

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

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35 **ABSTRACT**

36 The corticospinal-responses to high-intensity and low-intensity strength-training of the upper-limb are modulated  
37 in an intensity-dependent manner. Whether an intensity-dependent threshold occurs following acute strength-  
38 training of the knee extensors (KE) remains unclear. We assessed the corticospinal-responses to an acute bout  
39 of either high-intensity (85% of maximal strength) or low-intensity (30% of maximal strength) KE strength-training  
40 with measures taken during an isometric KE task at baseline, post 5, 30 and 60 minutes. Twenty-eight healthy  
41 volunteers ( $23 \pm 3$  years) were randomized to high-intensity ( $n = 11$ ), low-intensity ( $n = 10$ ) or to a control group ( $n$   
42  $= 7$ ). Corticospinal-responses were evoked with transcranial magnetic stimulation (TMS) at intracortical and  
43 corticospinal levels. An acute bout of high- or low- intensity KE strength-training had no effect on maximum  
44 voluntary contraction (MVC) force post-exercise ( $P > 0.05$ ). High-intensity training increased corticospinal  
45 excitability (range 130% to 180%) from 5-60 minutes post-exercise compared to low-intensity training (17-30%  
46 increase). Large effect sizes (ES) showed that short-interval cortical inhibition (SICI) was reduced only for the high-  
47 intensity training group from 5-60 minutes post-exercise (24-44% decrease), compared to low-intensity (ES ranges  
48 1-1.3). These findings show a training-intensity threshold is required to adjust CSE and SICI following strength  
49 training in the lower-limb.

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

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72 **INTRODUCTION**

73 It is axiomatic that short-term strength training (i.e., 4-8 weeks) is associated with increases in muscle strength  
74 (Tallent, Woodhead et al. 2021). However, during the early phases of strength development, gains in strength  
75 cannot be explained completely by muscular factors alone (Siddique, Rahman et al. 2020). Rather, much of the  
76 initial increase in strength is due to subtle changes along the neuroaxis which include a change in plasticity at  
77 supraspinal (Latella, Kidgell et al. 2012, Weier, Pearce et al. 2012) and spinal levels (Aagaard, Simonsen et al.  
78 2002). Common short-term neural adaptations to strength training include increased muscle activation as assessed  
79 by increased integrated electromyography (EMG) (Moritani and deVries 1979, Narici, Roi et al. 1989), increased  
80 recruitment and/or discharge rates of spinal motoneurons (Del Vecchio, Casolo et al. 2019), reduced co-contraction  
81 of antagonists (Mason, Howatson et al. 2019), changes in corticospinal excitability (CSE) and inhibition as  
82 assessed by transcranial magnetic stimulation (TMS) (Siddique, Rahman et al. 2020).

83  
84 From only a single set of strength training (Ruotsalainen, Ahtiainen et al. 2014) and following a single session of  
85 strength training, recent studies using TMS have reported a modulation in neuroplasticity of the corticospinal tract  
86 (CST) (Latella, Teo et al. 2017, Mason, Frazer et al. 2019, Mason, Frazer et al. 2019, Mason, Howatson et al.  
87 2019, Ansdell, Brownstein et al. 2020, Colomer-Poveda, Hortobágyi et al. 2020). TMS involves passing single or  
88 paired magnetic pulses over the primary motor cortex (M1) by placing a magnetic coil on the scalp. The magnetic  
89 pulse propagates volleys of action potentials along the CST and peripheral motor nerve (Di Lazzaro, Oliviero et al.  
90 2004), which in turn causes a motor response in the associated target muscle (Di Lazzaro and Rothwell 2014).  
91 The motor response is recorded from the target muscle via EMG and is termed the motor-evoked potential (MEP).  
92 The muscle activity generated by TMS is dependent on neuronal excitability in both the M1 and spinal cord, and is  
93 typically considered a measure of CSE (Chen 2000, Kobayashi and Pascual-Leone 2003).

