Author(s): Alibazi, Razie J.; Frazer, Ashlyn K.; Pearce, Alan J.; Tallent, Jamie; Avela, Janne; Kidgell, Dawson J.

Title: Corticospinal and intracortical excitability is modulated in the knee extensors after acute strength training

Year: 2022

Version: Accepted version (Final draft)

Please cite the original version:

Alibazi, R. J., Frazer, A. K., Pearce, A. J., Tallent, J., Avela, J., & Kidgell, D. J. (2022). Corticospinal and intracortical excitability is modulated in the knee extensors after acute strength training. Journal of Sports Sciences, 40(5), 561-570. https://doi.org/10.1080/02640414.2021.2004681

Corticospinal and intracortical excitability is modulated in the knee extensors after acute strength training.

Razie J Alibazi M.Sc[1], Ashlyn K Frazer PhD[1], Alan J Pearce PhD[2], Jamie Tallent PhD[1,3], Janne Avela PhD[4], Dawson J Kidgell PhD[1].

[1]Department of Physiotherapy, School of Primary and Allied Health Care, Faculty of Medicine, Nursing and Health Science, Monash University, Melbourne, Australia.

[2]College of Science, Health and Engineering, La Trobe University, Melbourne, Australia

[3] School of Sport, Rehabilitation and Exercise Sciences, University of Essex, Wivenhoe Park, Colchester, England.

[4]NeuroMuscular Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Finland

Address for Corresponding author:

Dawson J Kidgell, PhD.

Department of Physiotherapy, School of Primary and Allied Health Care, Faculty of Medicine, Nursing and Health Science, Monash University, PO Box 527 Frankston, Victoria, Australia, 3199.

Email: dawson.kidgell@monash.edu

ABSTRACT

The corticospinal-responses to high-intensity and low-intensity strength-training of the upper-limb are modulated in an intensity-dependent manner. Whether an intensity-dependent threshold occurs following acute strength-training of the knee extensors (KE) remains unclear. We assessed the corticospinal-responses to an acute bout of either high-intensity (85% of maximal strength) or low-intensity (30% of maximal strength) KE strength-training with measures taken during an isometric KE task at baseline, post 5, 30 and 60 minutes. Twenty-eight healthy volunteers (23 ± 3 years) were randomized to high-intensity (n = 11), low-intensity (n = 10) or to a control group (n = 7). Corticospinal-responses were evoked with transcranial magnetic stimulation (TMS) at intracortical and corticospinal levels. An acute bout of high- or low- intensity KE strength-training had no effect on maximum voluntary contraction (MVC) force post-exercise ($P > 0.05$). High-intensity training increased corticospinal excitability (range 130% to 180%) from 5-60 minutes post-exercise compared to low-intensity training (17-30% increase). Large effect sizes (ES) showed that short-interval cortical inhibition (SICI) was reduced only for the high-intensity training group from 5-60 minutes post-exercise (24-44% decrease), compared to low-intensity (ES ranges 1-1.3). These findings show a training-intensity threshold is required to adjust CSE and SICI following strength training in the lower-limb.

Key words: corticospinal excitability, exercise, intracortical inhibition, knee extension, maximal strength.

INTRODUCTION

It is axiomatic that short-term strength training (i.e., 4-8 weeks) is associated with increases in muscle strength (Tallent, Woodhead et al. 2021). However, during the early phases of strength development, gains in strength cannot be explained completely by muscular factors alone (Siddique, Rahman et al. 2020). Rather, much of the initial increase in strength is due to subtle changes along the neuroaxis which include a change in plasticity at supraspinal (Latella, Kidgell et al. 2012, Weier, Pearce et al. 2012) and spinal levels (Aagaard, Simonsen et al. 2002). Common short-term neural adaptations to strength training include increased muscle activation as assessed by increased integrated electromyography (EMG) (Moritani and deVries 1979, Narici, Roi et al. 1989), increased recruitment and/or discharge rates of spinal motoneurons (Del Vecchio, Casolo et al. 2019), reduced co-contraction of antagonists (Mason, Howatson et al. 2019), changes in corticospinal excitability (CSE) and inhibition as assessed by transcranial magnetic stimulation (TMS) (Siddique, Rahman et al. 2020).

From only a single set of strength training (Ruotsalainen, Ahtiainen et al. 2014) and following a single session of strength training, recent studies using TMS have reported a modulation in neuroplasticity of the corticospinal tract (CST) (Latella, Teo et al. 2017, Mason, Frazer et al. 2019, Mason, Frazer et al. 2019, Mason, Howatson et al. 2019, Ansdell, Brownstein et al. 2020, Colomer-Poveda, Hortobágyi et al. 2020). TMS involves passing single or paired magnetic pulses over the primary motor cortex (M1) by placing a magnetic coil on the scalp. The magnetic pulse propagates volleys of action potentials along the CST and peripheral motor nerve (Di Lazzaro, Oliviero et al. 2004), which in turn causes a motor response in the associated target muscle (Di Lazzaro and Rothwell 2014). The motor response is recorded from the target muscle via EMG and is termed the motor-evoked potential (MEP). The muscle activity generated by TMS is dependent on neuronal excitability in both the M1 and spinal cord, and is typically considered a measure of CSE (Chen 2000, Kobayashi and Pascual-Leone 2003).

Paired-pulse TMS assess the excitability of intrinsic intracortical connections within the M1 (Di Lazzaro and Ziemann 2014). Depending on the inter-stimulus interval between the conditioning and test pulse, paired-pulses can measure the excitability of the intracortical micro-circuitry of M1 in particular short-interval intracortical inhibition (SICI) (e.g., 2-5ms) and long-interval intracortical inhibition (LICI) (e.g., 100-150ms) as well as the intracortical facilitatory (ICF) circuits (e.g., 8-15ms). Adjustments in SICI have been reported to be critical in the selective activation of muscles and the conditioned MEP increases with increasing force levels (Stinear and Byblow 2003); thus, changes in SICI may occur in a intensity-specific manner following strength training. For this reason, the current study assessed SICI following a single session of either high- or low-intensity strength training in an attempt to determine the training intensity effects on modulating SICI as a potential acute neural adaptation to strength training.

Relatively few studies have examined the corticospinal responses to a single session of strength training, and the existing evidence is conflicting (Brandner, Warmington et al. 2015, Leung, Rantalainen et al. 2015, Latella, Hendy et al. 2016, Nuzzo, Barry et al. 2016, Latella, Goodwill et al. 2019). Increases in CSE have been reported when

TMS is applied during muscle activity following high-intensity (i.e., heavy-load) strength training of the biceps brachii (Brandner, Warmington et al. 2015, Leung, Rantalainen et al. 2015, Latella, Teo et al. 2017, Mason, Frazer et al. 2019, Colomer-Poveda, Hortobágyi et al. 2020, Ruotsalainen, Ahtiainen et al. 2014), but there is limited evidence for the lower-limb muscles (Ansdell, Brownstein et al. 2020). The inhibitory responses to a single session of strength training are even less well characterized (Leung, Rantalainen et al. 2015, Ruotsalainen, Ahtiainen et al. 2014, Mason, Frazer et al. 2018, Latella, Goodwill et al. 2019, Mason, Frazer et al. 2019), but there is emerging evidence that SICI is reduced by a single session of strength training in the upper-limb (Hendy and Kidgell 2014, Brandner, Warmington et al. 2015, Leung, Rantalainen et al. 2015, Latella, Goodwill et al. 2019). However, the findings are limited and inconsistent (Latella, Teo et al. 2017, Latella, Goodwill et al. 2019) and there is only one study that reported null findings in the lower-limb (Ansdell, Brownstein et al. 2020). Latella et al. (2019) reported that, following heavy-load eccentric strength training of the biceps brachii, the conditioned MEP responses increased for both the SICI and LICI paradigm. However, this is in contrast to previous findings from the same research group which indicated no change in SICI or LICI following heavy-load isotonic training of the biceps brachii (Latella, Teo et al. 2017). More recently, Ansdell, Brownstein et al. (2020) reported that a single session of squat training had no effect on CSE and SICI, but increased spinal excitability as assessed by lumbar-evoked potentials (LEPs).

