Fourteen healthy adults performed three sets of 10 ECC and CON right elbow flexor contractions at 75% of respective maximum on separate days. Elbow flexor maximal voluntary isometric contraction (MVIC) torques were measured before and after exercise, and responses to single- and paired-pulse TMS were recorded from the non-exercised left and exercised right biceps brachii. Pre-exercise and post-exercise responses for ECC and CON were compared by repeated measures analyses of variance (ANOVAs). MVIC torque of the exercised arm decreased ($p < 0.01$) after CON ($-30 \pm 14\%$) and ECC ($-39 \pm 13\%$) similarly. For the non-exercised left biceps

Abbreviations: 1-RM, one repetition maximum; BB, biceps brachii; CON, concentric; ECC, eccentric; EMG, electromyogram; FDI, first dorsal interosseous; ICF, intracortical facilitation; LICI, long interval intracortical inhibition; M1, primary motor cortex; MEP, motor evoked potential; MSO, maximum stimulator output; MVIC, maximal voluntary isometric contractions; RMS, root mean square; RMT, resting motor threshold; RPE, rating of perceived exertion; SICI, short interval intracortical inhibition; TMS, transcranial magnetic stimulation.

Onno van der Groen and Christopher Latella have equal contribution.

brachii, resting motor threshold (RMT) decreased after CON only (−4.2 ± 3.9% of maximum stimulator output [MSO], $p < 0.01$), and intracortical facilitation (ICF) decreased (−15.2 ± 20.0%, $p = 0.038$) after ECC only. For the exercised right biceps, RMT increased after ECC (8.6 ± 6.2% MSO, $p = 0.014$) but not after CON (6.4 ± 8.1% MSO, $p = 0.066$). Thus, unilateral ECC and CON elbow flexor exercise modulated excitability differently for the non-exercised hemisphere. These findings suggest that responses after a single bout of exercise may not reflect longer term adaptations.

KEYWORDS

cross-education, intracortical facilitation, resting motor threshold, short interval intracortical inhibition, strength training

1 | INTRODUCTION

Unilateral strength training can increase muscle strength of the non-trained homologous muscle, known as the 'cross-education' effect. First described by Scripture and colleagues in 1894 (Scripture et al., 1894), cross-education has since been reported in numerous studies (for reviews, see Carroll et al., 2006; Ruddy & Carson, 2013). Indeed, unilateral strength training of the contralateral limb has been postulated to benefit recovery after unilateral limb injuries (Andrushko et al., 2018; Hendy et al., 2012; Pearce et al., 2013) or in neurological rehabilitation settings such as stroke where impairments to one limb are evident (Ehrensberger et al., 2016). Importantly, the type of muscle contractions (i.e. lengthening or shortening) performed appears to affect the magnitude of cross-education effect with greater effects observed after lengthening (eccentric) contraction training paradigms (Kidgell et al., 2015). Neural adaptations are thought to underpin the cross-education effect (Carroll et al., 2006; Fimland et al., 2009; Kidgell et al., 2015; Latella et al., 2012).

Transcranial magnetic stimulation (TMS) studies have shown that modulation of the motor pathway for muscles of the non-exercised side of the body occurs even after a single bout of strength training, but the reported changes vary (for review, see Colomer-Poveda et al., 2019). With isometric training contractions, the MEP of the non-exercised contralateral homologous muscle was largely unchanged (Colomer-Poveda et al., 2019). However, after a session of dynamic contractions, motor evoked potentials (MEPs) from the non-exercised muscle have been reported to increase, decrease or stay the same. One influence on this response may be duration of exercise and consequent fatigue of the exercised muscle. Low-load biceps curls performed to task failure resulted in decreased MEPs (Humphry et al., 2004; Triscott et al., 2008), whereas the same exercise for 25% of the time resulted in increased MEPs. A second influence may involve matching to sensory cues as MEPs increased with high-load biceps curls (four sets of six to eight repetitions) performed in time to a metronome (Frazer et al., 2017; Leung et al., 2015) but not when the contractions were self-paced (Leung et al., 2015). For the externally paced condition, intracortical inhibition also decreased (Leung et al., 2015). Finally, MEPs reported as unchanged were recorded during weak contractions (Edgley & Winter, 2004; Leung et al., 2015), which may have obscured any MEP decrease as contraction typically abolishes post-contraction MEP depression for exercised muscles (Sacco et al., 2000). Of these studies that examined the non-exercised motor pathway after unilateral dynamic contractions, two of them (Frazer et al., 2017; Leung et al., 2015) used exercise that was most similar to a strength training session with the exception of pacing by metronome such that the concentric phase of the biceps curl took 3 s and the eccentric phase 4 s.

Although the longer-term cross-education of strength may be greater with eccentric than concentric unilateral strength training programmes (Carroll et al., 2006), no studies have yet determined whether single sessions of concentric or eccentric phases of weight training have different after effects on the non-exercised motor cortex. In preliminary support for contraction specific modulation, our previous study (Latella et al., 2019) found that either unilateral eccentric or concentric contractions of the elbow flexors resulted in a post-exercise reduction in intracortical inhibition [short-interval intracortical inhibition (SICI)] and an increase in intracortical facilitation (ICF) in the exercised hemisphere, but these changes were longer lasting (up to 1 h) after eccentric contractions. Additionally, eccentric contractions resulted in reduced long interval intracortical inhibition (LICI) (increased conditioned MEP amplitude). Potential contraction-specific effects are also suggested by differences in the excitability of the hemisphere corresponding to the non-exercised limb 'during' eccentric and concentric contractions (Howatson et al., 2011; Uematsu et al., 2010). MEP amplitude of the contralateral resting limb increased more during eccentric than concentric contractions, whereas the H-reflex was reduced similarly for both contraction types (Edgley & Winter, 2004; Uematsu et al., 2010), suggesting increased cortical drive and decreased spinal excitability. Moreover, for strong contractions, SICI was decreased more, and ICF increased more when measured during eccentric than concentric contractions (Howatson et al., 2011). These findings indicate an increase in excitability of the ipsilateral motor cortex during unilateral contractions and that this increase in excitability in the hemisphere controlling the non-exercised limb is greater when the unilateral contractions are performed eccentrically. However, these responses were obtained during the exercise itself, meaning that the observed responses are a function of the ongoing muscle contraction, rather than potential acute post-contraction modulation in response to the performed exercise.

Therefore, the aim of this study was to investigate the neurophysiological responses in both motor cortices following a single bout of unilateral eccentric versus concentric elbow flexor exercise. Based on our previous work (Latella et al., 2019), we hypothesised that a greater increase in corticospinal excitability would occur in the non-exercised limb following eccentric than concentric unilateral exercise. This would be observed as larger amplitude MEP and lower resting motor threshold (RMT) and be associated with increased ICF and reduced intracortical inhibition (SICI and LICI). The findings of this study may provide further insight into the effects of unilateral resistance training on the central nervous system.