94  
95 Paired-pulse TMS assess the excitability of intrinsic intracortical connections within the M1 (Di Lazzaro and  
96 Ziemann 2014). Depending on the inter-stimulus interval between the conditioning and test pulse, paired-pulses  
97 can measure the excitability of the intracortical micro-circuitry of M1 in particular short-interval intracortical inhibition  
98 (SICI) (e.g., 2-5ms) and long-interval intracortical inhibition (LICI) (e.g., 100-150ms) as well as the intracortical  
99 facilitatory (ICF) circuits (e.g., 8-15ms). Adjustments in SICI have been reported to be critical in the selective  
100 activation of muscles and the conditioned MEP increases with increasing force levels (Stinear and Byblow 2003);  
101 thus, changes in SICI may occur in a intensity-specific manner following strength training. For this reason, the  
102 current study assessed SICI following a single session of either high- or low-intensity strength training in an attempt  
103 to determine the training intensity effects on modulating SICI as a potential acute neural adaptation to strength  
104 training.

105  
106 Relatively few studies have examined the corticospinal responses to a single session of strength training, and the  
107 existing evidence is conflicting (Brandner, Warmington et al. 2015, Leung, Rantalainen et al. 2015, Latella, Hendy  
108 et al. 2016, Nuzzo, Barry et al. 2016, Latella, Goodwill et al. 2019). Increases in CSE have been reported when

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

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126 Given that strength training is one of the most robust methods for improving muscular fitness, manipulating the  
127 acute training variables, such as relative intensity (i.e., percentage of one-repetition maximum), could be a critical  
128 determinant of the type (i.e., reduced inhibition) of neural adaptation to strength training. Therefore, determining  
129 the neural adaptations to high-intensity and low-intensity strength training appears important. Most previous  
130 research has only focused on the acute corticospinal responses to high-intensity strength training of the upper-  
131 limb (Leung, Rantalainen et al. 2015, Latella, Hendy et al. 2016, Nuzzo, Barry et al. 2016, Latella, Goodwill et al.  
132 2019), therefore, there is a need to determine the corticospinal responses following both high- and low-intensity  
133 strength training of the lower-limb. Given that low-intensity compared with high-intensity strength training can also  
134 improve muscle strength (Schoenfeld, Ogborn et al. 2017) and because the hypertrophy response to strength  
135 training seems to be independent of relative intensity (Lopez, Radaelli et al. 2021), the differences in the increase  
136 in muscle strength brought about by low- and high-intensity strength training, may be related to modifications in  
137 the corticospinal responses to strength training.

138

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

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

149

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

162

## 163 **Methods:**

164

### 165 ***Experimental Approach and Participants***

166 Figure 1 outlines the experimental design. Before commencing the study, participants underwent a familiarization  
167 session that involved: (a) anthropometric measurements of height and weight; (b) strength testing to evaluate  
168 maximal voluntary isometric strength of the knee extensors (MVC); and (c) exposure to TMS, surface  
169 electromyography (sEMG), and peripheral nerve stimulation. After this visit, in a randomized-control design,  
170 participants attended the laboratory once, which was separated by seven days from the familiarization session. A  
171 purpose-made Excel macro was used to randomize participants to the experimental groups. Participants were  
172 randomly allocated to a control group ( $n = 7$ , 2 females, 5 males), low-intensity strength training ( $n = 10$ , 3 females,  
173 7 males) and high-intensity strength training group ( $n = 11$ , 4 females, 7 males) that involved a single-bout of  
174 strength training of the KE. Participants were selected on a voluntary basis and all experiments were conducted  
175 according to the standards established by the Declaration of Helsinki, and the project was approved by the  
176 University Human Research Ethics Committee (ID:11882). Twenty-eight healthy participants (9 females and 19  
177 males, aged  $23 \pm 3$  years, height  $176 \pm 11$ cm and body mass of  $73 \pm 15$ kg) took part in this study without any  
178 known history of neurological impairment or current physical illness or injuries, and all participants provided  
179 informed consent prior to the commencement of the study. Overall, subjects had little or no history of strength  
180 training and were included if they had not participated in strength training within the last six months. Participants  
181 were screened for contraindication to TMS and strength training (Chipchase, Schabrun et al. 2012). Only one of  
182 the participants reported that they had been completing strength training of the KE > 1 day per week two months