Given that strength training is one of the most robust methods for improving muscular fitness, manipulating the acute training variables, such as relative intensity (i.e., percentage of one-repetition maximum), could be a critical determinant of the type (i.e., reduced inhibition) of neural adaptation to strength training. Therefore, determining the neural adaptations to high-intensity and low-intensity strength training appears important. Most previous research has only focused on the acute corticospinal responses to high-intensity strength training of the upper-limb (Leung, Rantalainen et al. 2015, Latella, Hendy et al. 2016, Nuzzo, Barry et al. 2016, Latella, Goodwill et al. 2019), therefore, there is a need to determine the corticospinal responses following both high- and low-intensity strength training of the lower-limb. Given that low-intensity compared with high-intensity strength training can also improve muscle strength (Schoenfeld, Ogborn et al. 2017) and because the hypertrophy response to strength training seems to be independent of relative intensity (Lopez, Radaelli et al. 2021), the differences in the increase in muscle strength brought about by low- and high-intensity strength training, may be related to modifications in the corticospinal responses to strength training.

To address this gap in the literature, two recent studies reported that there is a dose-response relationship between isometric strength training and CSE of the elbow flexors (Colomer-Poveda, Romero-Arenas et al. 2019; Colomer-Poveda, Romero-Arenas et al. 2020). Of important note is the Colomer-Poveda, Romero-Arenas et al. (2020) study which reported no changes in the intracortical response (SICI or ICF) following strength training at different strength training intensities (Colomer-Poveda, Romero-Arenas et al. 2020). Thus, one of the aims of the current study was to assess the intracortical responses (SICI) following high- and low-intensity strength training of the lower-limb. In regards to the two previous intensity-related studies that reported changes in CSE following high-intensity training,

the type of exercise employed may explain the null finding of no change in CSE following low-intensity strength training. Previously, it has been suggested that dynamic rather than isometric contractions activate the M1 more strongly and sustainably throughout the contraction (Gwin and Ferris 2012).

As it stands, there is limited evidence on the acute effects of lower-limb strength training on CSE and SICI and there is no experimental data for the effects of low-intensity lower-limb strength training on the corticospinal responses. Understanding the acute neural responses of the lower-limb muscles to strength training will pave the way to prescribe effective and targeted exercise guidelines for the management of neuromuscular pathology of the lower-limbs. This is important because sufficient knee extensor torque is required for the successful completion of many activities of daily living (e.g., locomotion, chair sitting and rising, and stair climbing) and athletic tasks, so it is an important muscle group to study. Therefore, the aim of this study was to identify the acute corticospinal responses (CSE and SICI) following an acute bout of either low- or high-intensity KE strength training. Based upon our previous experiments (Mason, Frazer et al. 2019), where we showed that heavy-load strength training compared to light-load strength training of the elbow flexors modulated SICI in an intensity-specific manner, we hypothesized that high-intensity strength training (85% 1-repetition maximum) would increase CSE and reduce SICI, whilst low-intensity strength training (<30% 1-RM), would increase CSE and have no effect on SICI.

Methods:

Experimental Approach and Participants

Figure 1 outlines the experimental design. Before commencing the study, participants underwent a familiarization session that involved: (a) anthropometric measurements of height and weight; (b) strength testing to evaluate maximal voluntary isometric strength of the knee extensors (MVC); and (c) exposure to TMS, surface electromyography (sEMG), and peripheral nerve stimulation. After this visit, in a randomized-control design, participants attended the laboratory once, which was separated by seven days from the familiarization session. A purpose-made Excel macro was used to randomize participants to the experimental groups. Participants were randomly allocated to a control group (n = 7, 2 females, 5 males), low-intensity strength training (n = 10, 3 females, 7 males) and high-intensity strength training group (n = 11, 4 females, 7 males) that involved a single-bout of strength training of the KE. Participants were selected on a voluntary basis and all experiments were conducted according to the standards established by the Declaration of Helsinki, and the project was approved by the University Human Research Ethics Committee (ID:11882). Twenty-eight healthy participants (9 females and 19 males, aged 23 ± 3 years, height 176 ± 11cm and body mass of 73 ± 15kg) took part in this study without any known history of neurological impairment or current physical illness or injuries, and all participants provided informed consent prior to the commencement of the study. Overall, subjects had little or no history of strength training and were included if they had not participated in strength training within the last six months. Participants were screened for contraindication to TMS and strength training (Chipchase, Schabrun et al. 2012). Only one of the participants reported that they had been completing strength training of the KE > 1 day per week two months

before data collection. Consequently, they were randomly allocated to either the control group or low-intensity strength training group.

Insert Figure 1

Maximum Isometric Strength Testing

The order of strength testing (i.e., dynamic and isometric testing) was randomized across participants. Maximum isometric torque (maximum voluntary contraction) of the quadriceps femoris was determined prior to (T_{0min}) and following the training intervention at T_{5min} (Post 5 min), T_{30min} (Post 30 min) and T_{60min} (Post 60 min) using an isokinetic dynamometer (Biodex system 4 Pro, Biodex Medical Systems, Shirley, NY, USA). All participants completed a warm-up that consisted of 5 minutes of cycling on a cycle-ergometer at an intensity of 70% age-predicted maximum heart rate (± 5 beats·per·min), and five warm-up leg extensions with gradually increasing weight. Participants were placed in a seated position with a trunk-thigh angle of 110°. The axis of the dynamometer was then aligned with the anatomical axis of the knee joint, and the leg was fastened to the dynamometer lever arm using a padded strap positioned 1 cm superior to the malleoli of the ankle. To ensure that the trunk was stabilized during testing, a waist strap and two cross-over shoulder straps were used. During isometric testing, the knee was positioned at a 60° angle and the participant was required to perform three maximal isometric leg extensions for 5 seconds with 2 minutes rest period between each repetition. Verbal instructions and encouragement were provided to ensure that each participant achieved their true MVC. The highest peak torque of the three trials was taken and recorded as the participants MVC torque. Only the dominant limb was tested.