2 | MATERIALS AND METHODS

2.1 | Familiarisation session

This study comprised one familiarisation session and two experimental sessions, each separated by ~1 week. The familiarisation session served to determine participant responses to TMS (i.e. RMT and to optimise the conditioning pulse intensity for the measurement of SICI). During familiarisation, participants were asked to perform maximal voluntary isometric contractions (MVIC) of the right elbow flexors to minimise learning effects in subsequent experimental sessions. One-repetition maximum (1-RM) right elbow flexor eccentric and concentric strength was determined as described below. Lastly, participants performed one set of 10 eccentric contractions at 50% of their eccentric 1-RM. This served to induce a protective effect against muscle damage from eccentric contractions subsequently performed during the respective experimental session (Barreto et al., 2019). During the experimental sessions, left and right biceps brachii (BB) responses to peripheral nerve stimulation, and single- and paired-pulse TMS were recorded pre- and post-exercise. MVIC torque was measured before, immediately post-exercise and ~30 min post-exercise on each day. For the exercise session, participants performed eccentric contractions on 1 day (ECC), and on the other day, they performed concentric contractions of the right elbow flexors (CON) in a randomised crossover fashion.

2.2 | Participants

Eighteen right-handed individuals attended the laboratory for familiarisation. Four individuals were excluded due to high RMTs, which did not allow collection of paired-pulse data. Thus, 14 participants completed the full testing protocol (12 males, two females) (age, 28.2 ± 5.7). Previous meta-analytical investigations have shown moderate-to-large effect size of strength cross-transfer after repeated training sessions (Cohen's *d*: 0.6) (Manca et al., 2017). However, as such effects are unlikely to accurately represent the sample size required for this acute study of corticomotor responses we recruited participants based on convenience sampling in line with typical sample sizes in this field. All participants reported no incidence of neuromuscular injury to the right or left arm in the last 6 months. Written informed consent was obtained, and both a pre-exercise medical screening and a TMS safety questionnaire were completed. Participants with contraindications to exercise or to TMS (Rossi et al., 2009) were excluded prior to experimental participation. All procedures used were approved by the Edith Cowan University Human Research Ethics Committee (Project ID: 2019-00285) and conducted to the standards set by the Declaration of Helsinki.

2.3 | Experimental protocol

On 2 days, separated by at least 1 week, single- and paired-pulse TMS and supramaximal peripheral nerve stimuli were delivered to evoke responses from the left and right BB before and after either ECC or CON contractions of the right elbow flexors (Figure 1a).

First, the left arm was placed in the arm bar (see setup below). RMT for the left BB was assessed, and then, with the muscle at rest, stimuli were delivered at 0.2 Hz in five sets of 16 single- and paired-pulse TMS (4 × single pulse, 4 × $SICI_2$, 4 × $SICI_3$ and 4 × ICF in a randomised

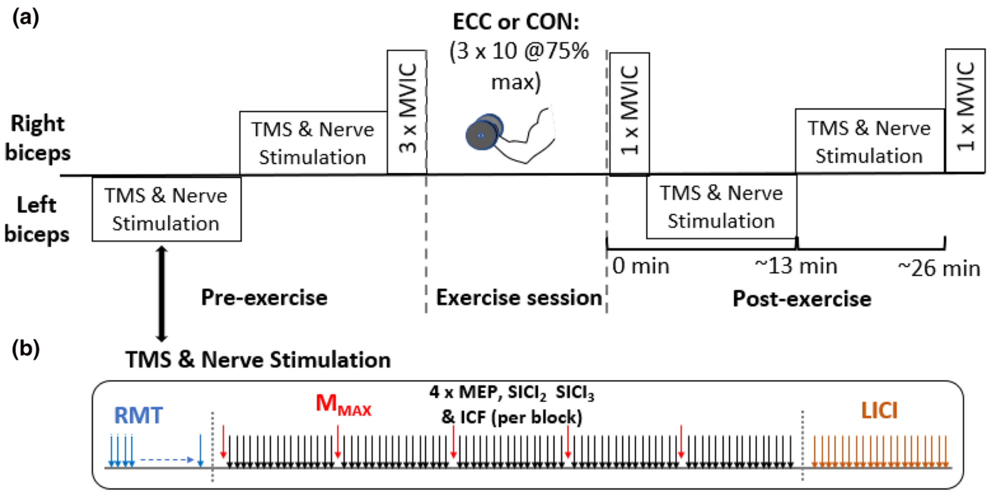

FIGURE 1 Schematic overview of study protocol (a) and example of TMS nerve stimulation protocol delivered during each testing block (b). CON, concentric; ECC, eccentric; ICF, intracortical facilitation; LICI, long interval intracortical inhibition; MEP, motor evoked potential; MVIC, maximal voluntary isometric contraction; RMT, resting motor threshold; SICI, short interval intracortical inhibition (2- or 3-ms interstimulus interval); TMS, transcranial magnetic stimulation.

order in each set). That is, a total of 20 of each stimulus type were delivered pre-exercise and again at post-exercise over each primary motor cortex M1. Prior to each set, one stimulus over Erb's point was also delivered. Following this, 20 paired-pulse stimuli were delivered to assess LICI (Figure 1b). Next, the right arm was placed in the arm bar, and RMT and other TMS testing was completed for the right BB. MVICs of the right elbow flexors were performed. The participant moved to the preacher bench and performed either the ECC or CON session as described below. Immediately after the third set of contractions, the participant moved back to the isometric set-up to perform a right elbow flexor MVIC. Then, the left (non-exercised) arm was placed in the arm bar. RMT was assessed, and paired-pulse TMS carried out for left BB. Finally, the right (exercised) arm was placed in the arm bar, RMT assessed, and paired-pulse testing completed for right BB. A final MVIC of the right elbow flexors was performed. Testing conducted over each M1 at each time point took ∼12–13 min. All experimental procedures are described in detail below.

2.4 | Experimental set-up

Participants were seated on a custom-built chair (80/20 Australia), with the shoulder and elbow of one arm flexed to 90° and held in a custom-made device (i.e. isometric myograph) that measured elbow flexion torque. The forearm was secured via a Velcro strap (2 cm in width) fastened around the wrist to an arm bar attached to a fixed force transducer (UU-K200 200 kg, load cell, DACELL, Korea). The myograph was moved at times during the experiment to allow the left or right arm to be secured. After skin preparation, surface electrodes (Ag-AgCL) were placed on the skin over right and left BB to measure electromyographic activity (EMG). The electrodes for each EMG recording were positioned over the middle of the muscle belly and 4–9 cm distal over the tendon. These locations were recorded with reference to anatomical landmarks (i.e. the anterior elbow crease with elbow at 90° of flexion) for each participant on the familiarisation day and replicated on subsequent experimental days. EMG signals were amplified (1000×), filtered (20 Hz–1 kHz, CED 1902 amplifier, Cambridge Electronic Designs) and digitised at 2 kHz (CED 1401) and stored for offline analysis (CED Spike 2 V7.20 software), whereas the torque signal was sampled at 2 kHz.