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

185 **Insert Figure 1**

186

187 ***Maximum Isometric Strength Testing***

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

202

203 ***Dynamic Strength Testing***

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

214 ***Strength Training Protocol***

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

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

223

### 224 ***Electromyography***

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

234

### 235 ***Transcranial magnetic stimulation***

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

244

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

251

### 252 ***Assessment of CSE: Single-pulse TMS-induced MEPs***

253 Once AMT was established, ten single-pulse TMS induced MEPs were recorded using 130% AMT before ( $T_{0\text{min}}$ ),  
254 post 5 min ( $T_{5\text{min}}$ ), 30 min ( $T_{30\text{min}}$ ) and 60 min ( $T_{60\text{min}}$ ) after the training (Ansdell, Brownstein et al. 2020). Providing  
255 10 single-pulse MEPs has been shown to be a reliable number to estimate CSE (Ansdell, Brownstein et al. 2020).  
256 Each stimulus was delivered in random intervals every 10 to 12 seconds to avoid stimulus anticipation. The average

257 stimulator intensity was 55% of maximal stimulator output (MSO) for high-intensity and low-intensity training and  
258 50% MSO for the control group.

259

### 260 **Assessment of Short-Interval Intracortical Inhibition**

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

264

### 265 **Percutaneous Nerve Stimulation**

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

274

### 275 **Data Analysis**

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

282

### 283 **Statistical Analysis**

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

289

290 All data were first screened to ensure they were normally distributed. To have sufficient data to test for questions  
291 of normality, all data from baseline MEPs, SICI, and MVC trials were used to establish the distributional properties.  
292 The Shapiro-Wilk test suggested that CSE for the low-intensity group was not normally distributed ( $W = 0.75$ ;  $P =$   
293  $0.003$ ). However, this violation was mild after examining frequency histograms and detrended Q-Q plots, and was



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

308

## 309 **Results:**

### 310 ***Isometric, Dynamic Knee Extensor Strength and Load-Volume***

311 Figure 2 shows the mean change  $\pm$  95% CI for isometric KE torque. At baseline, there were no differences in KE  
312 MVC ( $F_{2, 24} = 1.128, P = 0.34$ ) or 1RM dynamic strength ( $F_{2, 24} = 0.19$ ) detected between groups. Baseline KE  
313 MVC torque for the high-intensity group was  $161 \pm 43$  N·m, low-intensity  $154 \pm 38$  N·m and control  $180 \pm 46$  N·m.  
314 Baseline KE 1RM strength for the high-intensity group was  $80 \pm 19$  Kg and for the low-intensity group it was  $78 \pm$   
315  $20$  kg. After the acute bout of strength training, there were no main effects of Group ( $F_{2, 24} = 0.70, P = 0.51$ ); Time  
316 ( $F_{3, 61} = 0.41, P = 0.71$ ; or Group  $\times$  Time interactions for KE MVC ( $F_{6, 72} = 0.78, P = 0.58$ , Figure 2). There was a  
317 significant difference in the load-volume between the high-intensity and low-intensity groups, with the low-intensity  
318 group having a greater overall load-volume compared to the high-intensity group ( $t = 2.5, df=19, P = 0.02, g = 0.40$ )

319

**Insert Figure 2**

320

321

322

### 323 ***M<sub>MAX</sub>***

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

327

### 328 ***Active Motor Threshold***

329 There were no significant differences in active motor threshold between groups at baseline ( $F_{2,25} = 0.13, P = 0.87$ )  
330 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  $\times$  Time interactions  
331 ( $F_{6,74} = 0.23, P = 0.96$ , Table 1).

332

### 333 **SICI ratio**

334 No differences in SICI were detected at baseline between groups ( $F_{2,24} = 0.83, P = 0.44$ ; Figure 3). Following the  
335 acute strength training bout, there was a Group  $\times$  Time interaction ( $F_{6,74} = 3.0, P = 0.01$ ), however, there were no  
336 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  
337 3). Post hoc Bonferroni pairwise comparisons showed that SICI was reduced following high- compared to low-  
338 intensity training at all post time points (all  $P < 0.05$ , Table 2). SICI decreased at  $T_{5min}$  following high-intensity  
339 training compared to low-intensity training (mean difference 22, 95% CI 3.8 to 41;  $P = 0.01$ ;  $g = 1.29$ ), but not  
340 compared to control, despite a large effect size (mean difference 9.4, 95% CI -25 to 43;  $P = 0.75$ ;  $g = 1.03$ ). At  
341  $T_{30min}$  SICI was still reduced for the high-intensity group compared to low- intensity (mean difference 18, 95% CI  
342 2.2 to 33;  $P = 0.02$ ;  $g = 1.16$ ), but not compared to control (mean difference 15, 95% CI - 5.6 to 35;  $P = 0.17$ ;  $g =$   
343 1.15). At  $T_{60min}$  SICI was reduced compared to low-intensity training (mean difference 20, 95% CI 1.5 to 38,  $P =$   
344 0.03,  $g = 1.17$ , Table 2).