Dynamic Strength Testing

Participants completed a bilateral one-repetition maximum knee extension strength test (1RM) through a full range of motion (Nautilus Nitro® Plus Leg Extension, Vancouver, WA, USA). Prior to commencing the knee extension tests, participants completed a warm up that involved completing 10 repetitions at 50% of their estimated knee extensor 1RM. Following this, participants then completed a single repetition, whereby each single repetition progressed with heavier loads until failure, which was defined as the final load that could be lifted successfully with correct technique where an additional 0.5–5.0 kg could not be successfully lifted. Between each 1RM trial, a 2-minute recovery period was allocated and, in general, participants took between four to six attempts to determine their 1RM. The maximum weight lifted was then used to calculate the training-intensity for the single session of strength training for both the high-intensity (85% 1RM) and low-intensity (30% 1RM) training groups. 1RM testing was only performed at baseline (T_{0min}).

Strength Training Protocol

Participants in the high-intensity (relative load-intensity of 1RM) group were required to exercise at 85% 1RM (average load was 67 ± 17 Kg). Participants performed four sets of 6-8 repetitions of bilateral knee extension, separated by 2-minutes rest between sets. Participants in the low-intensity (relative load-intensity) group were required to exercise at 30% 1RM (average load was 24 ± 6 Kg). Participants performed four sets of 30 repetitions separated by 30 seconds rest between sets. The total time to complete the high-intensity training was 9 minutes,

and it was 6.5 minutes in the low-intensity group. The total load-volume (weight × repetitions) for the high-intensity group was 2,156 ± 533 and 2,836 ± 725 for the low-intensity group, respectively. Participants in the control group were sitting in a chair in the laboratory for 10 minutes.

Electromyography

Surface electromyography (sEMG) was recorded from the right (dominant) rectus femoris muscle using bipolar Ag-AgCl electrodes (Brownstein, Ansdell et al. 2018). The area of electrode placement was shaved to remove fine hair, rubbed with an abrasive skin gel to remove dead skin, and then cleaned with 70% isopropyl alcohol. The site of measurement for the rectus femoris was determined by marking the skin three-fifths of the distance between the anterior superior iliac spine (ASIS) and the upper border of the patella, with an inter-electrode distance (centre to centre) of 20 mm. The reference electrode was placed on the patella to ensure no muscle activity was recorded. sEMG signals were measured with an impedance meter to ensure impedance did not exceed 10 kΩ prior to testing. sEMG signals were amplified (×1,000), bandpass filtered (high pass at 13 hz, low pass at 1,000 Hz), digitized online at 2 kHz for 1 s, recorded and analysed using Powerlab 4/35 (ADInstruments, Bella Vista, Australia).

Transcranial magnetic stimulation

Single- and paired-pulse TMS was delivered over the M1 via a concave double-cone coil using a Magstim 200^2 magnetic stimulator (Magstim Co., Ltd, Whitland, UK). The junction of the double-cone coil was placed 1–2 cm left of the vertex and oriented to induce posterior-to-anterior cortical current flow. Sites near the estimated centre of the rectus femoris area (motor hotspot) were explored to determine the sites at which the largest MEP amplitude was evoked and active motor threshold (AMT) was established as the intensity at which at least 5 of 10 stimuli produced MEP amplitudes of greater than 200 μV (Kidgell, Stokes et al. 2010) during a low-level isometric contraction. After the single session of strength training, AMT was retested and adjusted if required. To ensure all stimuli were delivered to the optimal motor hotspot throughout testing, the position of the coil was marked.

All stimuli were delivered during low-level isometric contraction of the KE, which were performed by exerting 10% of their pre-determined MVC torque as indicated by a visual line representing voluntary KE force on a computer monitor connected to an isokinetic dynamometer (Biodex system 4 Pro, Biodex Medical Systems). Root mean square (rms) of the rectus femoris electromyogram (EMG) was obtained 100 ms before the delivery of each TMS stimulus to ensure that there were no changes in pre-stimulus rmsEMG prior to, and following, KE training which may have altered the MEP amplitude.

Assessment of CSE: Single-pulse TMS-induced MEPs

Once AMT was established, ten single-pulse TMS induced MEPs were recorded using 130% AMT before (T_{0min}), post 5 min (T_{5min}), 30 min (T_{30min}) and 60 min (T_{60min}) after the training (Ansdell, Brownstein et al. 2020). Providing 10 single-pulse MEPs has been shown to be a reliable number to estimate CSE (Ansdell, Brownstein et al. 2020). Each stimulus was delivered in random intervals every 10 to 12 seconds to avoid stimulus anticipation. The average

stimulator intensity was 55% of maximal stimulator output (MSO) for high-intensity and low-intensity training and 50% MSO for the control group.

Assessment of Short-Interval Intracortical Inhibition

SICI was assessed by a TMS paired-pulse protocol, including 10 stimuli with an interstimulus interval of 3 ms (Brownstein, Ansdell et al. 2018). In this protocol, SICI was assessed by combining a subthreshold conditioning stimulus (70% AMT) with a suprathreshold test stimulus (130% AMT).

Percutaneous Nerve Stimulation

Direct muscle responses were obtained under resting conditions from the right rectus femoris by supra-maximal percutaneous electrical stimulation of the femoral nerve approximately 3-5 cm below the inguinal ligament in the femoral triangle. A digitimer (Hertfordshire. UK) DS7A constant-current electrical stimulator (pulse duration 1 ms) was used to deliver each electrical pulse. The cathode was placed over the femoral nerve in the femoral triangle with the anode positioned between the greater trochanter and iliac crest. An increase in current strength was applied to the femoral nerve until there was no further increase in the amplitude of sEMG response (M_{MAX}). To ensure maximal responses, the current was increased an additional 20% and the average M_{MAX} was obtained from five stimuli, with a period of 6-9 seconds separating each stimulus (Ansdell, Brownstein et al. 2020)

Data Analysis

The peak-to-peak amplitude of MEPs evoked as a result of stimulation was measured in the dominant right rectus femoris muscle contralateral to the cortex being stimulated in the period 10-50 ms after stimulation. MEP amplitudes were analysed (LabChart 8 software, ADInstruments, Australia) after each stimulus was automatically flagged with a cursor, providing peak-to-peak values in μV, averaged and normalized to the maximum compound wave (M_{MAX}), and multiplied by 100. SICI was quantified as the size of the conditioned paired-pulse MEP expressed relative to the size of the unconditioned MEP and multiplied by 100.

Statistical Analysis

The target sample size was based on an *a priori* calculation, which included the observed effect size from our previous experiments (Mason, Frazer et al. 2019). The number of subjects to be included in the study was computed using an α level of 0.05, a β level of 0.80, and an effect size of 0.8. In previous experiments, samples sizes around 10 have been adequate to observe statistically significant changes in MEPs and SICI following unilateral strength training (Mason et al. 2019).