2.5 | Unilateral strength assessment and exercise

Maximal eccentric and concentric strength (1-RM) of the right elbow flexors was assessed during the familiarisation session. Participants were seated on a commercial preacher curl bench and the seat and elbow pad adjusted for each participant's torso length. The weight (an adjustable dumbbell) was passed to the participant when the arm was in the starting position for either eccentric (elbow joint angle at 90°) or concentric (elbow joint angle at 10°) contraction. Once each repetition was complete, the dumbbell was taken by the researcher, and the arm moved by the participant without load back to the starting position. The duration of each of these phases was 3 s, and if the participant could not control the movement for the duration of this period, the trial was deemed unsuccessful. The concentric 1-RM test was performed first, followed by the eccentric 1-RM test. For each, the warm-up consisted of five and three repetitions at an estimated 50% and 80% of perceived maximum with 1-min of rest between each set. Then single repetition attempts were performed with 2 min of rest between each attempt. The weight was gradually increased for each attempt until a full repetition could not be completed under the sole control of the participant. 1-RM values were achieved within three to five attempts for all participants. The weights of the last successful lifts were determined as the 1-RM for concentric contraction (1-RMcon) and eccentric contraction (1-RMecc).

The exercise protocol consisted of warm-up (one set of 10 contractions at 50% of 1-RM) and then three sets of 10, 3-s eccentric or concentric elbow flexor contractions on a preacher curl bench using a dumbbell. The weight used during the sessions was 75% of the maximum 1-RM achieved for each contraction type for each participant. This resulted in 14.9 ± 3.4 (range: 11–22) kg and 11.1 ± 2.5 (9–17) kg being used for the ECC and CON sessions, respectively. Participants were asked to report their rating of perceived exertion (RPE), for the bicep curl task(s), during the determination of the 1-RM on the familiarisation day, and also after each set of exercise on both experimental days using a 0–10 numerical scale with descriptors (0 = *extremely easy* to 10 = *extremely hard*).

Participants were given 3 min of passive rest between sets. When the load could not be solely lifted by the participant for 10 repetitions, a researcher provided minimal support to complete each repetition and the set. The load was not reduced across sets. During the ECC and CON exercise sessions, participants were instructed to keep their left arm hanging by their side and as relaxed as possible. The order of the two exercise conditions (ECC and CON) were randomised across participants. During the exercise protocol, EMG of both BB was recorded to detect contraction of the non-exercised arm.

2.6 | MVIC torque

MVIC torque, recorded during 3-s isometric contraction of the right arm only, was assessed pre-exercise (three trials), immediately post-exercise (one trial) and at ~30 min post-exercise (one trial) on each experimental day with a 60-s recovery period between attempts. The highest peak torque (Nm) from each time point was used for further analysis. Prior to each trial, participants were instructed to contract 'as hard and as fast as possible'. Visual feedback of the torque signal and strong verbal encouragement were provided to participants during each trial.

2.7 | Peripheral nerve stimulation

To elicit compound muscle action potentials from the left and right BB, supramaximal electrical stimuli (pulse duration: 200 μs; Digitimer DS8R, UK) were delivered via surface electrodes stuck to the skin, with the cathodes placed in the supraclavicular fossae over the brachial plexus (Erb's point) and the anodes posterior to the acromions. For each side, the stimulus intensity was increased until a plateau in the peak-to-peak amplitude of EMG response in the BB was reached (M_{MAX}). The intensity was increased by a further 40% to account for potential reductions in axonal excitability with fatigue and used throughout the study (range used: 42–238 mA).

2.8 | TMS

Single- and paired-pulse TMS were delivered over the M1 representations of the left and right BB at rest. Rest was chosen to avoid confounding factors associated with fatigue-related changes in neural drive to the muscle during contraction. A 70-mm figure-of-eight coil attached to a BiStim 200^2 magnetic stimulator (Magstim Co., Dyfed, UK) was held by an investigator. The coil was held tangential to the surface of the scalp with the handle pointing backward and laterally at 45° away from the nasion–inion mid-sagittal line, resulting in a posterior–anterior direction of current flow in the brain. This coil orientation is thought to be optimal for inducing the electric field perpendicular to the central sulcus, resulting in the stimulation of M1 neurons (Mills et al., 1992). The 'hotspots' were the sites that elicited the largest and most consistent MEPs from each BB. Once the optimal sites were located, they were marked on a swim cap worn by the participant. A threshold hunting program (TMS Motor Threshold Assessment Tool 2.0) (http://www.clinicalresearcher.org/software.html) was used to determine the RMT before and after exercise with 95% confidence. Criterion for an above threshold response was set at 0.05 mV. To set stimulus intensities for single- and paired-pulse testing, RMT was measured during the familiarisation session and rechecked at the start of the first experimental session. Stimulus intensities were then kept constant for the first and second experimental sessions regardless of any changes in RMT.

For single-pulse TMS, an intensity corresponding to 140% of RMT was used as similarly used in other research in this muscle group (Latella et al., 2019). For paired-pulse responses, the test pulse (140% RMT) was preceded by subthreshold TMS at interstimulus intervals of 2 and 3 ms for $SICI_2$ and $SICI_3$, respectively. For ICF, an interstimulus interval of 10 ms was used. The subthreshold conditioning stimulus intensity was set to optimise the measurement of SICI (see Latella et al., 2019; Ruas et al., 2020). This was first determined during the familiarisation session and adjusted during the set-up period of the first experimental session if required. SICI stimulation parameters remained constant thereafter. To set the conditioning stimulus intensity, SICI responses were assessed using conditioning pulses between 55 and 90% of RMT with 5% adjustments in stimulation intensity performed in descending order. For each tested intensity, five paired-pulse and five single-pulse stimuli were delivered and were immediately analysed. The conditioning stimulus intensity eliciting SICI that was ~50% of the maximal inhibition achievable for each individual was used during the experiment (68.5 ± 6.5% of RMT, range: 54–87% of RMT, 41.9 ± 6.4% of maximum stimulator output [MSO]). For LICI, pairs of stimuli (140% RMT) were delivered with an interstimulus interval of 100 ms.