345

### 345 **Insert Figure 3**

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### 347 **Corticospinal Excitability**

348 Figure 4 displays the mean and 95% CI for changes in CSE. At baseline, there were no significant differences in  
349 CSE between groups ( $F_{2,24} = 0.83, P = 0.44$ , Table 1). The Mixed-Factorial ANOVA revealed a main effect for  
350 Time ( $F_{1.6,36} = 6.5, P = 0.007$ ), Group ( $F_{2,24} = 6.3, P = 0.006$ ) and a Group  $\times$  Time interaction ( $F_{6,69} = 9.6, P <$   
351 0.001). Bonferroni post hoc analysis revealed that CSE for the high-intensity group increased ( $F_{3,30} = 24.41, P <$   
352 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%  
353 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  
354 to the control and low-intensity groups (all  $P < 0.001$ , Table 2).

355

### 355 **Insert Figure 4**

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### 361 **Discussion:**

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

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

371

372 The present findings suggest that a single session of KE strength training increases the responsiveness of the  
373 CST to stimulation. This increase is likely due to some level of change in plasticity at the M1 and motoneuron pool  
374 that manifests as improved synaptic efficacy with the CST (Nuzzo, Barry et al. 2016). Our results are in line with  
375 previous acute strength training studies, whereby training-intensity appears to be an important acute strength  
376 training variable to modulate the corticospinal pathway (Colomer-Poveda, Hortobágyi et al. 2020). The present  
377 data confirm the previously described effect of training intensity in the upper-limb by showing that a training intensity  
378 of greater than 75% maximum appears to be the threshold for acute strength training to produce meaningful  
379 changes in CSE (Colomer-Poveda, Hortobágyi et al. 2020), suggesting a similar threshold is required for the lower-  
380 limb. Despite this, our findings are in contrast to a recent KE strength training study where an acute bout of squat  
381 training had no effect on CSE; rather, there was an increase in spinal excitability (Ansdell, Brownstein et al. 2020).  
382 Although unlikely, there are some differences between the current study and that of Ansdell, Brownstein et al.  
383 (2020) that may in part explain the discrepant findings. For example, we performed strength training of the KE  
384 using an isolated leg extension exercise whilst Ansdell, Brownstein et al. (2020) performed squat training, but it is  
385 unclear how the corticospinal responses would differ between the two exercises. Further, it has been reported that  
386 the assessment of the corticospinal pathway should have a degree of relative specificity to the training task  
387 (Brownstein, Ansdell et al. 2018); however, both the current study and Ansdell, Brownstein et al. (2020) matched  
388 training and testing to reduce this bias. The only difference that may account for the disparity of responses for the  
389 lower-limb could be the target muscle used to produce MEPs. In the current study, we recorded evoked-responses  
390 from the rectus femoris with the knee at 60° optimizing the moment arm of the extensor mechanism (Oatis 2016),  
391 whilst previous research used 90° (Ansdell, Brownstein et al. 2020). In addition, it seems that there was a sufficient  
392 level of fatigue, depicted by the decrease in MVC force post strength training in the Ansdell, Brownstein et al. (2020)  
393 study, which was not the case for the present study. Also, the timing of the post TMS measures were different,  
394 with the current study recording MEPs five minutes post the last set of strength training, whilst previous research  
395 measured MEPs immediately post. However, a potential limitation is we did not measure corticospinal activity at a  
396 force level that matched training intensity. Despite this, evidence now suggests that even at 50% MVC, SICl is  
397 abolished in the rectus femoris (Brownstein, Ansdell et al. 2018), which underscores this limitation.