All data were first screened to ensure they were normally distributed. To have sufficient data to test for questions of normality, all data from baseline MEPs, SICI, and MVC trials were used to establish the distributional properties. The Shapiro-Wilk test suggested that CSE for the low-intensity group was not normally distributed ($W = 0.75$; $P = 0.003$). However, this violation was mild after examining frequency histograms and detrended Q-Q plots, and was

not sufficient to warrant a more conservative analytical strategy; thus, it was decided to treat the data as essentially normally distributed. The remaining variables showed no variable z-scores of skewness or kurtosis. A one-way analysis of variance (ANOVA) was conducted on all baseline values, which included CSE (motor-evoked potential expressed as percentage of M_{MAX}), SICI (expressed as a percentage of the test response) and MVC torque to ensure that there were no differences between groups. Mixed factorial ANOVA appropriate for a 3 × 4 design (three groups [high-intensity, low-intensity, and control]) and four time points (Baseline testing [T_{0min}], post testing 5 min [T_{5min}], post testing 30 min [T_{30min}] and post testing 60 min [T_{60min}]), comparing multiple outcome measures (MVC strength, corticospinal excitability, and SICI) was used. If significant main effects were found, post-hoc analysis (Bonferroni correction) was used to compare means within (time effects) and between groups (interaction effects). An independent samples *t*-test was used to see if there were any difference in training load-volume between the high-intensity and low-intensity groups. For all comparisons, effect sizes (ES) of 0.2, 0.5, and 0.8 were established to indicate small, moderate, and large comparative effects (Cohen's *d*), respectively (Cohen, 1992). There were no outliers, as assessed by examination of studentized residuals for values greater than ±3. All data are presented as mean ± 95% confidence intervals (CI).

Results:

Isometric, Dynamic Knee Extensor Strength and Load-Volume

Figure 2 shows the mean change ± 95% CI for isometric KE torque. At baseline, there were no differences in KE MVC ($F_{2, 24}$ = 1.128, P = 0.34) or 1RM dynamic strength ($F_{2, 24}$ = *0.19*) detected between groups. Baseline KE MVC torque for the high-intensity group was 161 ± 43 N·m, low-intensity 154 ± 38 N·m and control 180 ± 46 N·m. Baseline KE 1RM strength for the high-intensity group was 80 ± 19 Kg and for the low-intensity group it was 78 ± 20 kg. After the acute bout of strength training, there were no main effects of Group ($F_{2, 24}$ = 0.70, P = 0.51); Time ($F_{3, 61}$ = 0.41, P = 0.71; or Group × Time interactions for KE MVC ($F_{6, 72}$ = 0.78, P = 0.58, Figure 2). There was a significant difference in the load-volume between the high-intensity and low-intensity groups, with the low-intensity group having a greater overall load-volume compared to the high-intensity group (t = 2.5, df=19, P = 0.02, g = 0.40)

Insert Figure 2

M_{MAX}

There were no significant differences in M_{MAX} between groups at baseline ($F_{2, 25}$ = 0.05, P = 0.95) and no main effects for Group ($F_{2,25}$ = 0.0052, P = 0.99), Time ($F_{2.5, 61}$ = *1.3*, P = 0.28) or Group × Time ($F_{6, 75}$ = *2.3*, P = 0.47, Table 1).

Active Motor Threshold

There were no significant differences in active motor threshold between groups at baseline ($F_{2, 25}$ = 0.13, P = 0.87) and no main effects for Group ($F_{2, 25}$ = 0.52, P = 0.66), Time ($F_{3, 53}$ = 0.16, P = 0.86) or Group × Time interactions ($F_{6, 74}$ = 0.23, P = 0.96, Table 1).

SICI ratio

No differences in SICI were detected at baseline between groups ($F_{2, 24}$ = 0.83, P = 0.44; Figure 3). Following the acute strength training bout, there was a Group × Time interaction ($F_{6, 74}$ = 3.0, P = 0.01), however, there were no main effect for Time ($F_{3, 52}$ = 0.8, P = 0.45) or any Group interactions, despite a trend ($F_{2,25}$ = 3.1, P = 0.06, Figure 3). Post hoc Bonferroni pairwise comparisons showed that SICI was reduced following high- compared to low-intensity training at all post time points (all P < 0.05, Table 2). SICI decreased at T_{5min} following high-intensity training compared to low-intensity training (mean difference 22, 95% CI 3.8 to 41; P = 0.01; g = 1.29), but not compared to control, despite a large effect size (mean difference 9.4, 95% CI -25 to 43; P = 0.75; g = 1.03). At T_{30min} SICI was still reduced for the high-intensity group compared to low- intensity (mean difference 18, 95% CI 2.2 to 33; P = 0.02; g = 1.16), but not compared to control (mean difference 15, 95% CI - 5.6 to 35; P = 0.17; g = 1.15). At T_{60min} SICI was reduced compared to low-intensity training (mean difference 20, 95% CI 1.5 to 38, P = 0.03, g = 1.17, Table 2).

Insert Figure 3

Corticospinal Excitability

Figure 4 displays the mean and 95% CI for changes in CSE. At baseline, there were no significant differences in CSE between groups ($F_{2, 24}$ = 0.83, P = 0.44, Table 1). The Mixed-Factorial ANOVA revealed a main effect for Time ($F_{1.6, 36}$ = 6.5, P = 0.007), Group ($F_{2, 24}$ = 6.3, P = 0.006) and a Group × Time interaction ($F_{6, 69}$ = 9.6, P < 0.001). Bonferroni post hoc analysis revealed that CSE for the high-intensity group increased ($F_{3, 30}$ = 24.41, P < 0.001, g = 0.71) at T_{5min} (mean difference 39, 95% CI 16 to 63, P = 0.02, g = 1.5), T_{30min} (mean difference 54, 95% CI 26 to 83, P <0.001, g = 1.3) and T_{60min} (mean difference 41, 95% CI 17 to 65, P = 0.002, g = 1.6) when compared to the control and low-intensity groups (all P < 0.001, Table 2).

Insert Figure 4

Discussion:

The aim of the present study was to determine the effects of acute unilateral strength training of the KE at high- and low-intensity compared to a resting control group on CSE and SICI. The main finding shows that high-intensity strength training of the KE increased CSE and reduced SICI for up to 60-minutes post-training. These findings are in contrast to previous studies in the upper-limb (Mason, Frazer et al. 2019) and recently for the lower-limb (Ansdell,

Brownstein et al. 2020). Unlike the elbow flexors, low-intensity strength training did not induce any change in CSE or SICI indicating that modulation of the CST in the lower-limb is intensity dependent and possible related to the functional role of the KE (i.e., force producing). This finding is interesting because skill training, a seemly low-intensity task reduces SICI which suggests there may be motor learning or skill acquisition adaptations that occur, but are not present during low-intensity strength training of the lower-limb (Mason, Frazer et al. 2019).