2.9 | Data analyses

Data were analysed offline using custom-made scripts in Matlab (Matlab 2020a, the MathWorks, Inc., USA). Peak-to-peak amplitudes were measured between cursors set to encompass each potential. The median amplitudes of evoked potentials elicited by each TMS condition and of M_{MAX} were calculated for the left and right BB in each participant. Median amplitudes have been used previously to analyse TMS data, since these are less sensitive to outliers (Cortes et al., 2012; Krakauer et al., 2021; Van den Berg et al., 2011). Paired-pulse responses (SICI and ICF) are reported as the ratio of the median conditioned MEP amplitude to median single-pulse MEP amplitude. LICI is reported as the ratio of the median of each conditioned MEP to the preceding test MEP. A ratio of less than one indicates inhibition and greater than one indicates facilitation. To quantify pre-stimulus EMG, the signal was first digitally filtered using a 50-Hz notch filter, and then the root mean square amplitude of the signal over a 100 ms time period prior to the delivery of each transcranial stimulus was calculated. In order to quantify EMG activity in the non-exercised and exercised arm during exercise, the root mean square (RMS) amplitude over each set was calculated. This value was normalised to M_{MAX}.

2.10 | Statistical analyses

Three participants showed no loss in MVIC torque after exercise for either the CON or ECC condition. As the exercise did not induce fatigue, the data from these participants were excluded from further analysis. Thus, statistical analyses were performed for 11 participants. Statistical analyses were performed with repeated measures ANOVAs in IBM SPSS statistics version 27.0 (IBM Corp.). Sphericity was tested using Mauchly's sphericity test. If sphericity was violated, Greenhouse–Geisser correction was applied. The threshold for statistical significance was set at $p = 0.05$, and all results are displayed as mean ± standard deviation (SD) unless otherwise specified. All post hoc tests were corrected for multiple comparisons using Bonferroni correction. Effect sizes are reported for each experiment in the form of partial η^2 (η_p^2; small $\eta_p^2 = 0.01$, medium $\eta_p^2 = 0.06$, large $\eta_p^2 = 0.14$; Lakens, 2013). Two-way ANOVAs with repeated measures were used to compare between conditions (ECC and CON) for changes in outcome measures (MEP, M_{MAX}, MEP/M_{MAX} ratio, $SICI_2$, $SICI_3$, ICF and LICI) across time (pre- and post-exercise) for the left and right BB. For this study, the left and right hemisphere measures were analysed independently as the recording of acute post-exercise responses for each occurred at different time points. Two-way ANOVAs (Condition × Time) with repeated measures were also performed for MVIC torque with time points: pre-exercise, post-exercise and 30-min post and for RPE after Set 1, Set 2 and Set 3. Paired-sample two-tailed *t*-tests were also conducted to test for differences in 1-RM strength between ECC and CON.

3 | RESULTS

3.1 | Elbow flexor strength, exercise and fatigue

1-RM elbow flexor strength, tested during the familiarisation session, was greater ($p < 0.001$) for ECC [19.7 ± 4.5 kg (range: 13.0–29.5 kg)] than CON [14.7 ± 3.4 kg (range: 10.0–22.5 kg)]. During the exercise sessions, the reported RPE (average of the three scores obtained after Sets 1–3) was similar ($p = 0.791$) between ECC [8.8 ± 0.69 (range: 8–10)] and CON [8.9 ± 0.95 (range: 8–10)].

Analysis of EMG during the exercise sets showed a condition × set interaction for EMG_{RMS}/M_{MAX} ($F_{2,20} = 4.198$, $p = 0.030$) in the exercised arm with lower values during eccentric compared with concentric contractions. A main effect of set was also observed ($F_{1,10} = 12.0072$, $p < 0.001$), with Bonferroni-corrected post hoc *t*-tests showing that EMG_{RMS}/M_{MAX} was greater in Set 3 compared with Set 1 or Set 2 ($t_{10} = 4.395$ and 3.389, $P_{corr} < 0.001$ and $P_{corr} = 0.009$), in Set 2 compared with Set 1 ($t_{10} = 3.116$, $P_{corr} = 0.015$). There was no main effect of contraction type ($F_{1,10} = 3.13$, $p = 0.107$). In the non-exercised arm, no condition x set interaction was observed ($F_{2,20} = 0.238$, $p = 0.791$) for EMG_{RMS}/M_{MAX} recorded during the exercise sets, nor were there effects observed across sets ($F_{1,10} = 2.552$, $p = 0.103$), or between conditions ($F_{1,10} = 3.145$, $p = 0.107$).

There was a main effect of time on MVIC torque ($F_{1,10} = 60.395$, $p < 0.001$). Post-exercise, MVIC torque decreased by 30.0 ± 14.1% and 38.8 ± 13.0% for CON and ECC conditions, respectively (both $P_{corr} < 0.001$) and was still reduced at ~30 min post-exercise (CON: −18.8 ± 13.1%, ECC: −28.2 ± 14.1%, both $P_{corr} \leq 0.001$) (Figure 2). There was no main effect of contraction type ($F_{1,10} = 3.561$, $p = 0.088$) or an interaction ($F_{2,20} = 3.200$, $p = 0.062$) on absolute MVIC torque values.

3.2 | Corticospinal excitability

For the non-exercised arm, there was a significant effect of time on the RMT ($F_{1,10} = 5.679$, $p = 0.038$, $\eta_p^2 = 0.362$). Post hoc tests demonstrated a decrease by 4.2 ± 3.9% of maximum stimulator output (MSO) ($t_{10} = 4.055$, $P_{corr} = 0.004$) post-exercise when compared with pre-exercise for CON, but no change following ECC (decrease of 1.64 ± 5.6% MSO, $t_{10} = 0.559$, $p = 0.588$, Figure 3a). For the exercised arm, there was a significant effect of time on corticospinal excitability ($F_{1,10} = 15.865$, $p = 0.003$, $\eta_p^2 = 0.563$). Post hoc tests demonstrated a RMT increase of 8.6 ± 6.2% MSO ($t_{10} = -3.36$, $P_{corr} = 0.0014$) post-exercise for ECC, but the 6.4 ± 8.1% MSO increase in RMT post-exercise for CON did not reach significance ($t_{10} = -2.48$, $P_{corr} = 0.066$) (Figure 3b). There was no difference in the MEP/M_{MAX} ratio between conditions (ECC or CON) or changes over time (Table 1 and Figure 3c,d).