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

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

403

404 Similar to our previous upper-limb study (Mason, Frazer et al. 2019), it seems that training-intensity may be  
405 important for modulating the excitability of the short-latency inhibitory network of the M1. In the present study, we  
406 report large comparative effects for reduced SICI post high-intensity strength training, but not following low-intensity  
407 strength training. Overall, the acute effect of strength training on modulating SICI is not consistent (Mason, Frazer  
408 et al. 2019). Our findings are consistent with Latella et al., (2018) and Mason et al., (2019), but in contrast to Latella  
409 et al. (2017), Ansdell et al. (2020) and Colomer-Poveda et al. (2020). It is unclear why these inconsistencies are  
410 present, but it is likely related to several factors around TMS methodology, type of strength training employed, and  
411 muscles used which likely have divergent corticospinal inputs (Brower and Ashby 1990). Irrespective of these  
412 findings, it seems that high-intensity KE training targets neurons within the cortex that use GABA<sub>A</sub> as their  
413 neurotransmitter, thus reducing the inhibitory synaptic efficacy between intracortical inhibitory neurons and  
414 corticospinal neurons (Weier, Pearce et al. 2012). Reduced synaptic efficacy between inhibitory interneurons and  
415 corticospinal neurons likely improves synaptic efficacy of the corticospinal synapse, leading to increased MEPs  
416 and potential spinal excitability (Ansdell, Brownstein et al. 2020). Reducing the net inhibitory input to the spinal  
417 motoneuron pool, by default, should increase the responsiveness of the corticospinal tract and spinal motoneuron  
418 pool to TMS in the period following acute strength training. This finding agrees with previous upper-limb studies  
419 (Nuzzo, Barry et al. 2016, Colomer-Poveda, Romero-Arenas et al. 2019, Colomer - Poveda, Hortobágyi et al.  
420 2020) whereby the corticospinal response is potentiated; however, this is a new finding for the lower-limb.

421

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

432

433 It is unclear why there were no changes in CSE or SICI following low-intensity training as other motor tasks, such  
434 as visuomotor tracking and ballistic motor tasks, modulate CSE, SICI and silent period (Leung, Rantalainen et al.  
435 2015, Mason, Frazer et al. 2019). In addition, early experimental work has shown that mechanisms associated  
436 with central fatigue recover within three minutes, thus we cannot be certain that we have captured all the acute

437 responses to strength training (Woods, Furbush, 1987). Despite this, at a minimum, this finding suggests that the  
438 adaptive responses of the lower-limb may be more sensitive to the parameters of the motor task compared to the  
439 upper-limb. The differential responses observed in the lower-limb, compared to the upper-limb following low- and  
440 high-intensity exercise, suggest that the high-intensity protocol distinctively and separately targets cortical neurons  
441 that use both glutamate and GABA<sub>A</sub> to increase the excitability of the corticospinal pathway. Because fatigue was  
442 not evident after five minutes in both protocols, it seems that the unique demand of high-intensity training is the  
443 primary mechanism modulating the corticospinal responses to acute lower-limb strength training. Recent  
444 experimental evidence supports this notion, whereby training-intensity is contingent for increasing the excitability  
445 of the corticospinal pathway (Colomer-Poveda, Romero-Arenas et al. 2019, Colomer - Poveda, Hortobágyi et al.  
446 2020).