The present findings suggest that a single session of KE strength training increases the responsiveness of the CST to stimulation. This increase is likely due to some level of change in plasticity at the M1 and motoneuron pool that manifests as improved synaptic efficacy with the CST (Nuzzo, Barry et al. 2016). Our results are in line with previous acute strength training studies, whereby training-intensity appears to be an important acute strength training variable to modulate the corticospinal pathway (Colomer-Poveda, Hortobágyi et al. 2020). The present data confirm the previously described effect of training intensity in the upper-limb by showing that a training intensity of greater than 75% maximum appears to be the threshold for acute strength training to produce meaningful changes in CSE (Colomer-Poveda, Hortobágyi et al. 2020), suggesting a similar threshold is required for the lower-limb. Despite this, our findings are in contrast to a recent KE strength training study where an acute bout of squat training had no effect on CSE; rather, there was an increase in spinal excitability (Ansdell, Brownstein et al. 2020). Although unlikely, there are some differences between the current study and that of Ansdell, Brownstein et al. (2020) that may in part explain the discrepant findings. For example, we performed strength training of the KE using an isolated leg extension exercise whilst Ansdell, Brownstein et al. (2020) performed squat training, but it is unclear how the corticospinal responses would differ between the two exercises. Further, it has been reported that the assessment of the corticospinal pathway should have a degree of relative specificity to the training task (Brownstein, Ansdell et al. 2018); however, both the current study and Ansdell, Brownstein et al. (2020) matched training and testing to reduce this bias. The only difference that may account for the disparity of responses for the lower-limb could be the target muscle used to produce MEPs. In the current study, we recorded evoked-responses from the rectus femoris with the knee at 60º optimizing the moment arm of the extensor mechanism (Oatis 2016), whilst previous research used 90º (Ansdell, Brownstein et al. 2020). In addition, it seems that there was a sufficient level of fatigue, depicted by the decrease in MVC force post strength training in the Ansdell, Brownstein et al. (2020) study, which was not the case for the present study. Also, the timing of the post TMS measures were different, with the current study recording MEPs five minutes post the last set of strength training, whilst previous research measured MEPs immediately post. However, a potential limitation is we did not measure corticospinal activity at a force level that matched training intensity. Despite this, evidence now suggests that even at 50% MVC, SICI is abolished in the rectus femoris (Brownstein, Ansdell et al. 2018), which underscores this limitation.

Although we have reported facilitated MEPs, the functional relevance of this is unclear (Hortobágyi, Granacher et al. 2020) and there are likely to be other sites of plasticity within the nervous system that may also be modulated. For example, increases in lumbar evoked potentials (LEPs), corticomedullary-evoked potentials (CMEP) and

CMEP-twitch forces also increase following acute strength training (Nuzzo, Barry et al. 2016, Colomer-Poveda, Romero-Arenas et al. 2019, Ansdell, Brownstein et al. 2020, Colomer‐Poveda, Hortobágyi et al. 2020).

Similar to our previous upper-limb study (Mason, Frazer et al. 2019), it seems that training-intensity may be important for modulating the excitability of the short-latency inhibitory network of the M1. In the present study, we report large comparative effects for reduced SICI post high-intensity strength training, but not following low-intensity strength training. Overall, the acute effect of strength training on modulating SICI is not consistent (Mason, Frazer et al. 2019). Our findings are consistent with Latella et al., (2018) and Mason et al., (2019), but in contrast to Latella et al. (2017), Ansdell et al. (2020) and Colomer-Poveda et al. (2020). It is unclear why these inconstancies are present, but it is likely related to several factors around TMS methodology, type of strength training employed, and muscles used which likely have divergent corticospinal inputs (Brower and Ashby 1990). Irrespective of these findings, it seems that high-intensity KE training targets neurons within the cortex that use $GABA_A$ as their neurotransmitter, thus reducing the inhibitory synaptic efficacy between intracortical inhibitory neurons and corticospinal neurons (Weier, Pearce et al. 2012). Reduced synaptic efficacy between inhibitory interneurons and corticospinal neurons likely improves synaptic efficacy of the corticospinal synapse, leading to increased MEPs and potential spinal excitability (Ansdell, Brownstein et al. 2020). Reducing the net inhibitory input to the spinal motoneuron pool, by default, should increase the responsiveness of the corticospinal tract and spinal motoneuron pool to TMS in the period following acute strength training. This finding agrees with previous upper-limb studies (Nuzzo, Barry et al. 2016, Colomer-Poveda, Romero-Arenas et al. 2019, Colomer‐Poveda, Hortobágyi et al. 2020) whereby the corticospinal response is potentiated; however, this is a new finding for the lower-limb.

Although we have reported increased corticospinal excitability, this finding is only evident following high-intensity training. This agrees with recent upper-limb studies where low-intensity training did not modulate the intrinsic motor circuits (MEP amplitude or SICI) of the corticospinal pathway (Colomer‐Poveda, Hortobágyi et al. 2020). Interestingly, unlike our previous finding where low-intensity training increased CSE, low-intensity training of the KE had no effect. In the present study, we saw no reduction in MVC or M_{MAX}, both of which are proxy measures for fatigue, suggesting that, at least for the KE, low-intensity training has no effect on the corticospinal pathway. However, a caveat to this interpretation is that we did not measure 1RM KE strength following strength training, thus we are unclear if there was an intensity-specific reduction in 1RM that may suggest fatigue was present. Nonetheless, the primary purpose of the study was not to assess fatigue and low-intensity training still had no effect on the TMS responses.

It is unclear why there were no changes in CSE or SICI following low-intensity training as other motor tasks, such as visuomotor tracking and ballistic motor tasks, modulate CSE, SICI and silent period (Leung, Rantalainen et al. 2015, Mason, Frazer et al. 2019). In addition, early experimental work has shown that mechanisms associated with central fatigue recover within three minutes, thus we cannot be certain that we have captured all the acute

responses to strength training (Woods, Furbush, 1987). Despite this, at a minimum, this finding suggests that the adaptive responses of the lower-limb may be more sensitive to the parameters of the motor task compared to the upper-limb. The differential responses observed in the lower-limb, compared to the upper-limb following low- and high-intensity exercise, suggest that the high-intensity protocol distinctively and separately targets cortical neurons that use both glutamate and $GABA_A$ to increases the excitability of the corticospinal pathway. Because fatigue was not evident after five minutes in both protocols, it seems that the unique demand of high-intensity training is the primary mechanism modulating the corticospinal responses to acute lower-limb strength training. Recent experimental evidence supports this notion, whereby training-intensity is contingent for increasing the excitability of the corticospinal pathway (Colomer-Poveda, Romero-Arenas et al. 2019, Colomer‐Poveda, Hortobágyi et al. 2020).

In light of the above, there are several limitations that should be considered when interpreting the data. Despite the sustained increase in CSE following high-intensity compared to the low-intensity training and control groups, the moderate width of the confidence interval suggests variable responses to acute strength training. This is certainly consistent with the effect sizes that we have reported (Herbert 2019). In addition, given the recent findings of facilitated LEPs (Ansdell, Brownstein et al. 2020), the increase in CSE could well be due to increased spinal excitability. Certainly, a limitation of MEPs is that they are influenced by several factors from the cortex to the muscle itself, namely the excitability of the corticospinal neurons and the efficacy of intracortical inhibitory neurons that are activated by TMS, and the excitability of interneurons located between corticospinal neurons and α-motoneurons, etc. (Di Lazzaro, Oliviero et al. 2004). Finally, it appears that there are likely several subtle adaptations or responses that occur within the nervous system (i.e., cortical, reticulospinal, spinal, and motor unit levels), and we have only examined the excitability of the corticospinal pathway. Certainly, emerging evidence suggest that the reticulospinal tract may also play a prominent role in both acute and chronic neural responses/adaptations to strength training (Glover and Baker 2020).