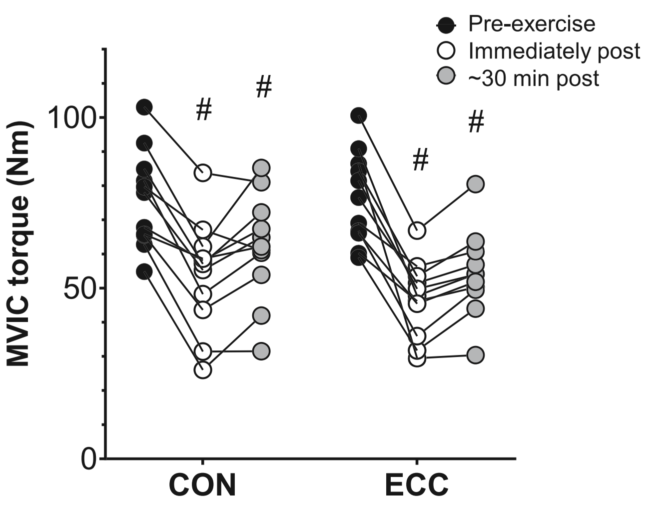

FIGURE 2 Changes in maximum voluntary isometric contraction torque of the exercised arm of 11 participants pre-exercise, immediately post-exercise and ~30 min after concentric and eccentric exercise of the elbow flexors. # indicates significant ($p < 0.05$) difference from pre-exercise.

3.3 | Intracortical facilitation and inhibition

In the non-exercised arm, there was a significant condition × time interaction for ICF ($F_{1,10} = 5.715$, $p = 0.038$, $\eta_p^2 = 0.364$) with a 15.2 ± 20.0% decrease in ICF post-exercise for ECC only ($t_{10} = 2.556$, $p = 0.029$) (Figure 4a). In the exercised arm, no difference between conditions was observed for ICF ($p = 0.111$) (Table 1 and Figure 4b) with ICF being higher for CON than ECC at baseline and post-exercise. However, there was no main effect of time, nor was there a condition × time interaction (Table 1). In the non-exercised arm, no interaction or main effects were observed for $SICI_2$ or $SICI_3$ (Figure 4c,e). This was also the case for $SICI_2$ in the exercised arm (Figure 4d), whereas a main effect for condition was observed for $SICI_3$ ($F_{1,10} = 5.242$, $p = 0.045$) (Table 1 and Figure 4f). Similarly, there were no interaction or main effects observed for LICI in the non-exercised arm, but there was a main effect of condition for LICI in the exercised arm ($F_{1,10} = 5.946$, $p = 0.035$) with no interaction or main effect of time (Table 1).

4 | DISCUSSION

This study investigated TMS-evoked responses in both M1s following unilateral ECC versus CON exercise sessions of the right elbow flexors. Despite a similar magnitude of fatigue after each exercise, some disparities in TMS-evoked responses were observed. RMT was reduced for the non-exercised arm after CON, but not after the ECC session. Conversely, ICF was reduced for the non-exercised arm following ECC, but not the CON session. In the M1 corresponding to the exercised arm, RMT increased significantly after ECC exercise but not after CON exercise. Based on previous work (Howatson et al., 2011), we hypothesised that greater increases in corticospinal excitability (i.e. larger amplitude MEP and lower RMT) and intracortical facilitation (i.e. ICF) and reduction in intracortical inhibition (i.e. SICI and LICI) would occur following ECC than CON exercise. However, our results do not support this hypothesis nor provide further clarity about the potential for acute neurophysiological responses to help explain the greater cross-education effect observed with repeated eccentric strength training.

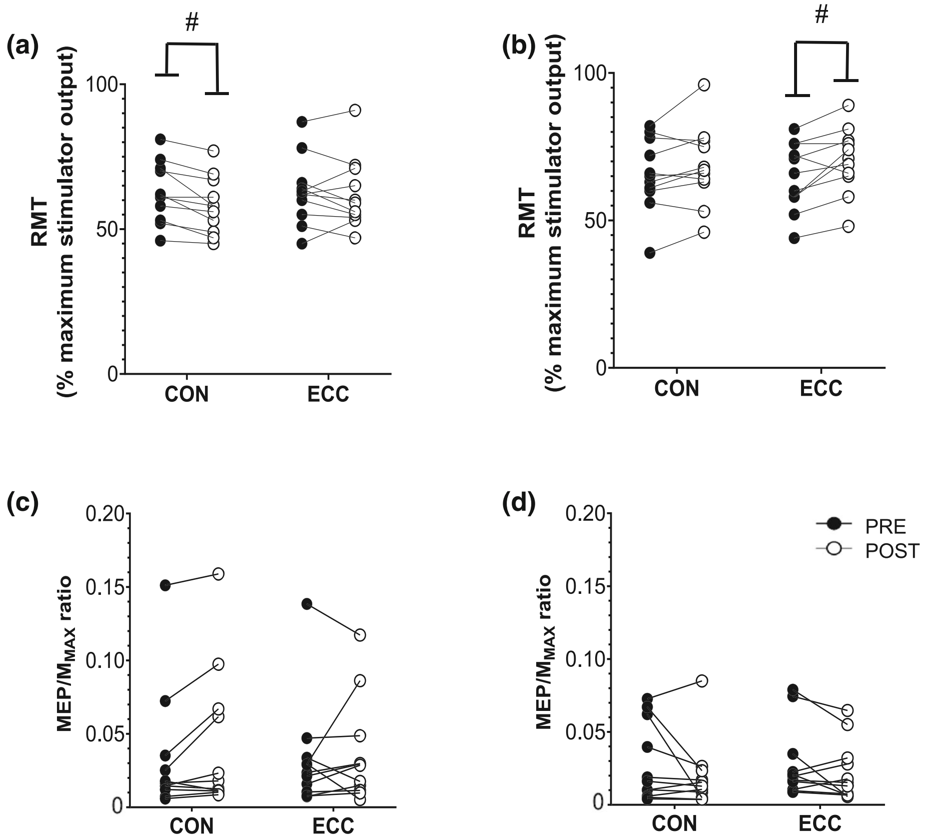

FIGURE 3 Changes in the stimulator intensities required to achieve resting motor threshold (RMT) of 11 participants before and after concentric (CON) and eccentric exercise (ECC) are shown in (a) for the non-exercised left biceps brachii (right motor cortex) and (b) for the exercised right biceps brachii (left motor cortex). Changes in ratio of motor evoked potential (MEP) and maximum compound muscle action potential (M_{MAX}) before and after concentric (CON) and eccentric exercise (ECC) are shown in (c) for the non-exercised left biceps brachii (right motor cortex) and (d) exercised right biceps brachii (left motor cortex). # indicates significant ($p < 0.05$) difference from pre-exercise.