447

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

461

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

470

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473

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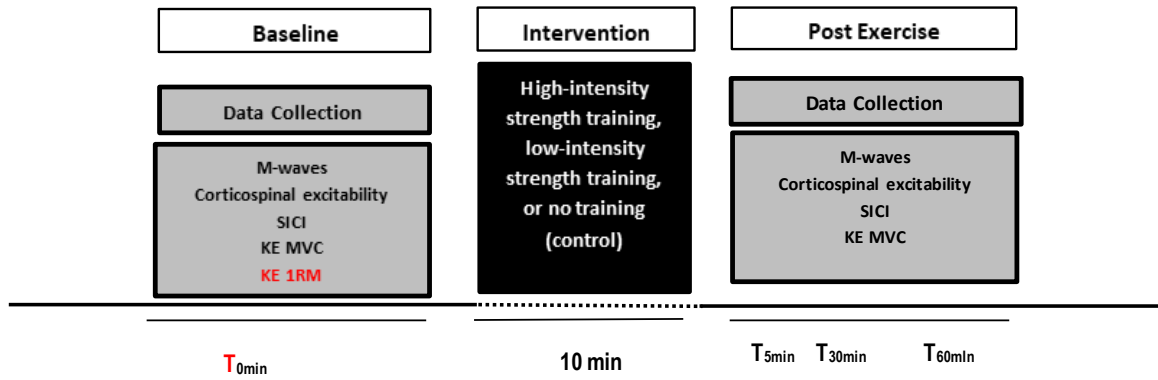
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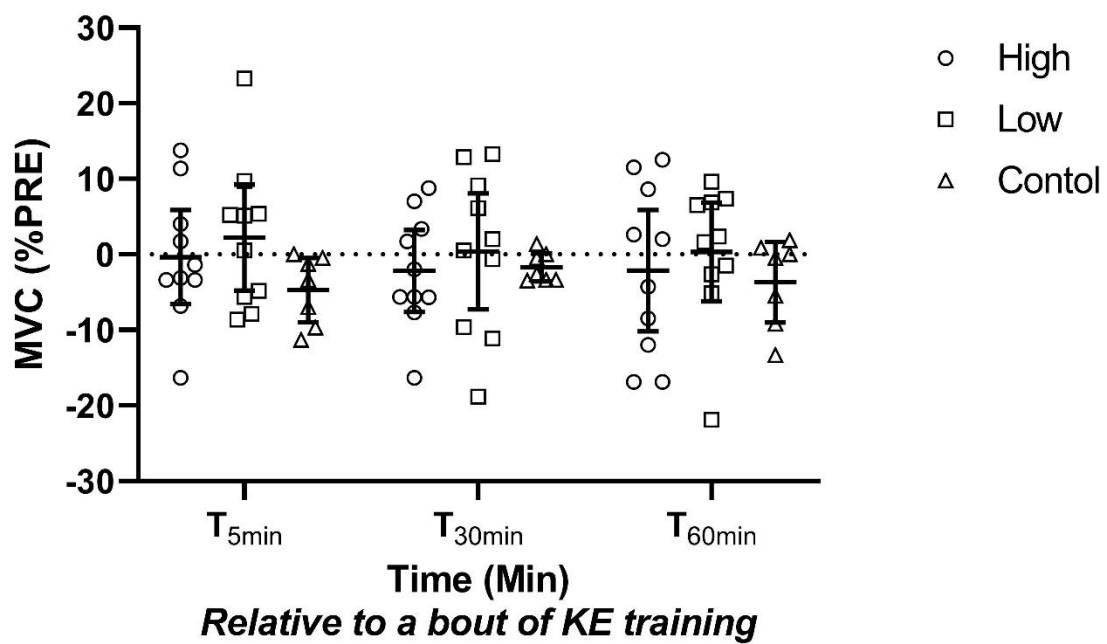
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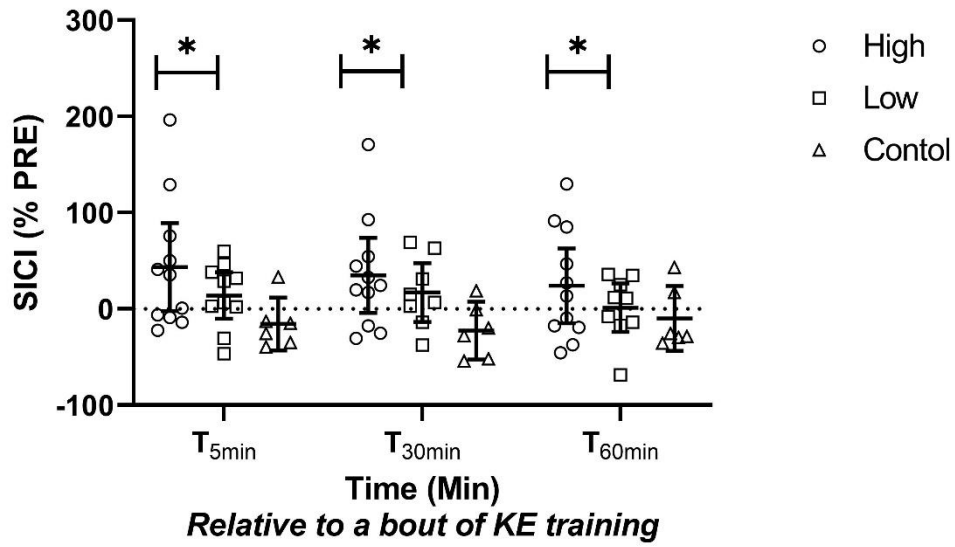
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Figure 1. Experimental design of the study. Post intervention testing was undertaken at three separate time points ( $T_{5min}$ ,  $T_{30min}$ ,  $T_{60min}$ ).