This is the only study that has examined the acute effect of strength training intensity on the corticospinal responses of the KE. The findings overall suggest that, at least for the KE, there is training-intensity dependent increase in CSE and a reduction in SICI. This finding is in partial agreement to the findings of the upper limb (Mason, Frazer et al. 2019), but in contrast to the findings of Ansdell, Brownstein et al. (2020) and Colomer-Poveda, Hortobágyi et al. (2020). Determining these early neural responses to strength training may provide a pathway to recognizing the longer-term training responses to strength training. Understanding how these responses relate to the development of strength will enable the establishment of targeted guidelines for exercise prescription following neuromuscular injury to the lower-limb.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References:

1. Aagaard, P., E. B. Simonsen, J. L. Andersen, P. Magnusson and P. Dyhre-Poulsen (2002). "Neural adaptation to resistance training: Changes in evoked V-wave and H-reflex responses." Journal of Applied Physiology **92**(6): 2309-2318.
2. Ansdell, P., C. G. Brownstein, J. Škarabot, L. Angius, D. Kidgell, A. Frazer, K. M. Hicks, R. Durbaba, G. Howatson and S. Goodall (2020). "Task-specific strength increases after lower-limb compound resistance training occurred in the absence of corticospinal changes in vastus lateralis." Experimental physiology **105**(7): 1132-1150.
3. Brandner, C. R., S. A. Warmington and D. J. Kidgell (2015). "Corticomotor Excitability is Increased Following an Acute Bout of Blood Flow Restriction Resistance Exercise." Front Hum Neurosci **9**: 652.
4. Brouwer, B, Ashby, P (1990). Corticospinal projections to upper and lower limb spinal motoneurons in man. "Electroencephalography and Clinical Neurophysiology" **76**(6):509-519.
5. Brownstein, C. G., P. Ansdell, J. Škarabot, A. Frazer, D. Kidgell, G. Howatson, S. Goodall and K. Thomas (2018). "Motor cortical and corticospinal function differ during an isometric squat compared with isometric knee extension." Experimental physiology **103**(9): 1251-1263.
6. Brownstein, C.G Ansdell,P, Škarabot, J, Howatsona, G, Goodall, S, Thomas, K (2018). "An optimal protocol for measurement of corticospinal excitability, short intracortical inhibition and intracortical facilitation in the rectus femoris." Journal of the Neurological Sciences 15**(394)**:45-56.
7. Chen, R. (2000). "Studies of human motor physiology with transcranial magnetic stimulation." Muscle Nerve Suppl **9**: S26-32.
8. Chipchase, L., S. Schabrun, L. Cohen, P. Hodges, M. Ridding, J. Rothwell, J. Taylor and U. Ziemann (2012). "A checklist for assessing the methodological quality of studies using transcranial magnetic stimulation to study the motor system: An international consensus study." Clinical Neurophysiology **123**(9): 1698-1704.
9. Cohen J. Statistical power analysis. Curr Dir Psychol Sci. 1992;1(3):98–101.
10. Colomer-Poveda, D., S. Romero-Arenas, J. Lundbye-Jensen, T. Hortobágyi and G. Márquez (2019). "Contraction intensity-dependent variations in the responses to brain and corticospinal tract stimulation after a single session of resistance training in men." Journal of Applied Physiology **127**(4): 1128-1139.
11. Colomer-Poveda, D., T. Hortobágyi, M. Keller, S. Romero-Arenas and G. Márquez (2020). "Training intensity-dependent increases in corticospinal but not intracortical excitability after acute strength training." Scandinavian journal of medicine & science in sports **30**(4): 652-661.
12. Del Vecchio, A., A. Casolo, F. Negro, M. Scorcelletti, I. Bazzucchi, R. Enoka, F. Felici and D. Farina (2019). "The increase in muscle force after 4 weeks of strength training is mediated by adaptations in motor unit recruitment and rate coding." The Journal of physiology 597(7): 1873-1887.
13. Di Lazzaro, V., A. Oliviero, F. Pilato, E. Saturno, M. Dileone, P. Mazzone, A. Insola, P. Tonali and J. Rothwell (2004). "The physiological basis of transcranial motor cortex stimulation in conscious humans." Clinical neurophysiology **115**(2): 255-266.

14. Di Lazzaro, V. and J. C. Rothwell (2014). "Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex." The Journal of physiology **592**(19): 4115-4128.
15. Glover, I. S. and S. N. Baker (2020). "Cortical, Corticospinal, and Reticulospinal Contributions to Strength Training." Journal of Neuroscience **40**(30): 5820-5832.
16. Gwin, J. T. and D. P. Ferris (2012). "An EEG-based study of discrete isometric and isotonic human lower limb muscle contractions." J Neuroeng Rehabil **9**: 35.
17. Hendy, A. M. and D. J. Kidgell (2014). "Anodal-tDCS applied during unilateral strength training increases strength and corticospinal excitability in the untrained homologous muscle." Exp Brain Res **232**(10): 3243-3252.
18. Herbert, R. (2019). "Research Note: Significance testing and hypothesis testing: meaningless, misleading and mostly unnecessary." J Physiother **65**(3): 178-181.
19. Hortobágyi, T., U. Granacher, M. Fernandez-del-Olmo, G. Howatson, A. Manca, F. Deriu, W. Taube, M. Gruber, G. Márquez and D. Colomer-Poveda (2020). "Functional relevance of resistance training-induced neuroplasticity in health and disease." Neuroscience & Biobehavioral Reviews.
20. Kidgell, D. J., M. A. Stokes, T. J. Castricum and A. J. Pearce (2010). "Neurophysiological responses after short-term strength training of the biceps brachii muscle." J Strength Cond Res **24**(11): 3123-3132.
21. Kobayashi, M. and A. Pascual-Leone (2003). "Transcranial magnetic stimulation in neurology." Lancet Neurol **2**(3): 145-156.
22. Latella, C., A. M. Goodwill, M. Muthalib, A. M. Hendy, B. Major, K. Nosaka and W. P. Teo (2019). "Effects of eccentric versus concentric contractions of the biceps brachii on intracortical inhibition and facilitation." Scand J Med Sci Sports **29**(3): 369-379.
23. Latella, C., A. M. Hendy, A. J. Pearce, D. VanderWesthuizen and W. P. Teo (2016). "The Time-Course of Acute Changes in Corticospinal Excitability, Intra-Cortical Inhibition and Facilitation Following a Single-Session Heavy Strength Training of the Biceps Brachii." Front Hum Neurosci **10**: 607.
24. Latella, C., D. J. Kidgell and A. J. Pearce (2012). "Reduction in corticospinal inhibition in the trained and untrained limb following unilateral leg strength training." Eur J Appl Physiol **112**(8): 3097-3107.
25. Latella, C., W.-P. Teo, D. Harris, B. Major, D. VanderWesthuizen and A. M. Hendy (2017). "Effects of acute resistance training modality on corticospinal excitability, intra-cortical and neuromuscular responses." European journal of applied physiology **117**(11): 2211-2224.
26. Leung, M., T. Rantalainen, W.-P. Teo and D. Kidgell (2015). "Motor cortex excitability is not differentially modulated following skill and strength training." Neuroscience **305**: 99-108.
27. Lopez, P., R. Radaelli, D. R. Taaffe, R. U. Newton, D. A. GalvÃO, G. S. Trajano, J. L. Teodoro, W. J. Kraemer, K. HÄKkinen and R. S. Pinto (2021). "Resistance Training Load Effects on Muscle Hypertrophy and Strength Gain: Systematic Review and Network Meta-analysis." Medicine & Science in Sports & Exercise 53(6).