4.1 | Responses in hemisphere associated with non-exercised arm

Modulation of post-exercise neurophysiological responses for the non-exercised left BB (right motor cortex) showed some disparity between CON and ECC sessions. Specifically, RMT intensity decreased by ~4.2% of MSO after CON, but not after the ECC session. This suggests increased motor corticospinal excitability of the non-exercised hemisphere after CON, but the reason for this is not clear as there were no supporting changes in MEP size nor in intracortical inhibition or facilitation. One suggestion is that interhemispheric inhibition is reduced during strong concentric and eccentric contractions (Howatson et al., 2011), which may serve to increase overall excitability of the non-exercised cortex. The reduction in interhemispheric inhibition is postulated to be greater during eccentric than concentric contractions as MEP amplitude and ICF in the resting wrist flexors were greater while muscles of the contralateral limb performed eccentric contractions (Howatson et al., 2011). Thus, we may have expected RMT to be reduced by the same, or a greater amount, after ECC. However, it is unclear whether the effects during contraction persist post-contraction and whether this would influence RMT. We did not see a difference in corticospinal excitability measured via the MEP/M_{MAX} ratio after CON or ECC exercise (see Figure 4a and Table 1). Although no studies have previously examined responses to TMS in the non-exercised limb after solely concentric or eccentric exercise, our findings are consistent with reports of no change in biceps MEP amplitude after one session of unilateral strength training comprising self-paced biceps curls with both concentric and eccentric components (Leung et al., 2015) or one session of unilateral strong isometric contractions (Cortes et al., 2012). However, changes in MEP amplitudes of the non-exercised muscle are seen under other specific conditions. For example, they were increased when biceps curls were externally paced by a metronome (Frazer et al., 2017; Leung et al., 2015) or decreased after low-load biceps curls were performed to task failure (Humphry et al., 2004; Triscott et al., 2008).

Responses to paired-pulse TMS measured in the non-exercised muscle also vary across studies. We observed a reduction in ICF (~15%) following ECC but not CON exercise and no changes in SICI. Similarly, ICF reductions in the left hemisphere have been reported after fatiguing exercises with the left hand (Bäumer et al., 2002). However, Colomer-Poveda et al. (2020) reported no change in ICF for either hemisphere after unilateral isometric elbow flexor contractions. For SICI, previous studies report no ipsilateral changes after a single session of repeated fatiguing pinch grips (Bäumer et al., 2002), high force finger abductions (Hortobágyi

TABLE 1 Results of statistical analysis for all outcome measures

	Bicepsbrachii	Concentric Pre	Concentric Post	Eccentric Pre	Eccentric Post		Interaction	Condition	Time
M_{MAX} (mV)	**Left** (non-ex)	21.9 ± 4.5	21.8 ± 4.1	22.0 ± 5.2	21.6 ± 4.5	Log	$F_{1,10} = 0.484$ $p = 0.502$	$F_{1,10} = 0.002$ $p = 0.963$	$F_{1,10} = 0.044$ $p = 0.839$
	Right (exerc)	22.4 ± 5.7	18.5 ± 6.1	22.6 ± 4.8	17.2 ± 5.9		$F_{1,10} = 2.417$ $p = 0.151$	$F_{1,10} = 0.234$ $p = 0.639$	$F_{1,10} = 22.811$ $\mathbf{p = 0.001^*}$
MEP (mV)	**Left** (non-ex)	0.74 ± 1.04	0.98 ± 1.21	0.70 ± 0.74	0.70 ± 0.57	Log	$F_{1,10} = 0.709$ $p = 0.420$	$F_{1,10} = 0.042$ $p = 0.842$	$F_{1,10} = 1.150$ $p = 0.247$
	Right (exerc)	0.58 ± 0.53	0.37 ± 0.48	0.59 ± 0.42	0.38 ± 0.31	Log	$F_{1,10} = 0.026$ $p = 0.875$	$F_{1,10} = 1.821$ $p = 0.207$	$F_{1,10} = 8.306$ $\mathbf{p = 0.016^*}$
MEP/M_{MAX}	**Left** (non-ex)	0.036 ± 0.045	0.0449 ± 0.049	0.0331 ± 0.037	0.0361 ± 0.035	Log	$F_{1,10} = 0.345$ $p = 0.570$	$F_{1,10} = 0.018$ $p = 0.897$	$F_{1,10} = 0.345$ $p = 0.570$
	Right (exerc)	0.028 ± 0.027	0.019 ± 0.023	0.029 ± 0.025	0.023 ± 0.020	Log	$F_{1,10} = 0.280$ $p = 0.608$	$F_{1,10} = 3.648$ $p = 0.085$	$F_{1,10} = 2.150$ $p = 0.173$
ICF (%)	**Left** (non-ex)	136.3 ± 26.6	150.4 ± 60.2	152.5 ± 32.4	126.8 ± 25.9		$F_{1,10} = 5.715$ $\mathbf{p = 0.038^*}$	$F_{1,10} = 0.148$ $p = 0.708$	$F_{1,10} = 0.514$ $p = 0.490$
	Right (exerc)	133.2 ± 34.5	136.5 ± 37.8	115.0 ± 29.3	122.2 ± 31.4	Log	$F_{1,10} = 0.196$ $p = 0.668$	$F_{1,10} = 3.604$ $p = 0.087$	$F_{1,10} = 0.267$ $p = 0.617$
$SICI_2$ (%)	**Left** (non-ex)	46.6 ± 24.4	55.3 ± 27.0	43.7 ± 19.6	48.8 ± 18.9		$F_{1,10} = 0.267$ $p = 0.617$	$F_{1,10} = 0.460$ $p = 0.513$	$F_{1,10} = 2.211$ $p = 0.168$
	Right (exerc)	43.1 ± 32.9	53.9 ± 32.7	39.4 ± 24.6	45.9 ± 25.4		$F_{1,10} = 0.605$ $p = 0.455$	$F_{1,10} = 2.189$ $p = 0.170$	$F_{1,10} = 3.024$ $p = 0.113$
$SICI_3$ (%)	**Left** (non-ex)	47.0 ± 20.9	53.6 ± 23.4	53.3 ± 26.0	52.7 ± 22.7		$F_{1,10} = 0.664$ $p = 0.434$	$F_{1,10} = 0.346$ $p = 0.569$	$F_{1,10} = 0.353$ $p = 0.566$
	Right (exerc)	43.5 ± 19.5	48.8 ± 19.5	35.7 ± 18.9	41.9 ± 16.9		$F_{1,10} = 0.025$ $p = 0.878$	$F_{1,10} = 5.242$ $\mathbf{p = 0.045^*}$	$F_{1,10} = 1.066$ $p = 0.326$
LICI (%)	**Left** (non-ex)	63.3 ± 83.5	62.0 ± 61.6	48.7 ± 57.4	41.6 ± 45.1	Log	$F_{1,10} = 0.890$ $p = 0.368$	$F_{1,10} = 1.313$ $p = 0.278$	$F_{1,10} = 0.036$ $p = 0.854$
	Right (exerc)	65.5 ± 57.9	77.2 ± 52.1	51.5 ± 53.2	56.9 ± 50.2	Log	$F_{1,10} = 0.327$ $p = 0.580$	$F_{1,10} = 5.946$ $\mathbf{p = 0.035^*}$	$F_{1,10} = 1.755$ $p = 0.215$