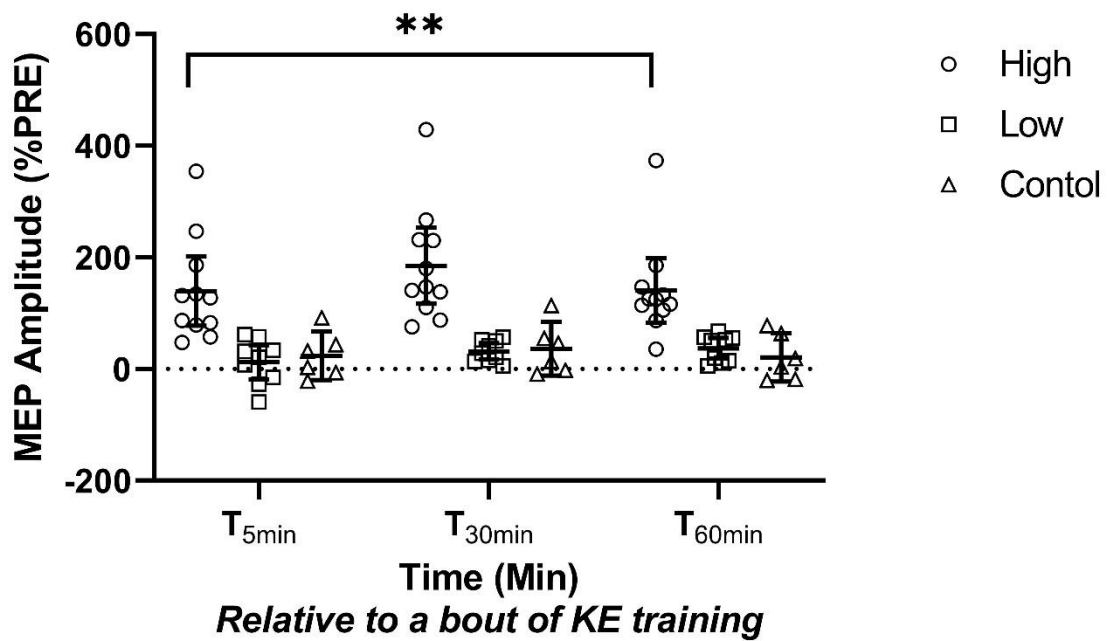
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Figure 2. Mean change ( $\pm$  95% Confidence Interval [CI]) for isometric knee extensor torque (N·m) at T<sub>5min</sub>, T<sub>30min</sub>, T<sub>60min</sub> post strength training.



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Figure 3. Mean change (± 95% CI) in SICI for the trained knee extensors. \*Denotes a decrease in SICI from T<sub>5min</sub>, T<sub>30min</sub> and T<sub>60min</sub> compared to the low-intensity (Group × Time effect).



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679 Figure 4. Mean change ( $\pm$  95% CI) in MEP amplitude for the trained knee extensors. ### Denotes a significant  
 680 increase in MEP at T<sub>5min</sub>, T<sub>30min</sub> and T<sub>60min</sub> compared to the low-intensity and the control group (Group  $\times$  Time  
 681 effect).

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**Table 1: Neurophysiological Outcomes Following KE Training**

	T <sub>0min</sub>	T <sub>s</sub>	T <sub>30</sub>	T <sub>60</sub>
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 <sub>MAX</sub> (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 <sub>MAX</sub> (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 <sub>MAX</sub> (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<sub>MAX</sub> = Maximal Compound Action Potential, mV = millivolts.

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**Table 2: Corticospinal Responses Following KE Training**

	T <sub>0min</sub>	T <sub>s</sub>	T <sub>30</sub>	T <sub>60</sub>
CSE (%M <sub>MAX</sub> ) _Control	23 (CI 11-35)	27 (CI 15-39)	29 (CI 16-42)	26 (CI 14-39)
CSE (%M <sub>MAX</sub> ) _High Int	30 (CI 22-37)	69 (CI 48-89)**	84 (CI 58-109)**	70 (CI 48-93)**
CSE (%M <sub>MAX</sub> ) _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-Late Intracortical Inhibition. \*\* Significantly different to control and low-intensity groups  $P < 0.05$ . # Significantly different to low-intensity training  $P < 0.05$ .

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