28. Mason, J., A. K. Frazer, S. Jaberzadeh, J. P. Ahtiainen, J. Avela, T. Rantalainen, M. Leung and D. J. Kidgell (2019). "Determining the corticospinal responses to single bouts of skill and strength training." The Journal of Strength & Conditioning Research **33**(9): 2299-2307.
29. Mason, J., A. K. Frazer, A. J. Pearce, A. M. Goodwill, G. Howatson, S. Jaberzadeh and D. J. Kidgell (2019). "Determining the early corticospinal-motoneuronal responses to strength training: a systematic review and meta-analysis." Reviews in the Neurosciences **30**(5): 463-476.
30. Mason, J., G. Howatson, A. K. Frazer, A. J. Pearce, S. Jaberzadeh, J. Avela and D. J. Kidgell (2019). "Modulation of intracortical inhibition and excitation in agonist and antagonist muscles following acute strength training." European journal of applied physiology **119**(10): 2185-2199.
31. Moritani, T. and H. A. deVries (1979). "Neural factors versus hypertrophy in the time course of muscle strength gain." Am J Phys Med **58**(3): 115-130.
32. Narici, M. V., G. S. Roi, L. Landoni, A. E. Minetti and P. Cerretelli (1989). "Changes in force, cross-sectional area and neural activation during strength training and detraining of the human quadriceps." Eur J Appl Physiol Occup Physiol **59**(4): 310-319.
33. Nuzzo, J. L., B. K. Barry, S. C. Gandevia and J. L. Taylor (2016). "Acute Strength Training Increases Responses to Stimulation of Corticospinal Axons." Medicine and science in sports and exercise **48**(1): 139-150.
34. Oatis, C. (2016). "Kinesiology: The Mechanics and Pathomechanics of Human Movement 3rd Edition."
35. Schoenfeld, B. J., D. Ogborn and J. W. Krieger (2017). "Dose-response relationship between weekly resistance training volume and increases in muscle mass: A systematic review and meta-analysis." J Sports Sci **35**(11): 1073-1082.
36. Siddique, U., S. Rahman, A. K. Frazer, A. J. Pearce, G. Howatson and D. J. Kidgell (2020). "Determining the sites of neural adaptations to resistance training: A systematic review and meta-analysis." Sports Medicine **50**(6): 1107-1128.
37. Stinear, C. M. and W. D. Byblow (2003). "Role of intracortical inhibition in selective hand muscle activation." J Neurophysiol **89**(4): 2014-2020.
38. Tallent, J., A. Woodhead, A. K. Frazer, J. Hill, D. J. Kidgell and G. Howatson (2021). "Corticospinal and spinal adaptations to motor skill and resistance training: Potential mechanisms and implications for motor rehabilitation and athletic development." European journal of applied physiology: 1-13.
39. Weier, A. T., A. J. Pearce and D. J. Kidgell (2012). "Strength training reduces intracortical inhibition." Acta physiologica **206**(2): 109-119.
40. Woods, J. J., F. Furbush and B. Bigland-Ritchie (1987). "Evidence for a fatigue-induced reflex inhibition of motoneuron firing rates." Journal of Neurophysiology **58**(1): 125-137.

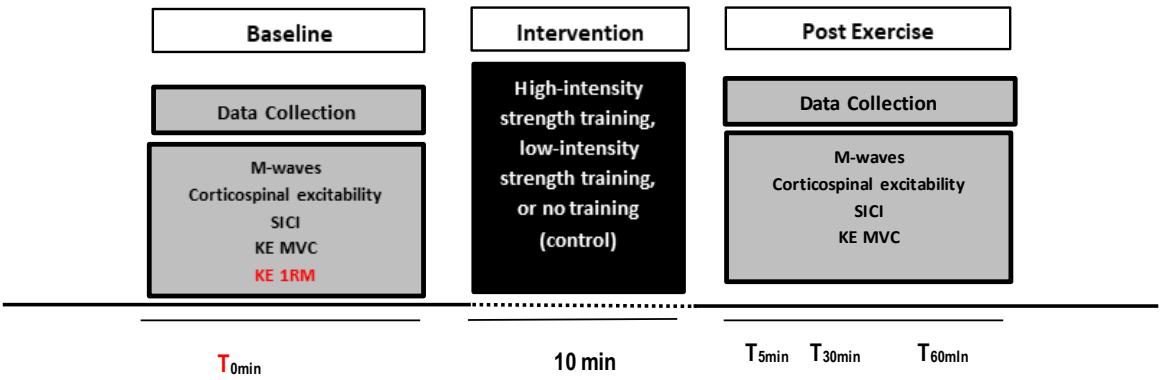
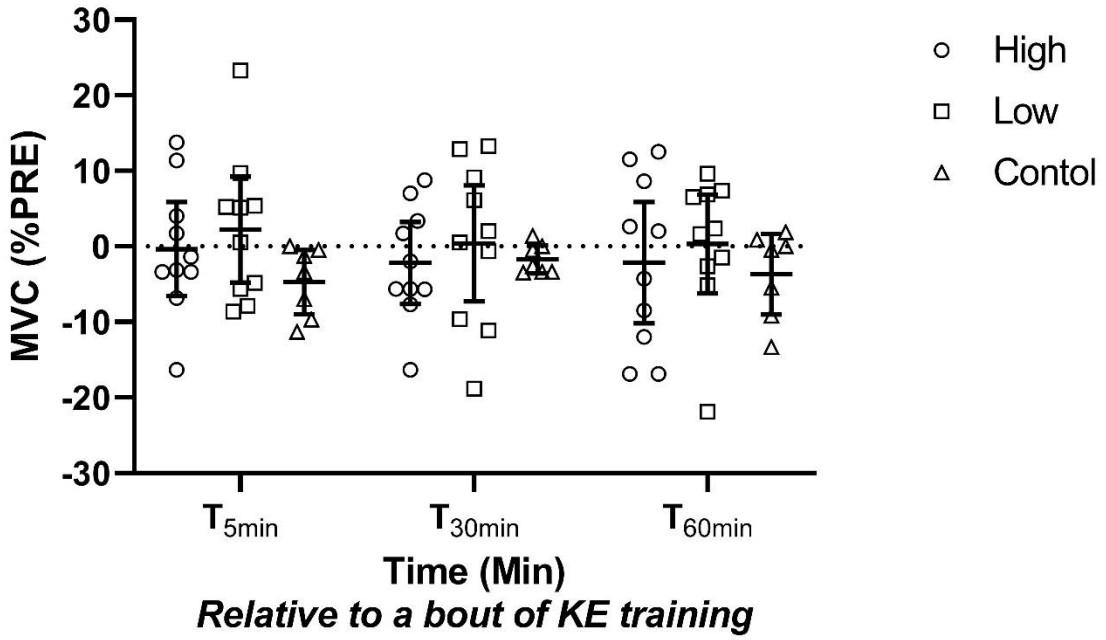
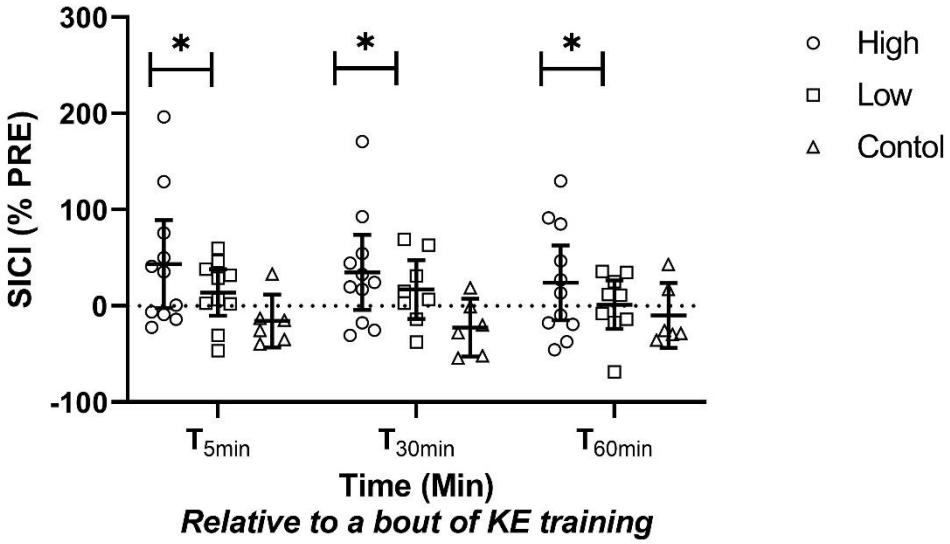