Notes: Log indicates analyses performed on log-transformed data. * indicates significance.
Abbreviations: Exerc, exercised biceps brachii; ICF, intracortical facilitation; LICI, long interval intracortical inhibition; MEP, motor evoked potential; M_{MAX}, maximum compound action potential; non-ex, non-exercised biceps brachii; $SICI_2$, short interval intracortical inhibition (2 ms interstimulus interval); $SICI_3$, short interval intracortical inhibition (3 ms interstimulus interval).

et al., 2011) or repeated thumb abductions at 35% of maximum (Schmidt et al., 2011). Conversely, other studies have reported a decrease in ipsilateral SICI after metronome paced, but not self-paced biceps curls (Leung et al., 2015) and after a fatiguing handgrip task (Takahashi et al., 2009). Additionally, the long-term corticospinal responses to cross-education seem to be influenced by the type of motor training (Leung et al., 2018), where externally paced, but not self-paced exercise increases ipsilateral corticospinal excitability and reduces ipsilateral SICI. Given the inconsistent differences in SICI, other measures of motor cortical interaction, such as interhemispheric inhibition, may provide better insight into the effect of unilateral exercise on the opposing motor cortex. Importantly, dynamic concentric and eccentric contractions likely require different neural control strategies compared with the tasks performed in previous studies (Colomer-Poveda et al., 2019; Nuzum et al., 2021); hence, direct comparison is difficult.

We were also interested to observe whether acute corticospinal and intracortical responses reflect adaptive responses that have been shown to occur after unilateral training interventions. In cross-education studies specifically, Kidgell et al. (2015) reported a greater MEP amplitude and reduced SICI (less inhibition) after 4 weeks of unilateral eccentric wrist flexor training. However, our current acute findings are not reflective of these longer-term adaptations with no change observed in either of these outcomes. The role of altered cortical excitability in longer-term strength cross-education is not clear. After weeks of unilateral biceps curl training, MEPs were increased, and SICI reduced with externally paced

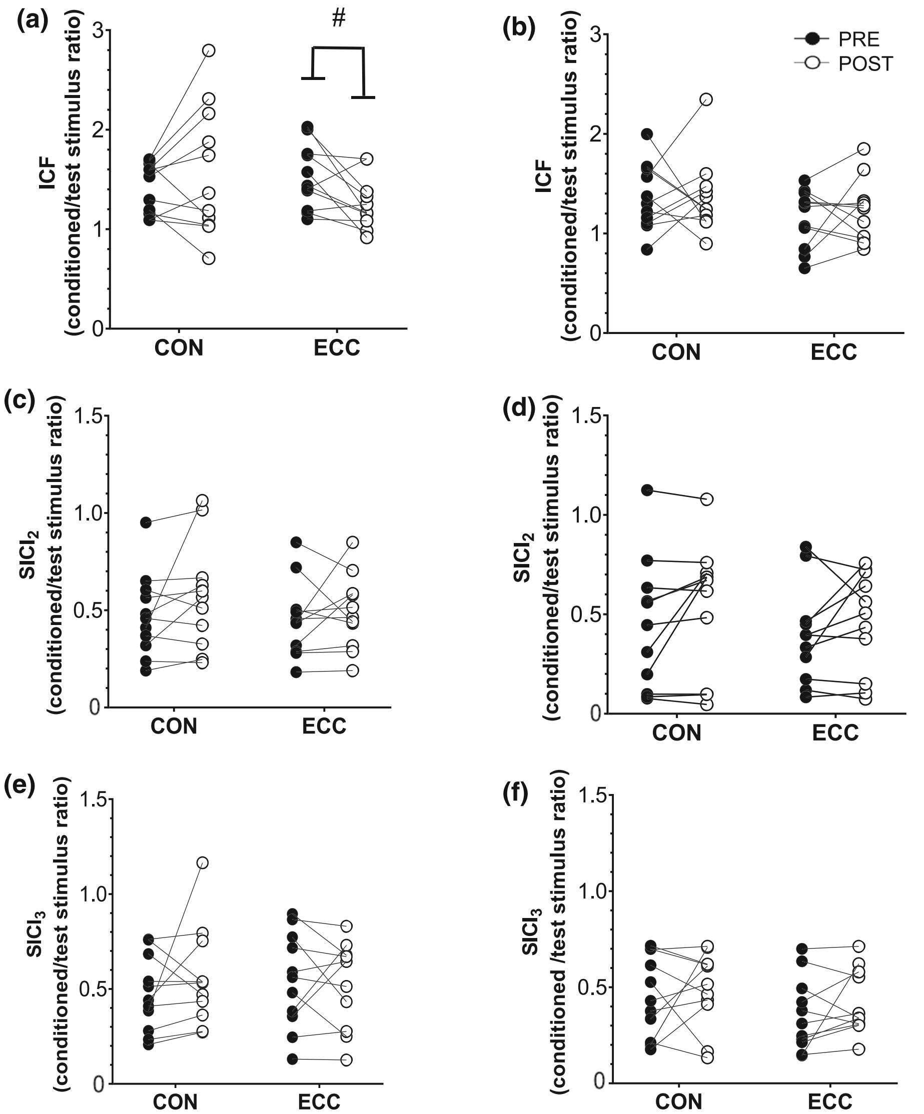

FIGURE 4 Changes in intracortical facilitation (ICF) of 11 participants before and after concentric (CON) and eccentric exercise (ECC) is shown in (a) for the non-exercised left biceps brachii (right motor cortex) and (b) for the exercised right biceps brachii (left motor cortex). Changes in short interval intracortical facilitation with a 2-ms ($SICI_2$) or 3-ms interstimulus interval ($SICI_3$) of 14 participants before and after concentric (CON) and eccentric exercise (ECC) are shown in (c) and (e) for the non-exercised left biceps brachii (right motor cortex) and (d) and (f) for the exercised right biceps brachii (left motor cortex). # indicates a significant ($p < 0.05$) difference from pre-exercise.

training but not self-paced training, whereas strength showed similar improvements with both training protocols (Leung et al., 2018). However, for unilateral training of FDI with strong isometric contractions, decreases in interhemispheric inhibition and increases in MEPs in the non-trained FDI correlated with increases in strength after multiple sessions (Hortobágyi et al., 2011).

4.2 | Responses in hemisphere associated with exercised arm

The only significant observation from the exercised right BB (left M1) was a ~7.5% increase in RMT after exercise (see Figure 3b). Interestingly, this increase was consistent and significant only after ECC exercise, despite a similar level of neuromuscular fatigue noted between conditions (MVIC decrease of ~30% and ~39% immediately post-exercise for CON and ECC, respectively). However, MEP amplitude (not normalised to M_{MAX}) did decrease for both conditions post-exercise (see Table 1). Similarly, post-exercise depression of MEPs (tested in resting muscle) has been reported in numerous studies (Latella et al., 2016; Samii et al., 1996) (for a review, see Taylor & Gandevia, 2001). Unlike a previous study however (Latella et al., 2019), no change in intracortical inhibition or facilitation was found from the exercised arm, although this is not uncommon after exercise (SICI examples: Gruet et al., 2013; Tergau et al., 2000, SICI with CON and ECC contractions: Löscher & Nordlund, 2002). Nevertheless, the reasons for the disparity between the current study and our previous work in elbow flexors are not entirely clear. One possibility is the difference in stimulation protocols used. For instance, in the current study, we individualised the conditioning stimulus intensity to elicit ~50% of maximal inhibition for each participant. This approach was chosen based on previous work from our laboratory, suggesting it provides acceptable inter-subject variability (Ruas et al., 2020). However, given many exercise-induced fatigue studies report less inhibition (greater conditioned to test pulse ratio) (Goodall et al., 2018; Maruyama et al., 2006), perhaps using a conditioning stimulus intensity that elicited maximum inhibition at baseline would allow better sensitivity to detect reductions in inhibition. Despite this thought, Hunter et al. (2016) used a similar conditioning stimulus paradigm to our current study and did report reduced SICI after exercise. Moreover, upon further analysis, baseline SICI ratios appear lower in the current study (i.e. CON: 43.1%–43.5%, ECC: 35.7%–39.4%) despite attempts to elicit only a moderate level of inhibition from each individual, compared with our previous work (CON: 50.8%, ECC: 58.7%) (Latella et al., 2019). Therefore, it is possible that other factors such as measurement timing (see Section 4.3) may have influenced the intracortical responses observed. In the familiarisation session, participants completed one set of 10 ECC contractions at 50% 1-RM, although the training intensity for the intervention part was set at 75% 1-RM. The 50% 1-RM might not have provided a strong protective effect because the higher the intensity of the initial bout, the greater the protective effect (Hyldahl et al., 2017). Muscle damaging exercises do have an effect on corticospinal excitability, which can influence cortical excitability for 3 days (Goodall et al., 2018; Pitman & Semmler, 2012). However, in the current study, experimental sessions were scheduled at least 1 week apart. Moreover, the pre-exercise MVICs were not different between the two experimental days, and experimental interventions (ECC or CON) were counterbalanced. This suggests that there were no lasting effects of eccentric strength exercises and that participants started each experimental session in a fully recovered state.

4.3 | Limitations and further considerations

In light of the findings, we acknowledge several factors that may have contributed, at least in part, to the overall results. For example, convenience sampling is in line with typical numbers of participants within the field. We acknowledge that the sample may have been too small to identify relatively small and transient acute effects; however, because this is the first study of its kind, our results can be used to determine sample sizes for future studies.

Moreover, as we were primarily interested in modulation of non-exercised arm (right M1), post-exercise stimulation occurred over this hemisphere first. This meant stimulation over the left hemisphere (exercised arm) commenced ∼14–15 min post-exercise (accounting for arm set-up and other factors). As studies that report changes in corticospinal and intracortical excitability often record responses in the first few (e.g. 3–5 min) minutes after exercise (e.g. Latella et al., 2020), the longer time frame in the current study may have meant that more subtle and transient changes could not be detected. However, we do note that our previous study comparing TMS-evoked responses to eccentric and concentric exercise (Latella et al., 2019) showed effects lasting up to 1-h post-exercise. Hence, it is not clear why such differences were observed between the current and previous work. One possible factor is that the isokinetic contractions performed in Latella et al. (2019) were maximal across the entire range of motion, meaning a greater mechanical stimulus was likely induced. In the current study, a paradigm based on a percentage of maximum was used, where maximum effort was intended to occur during the last repetition of each set. Moreover, the use of a free-weight dumbbell inevitably meant that the torque required to overcome the resistance changed as joint angle differed throughout each repetition. Despite this, the reduction in MVIC post-exercise appeared to be less in the previous study (ECC: ∼31%, CON: ∼23%) (Latella et al., 2019). Another point to consider is that we conducted a relatively high number of stimulation trials ($n = 20$) for each TMS-evoked outcome measure. This was chosen based on prior studies suggesting that a higher number of trials are required for reliable measurement (Biabani et al., 2018; Brownstein et al., 2018). However, this resulted in a prolonged time frame for each testing block, and therefore, transient modulatory responses may have become washed out across this period both within the same hemisphere (e.g. first minute of testing compared with 13th minute) and between hemispheres. Although all stimulation types were randomised (except for RMT assessment and LICI), the low number of trials in each block (i.e. four for each stimulus type) meant that we were not powered to analyse whether greater modulation occurred closer to exercise cessation. In the future, other TMS-based measures of cross activation (e.g. interhemispheric inhibition) may also help further elucidate any potential acute effects of unilateral eccentric exercise. Finally, we chose to obtain TMS measures with the trained muscle at rest to avoid potential alterations in neural drive associated with performing submaximal contractions after fatiguing exercise. Nevertheless, it is arguable that exercise-induced changes may be more apparent during exercise. If future studies examine this, it will require careful consideration of the level and type of contraction during testing and how to match this before and after fatiguing exercise (Clos et al., 2020; Garnier et al., 2019). Unfortunately, there appears to be no optimal testing paradigm, especially in time-sensitive experiments with multiple outcome measures. Regardless, the influence of such factors on measurement outcomes should at least be considered in future research attempting to elucidate acute, transient post-exercise responses to TMS stimulation.

5 | CONCLUSION

Collectively, the results of this study suggest that unilateral fatiguing concentric and eccentric contractions appear to elicit different effects on motor cortices corresponding to the exercised and non-exercised arm, when recorded post-exercise. However, these differences do not appear in the expected direction (i.e. lower ICF after ECC and lower RMT after CON exercise for the non-exercised arm) given the known greater effects of eccentric training on cross-education and associated neural adaptations. Further studies are required to better understand the effects of unilateral concentric and eccentric exercise training on the non-exercised M1 to elucidate whether such changes reflect the longer-term cross-education of strength.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors were responsible for the study design. OVDG, CL, JLT and KN contributed to data collection, OVDG performed data and statistical analysis, OVDG and CL drafted the manuscript, and JLT, KN, WPT and DE contributed to manuscript preparation and editing.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15897.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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