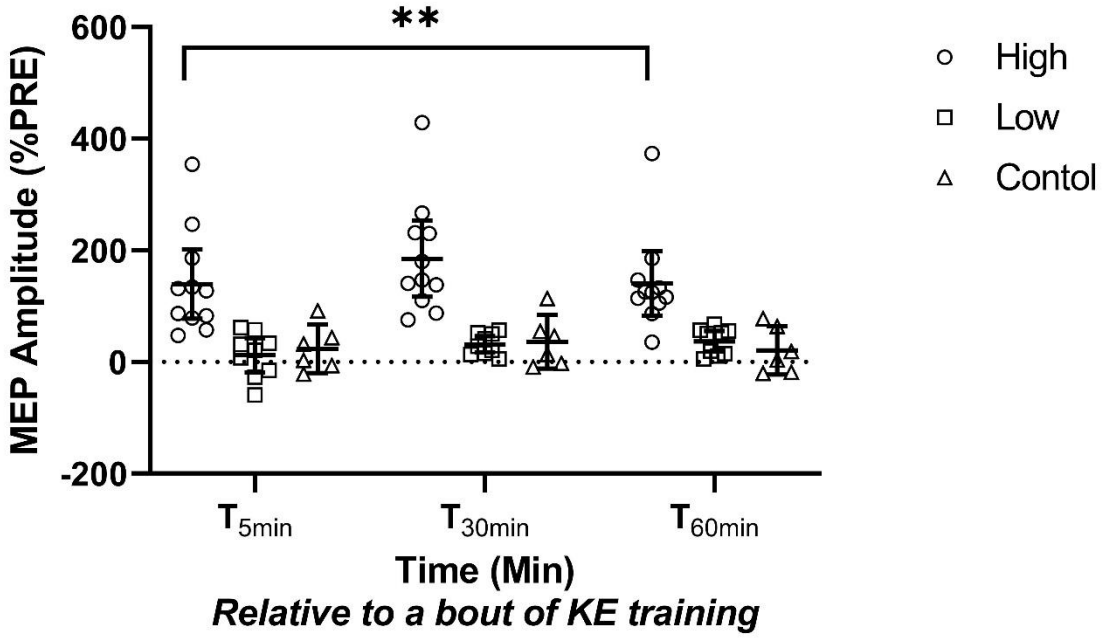
Figure 1. Experimental design of the study. Post intervention testing was undertaken at three separate time points (T5min, T30min, T60min).



645
646
647 Figure 2. Mean change (± 95% Confidence Interval [CI]) for isometric knee extensor torque (N·m) at T5min, T30min,
648 T60min post strength training.
649
650
651
652
653
654
655
656
657
658
659
660



661
662
663 Figure 3. Mean change (± 95% CI) in SICI for the trained knee extensors. *Denotes a decrease in SICI from T5min,
664 T30min and T60min compared to the low-intensity (Group × Time effect).
665
666
667
668
669
670
671
672
673
674
675
676
677



678
679 Figure 4. Mean change (± 95% CI) in MEP amplitude for the trained knee extensors. ### Denotes a significant
680 increase in MEP at T5min, T30min and T60min compared to the low-intensity and the control group (Group × Time
681 effect).
682
683
684
685
686
687
688
689
690
691
692

Table 1: Neurophysiological Outcomes Following KE Training

	T_{0min}	T_5	T_{30}	T_{60}
AMT _Control	41 (CI 34-48)	40 (CI 32-48)	41 (CI 32-50)	40 (CI 32-49)
AMT _High Int	43 (CI 38-47)	44 (CI 39-49)	44 (CI 39-50)	43 (CI 37-48)
AMT _Low Int	43 (CI 39-46)	44 (CI 39-50)	43 (CI 41-46)	43 (CI 39-47)
M_{MAX} (mV) _Control	4.5 (CI 3.3-5.7)	4.5 (CI 3.3-5.7)	4.3 (CI 3.1-5.2)	4.6 (CI 3.5-5.8)
M_{MAX} (mV) _ High Int	4.8 (CI 3.6-6.0)	4.5 (CI 3.3-5.6)	5.6 (CI 3.4-5.8)	4.4 (CI 3.3-5.6)
M_{MAX} (mV) _ Low Int	4.5 (CI 2.6-6.6)	4.5 (CI 2.4-6.1)	4.4 (CI 2.6-6.2)	4.5 (CI 2.6-6.4)

AMT = Active Motor Threshold, CI = 95% Confidence Interval, High Int = High-Intensity Strength Training, Low Int = Low-Intensity Strength Training, M_{MAX} = Maximal Compound Action Potential, mV = millivolts.

693

Table 2: Corticospinal Responses Following KE Training

	T_{0min}	T_5	T_{30}	T_{60}
CSE (%M_{MAX}) _Control	23 (CI 11-35)	27 (CI 15-39)	29 (CI 16-42)	26 (CI 14-39)
CSE (%M_{MAX}) _High Int	30 (CI 22-37)	69 (CI 48-89)**	84 (CI 58-109)**	70 (CI 48-93)**
CSE (%M_{MAX}) _Low Int	40 (CI 11-69)	35 (CI 18-52)	32 (CI 17-46)	37(CI 19-56)
SICI (% Test Response) _Control	60 (CI 21-98)	48 (CI 21-75)	40 (CI 25-55)	50 (CI 24-76)
SICI (% Test Response) _High Int	49 (CI 29-75)	57 (CI 45-69)#	54 (CI 44-65)#	50 (CI 38-62)#
SICI (% Test Response) _Low Int	36 (CI 24-49)	35 (CI 24-46)	37 (CI 28-45)	30 (CI 19-41)

CI = 95% Confidence Interval, CSE = Corticospinal Excitability, High Int = High-Intensity Strength Training, Low Int = Low-Intensity Strength Training, SICI = Short-Latency Intracortical Inhibition. ** Significantly different to control and low-intensity groups $P < 0.05$. # Significantly different to low-intensity training $P < 0.05$.

694