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2 **Tracking the corticospinal responses to strength training**  
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49 **Abstract**

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**Purpose:** The motor cortex (M1) appears to be a primary site of adaptation following both a single session, and repeated strength-training sessions across multiple weeks. Given that a single session of strength-training is sufficient to induce modification at the level of the M1 and corticospinal tract, this study sought to determine how these acute changes in M1 and corticospinal tract might accumulate across the course of a two-week heavy-load strength-training program.

**Methods:** Transcranial magnetic stimulation (TMS) was used to infer corticospinal excitability (CSE), intracortical facilitation (ICF), short and long-interval intracortical inhibition (SICI and LICI) and silent period duration prior to and following each training session during a two-week heavy-load strength-training period.

**Results:** Following two-weeks of strength-training, increases in strength (15.5%,  $P = 0.01$ ) were accompanied by an increase in CSE (44%,  $P = 0.006$ ) and reductions in both silent period duration (14%,  $P < 0.0001$ ) and SICI (35%,  $P = 0.0004$ ). Early training sessions acutely increased CSE and ICF, and acutely reduced silent period duration and SICI. However, later training sessions failed to modulate SICI and ICF, with substantial adaptations occurring offline between training sessions. No acute or retained changes in LICI were observed. Co-contraction of antagonists reduced by 36% following two-weeks of strength-training.

**Conclusions:** Collectively, these results indicate that corticospinal plasticity occurs within and between training sessions throughout a training period in distinct early and later stages that are modulated by separate mechanisms of plasticity. The development of strength is akin to the previously reported changes that occur following motor skill training.

**Keywords** Corticospinal excitability · Cortical plasticity · Intracortical facilitation · Short-interval cortical inhibition · Silent period · Strength training

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95	<b>ABBREVIATIONS</b>
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97	<b>1-RM:</b> One-repetition maximum
98	<b>AURC:</b> Area under the recruitment curve
99	<b>AMT:</b> Active motor threshold
100	<b>CSE:</b> Corticospinal excitability
101	<b>CI:</b> Confidence interval
102	<b>SD:</b> Standard deviation
103	<b>ECR:</b> Extensor carpi radialis
104	<b>EMG:</b> Electromyography
105	<b>FCR:</b> Flexor carpi radialis
106	<b>GABA:</b> $\gamma$ -Aminobutyric acid
107	<b>ICF:</b> Intracortical facilitation
108	<b>LICI:</b> Long-interval cortical inhibition
109	<b>MEP:</b> Motor-evoked potential
110	<b>M<sub>MAX</sub>:</b> Maximal compound wave
111	<b>MVIC:</b> Maximal voluntary isometric contraction
112	<b>M1:</b> Primary motor cortex
113	<b>rmsEMG:</b> Root-mean-square electromyography
114	<b>RMT:</b> Resting motor threshold
115	<b>sEMG:</b> Surface electromyography
116	<b>SICI:</b> Short-interval cortical inhibition
117	<b>SP:</b> Silent period
118	<b>TMS:</b> Transcranial magnetic stimulation
119	<b>rTMS:</b> Repetitive transcranial magnetic stimulation
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137 **Introduction**

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139 Adaptations within the central nervous system (CNS) underlie training-induced improvements in motor  
140 performance. These adaptations commence as early as a single session of training and continue to  
141 change between training sessions, due to neural mechanisms associated with use-dependent cortical  
142 plasticity (Dayan and Cohen 2011). Use-dependent plasticity has been well studied in the context of  
143 skill acquisition (Mawase et al. 2017; Dayan and Cohen 2011), but is lacking in the context of strength  
144 acquisition. The process of acquiring a new motor skill has been linked to functional modifications in  
145 the intrinsic micro-circuitry of the primary motor cortex (M1), which include the expansion of motor  
146 representations (Monfils et al. 2005), the strengthening of existing (Rioult-Pedotti et al. 1998; Rioult-  
147 Pedotti et al. 2000) and the formation of new synapses (Kleim et al. 2004; Taube 2011). Importantly,  
148 early improvements in motor skill performance are rapid, and there are distinct mechanisms of cortical  
149 plasticity that are associated with the early and late stages of skill acquisition (Karni et al. 1998; Floyer-  
150 Lea and Matthews 2005; Dayan and Cohen 2011).

151  
152 Although not as well examined as the motor learning literature, strength training can lead to rapid and  
153 substantial improvements in the ability to produce muscular force (Guizelini et al. 2018; Siddique et al.  
154 2019). Such increases in the force-generating capacity of the trained muscles are accompanied by  
155 changes in the excitability of the intrinsic micro-circuitry of the M1 due to use-dependant mechanisms  
156 (Siddique et al. 2019). Although the rapid development of muscular strength is thought to occur as a  
157 result of changes in the CNS (Folland and Williams 2007; Duchateau and Enoka, 2002; Weier et al.  
158 2012), the time-course, specific locus and mechanism of adaptation are poorly understood (Kidgell et  
159 al. 2017). Training-induced adaptations are reported to include reduced co-activation of antagonist  
160 muscles (Carolan and Cafarelli 1992), increased motoneurone excitability, revealed by increased H-  
161 reflexes and V-waves (Aagard et al. 2002) and alterations in motor unit behaviour (Kamen and Knight  
162 2004; Del Vecchio et al. 2019). Many of these changes are reported to have a supraspinal influence that  
163 implicate the role of cortical plasticity in strength development (Siddique et al. 2019).

164  
165 Over last 30 years, transcranial magnetic stimulation (TMS) has been used as a technique to examine  
166 the acute and training-related effects of motor training on cortical plasticity. Single- and paired-pulse  
167 TMS can quantify cortical plasticity by inferring corticospinal excitability (CSE) through the  
168 measurement of the motor-evoked potential (MEP) and intracortical facilitation (ICF), as well as  
169 corticospinal inhibition (via the silent period duration) and intracortical inhibition (short and long-  
170 latency intracortical inhibition; SICI and LICI, respectively) (Di Lazzaro and Rothwell 2014). Changes  
171 in these TMS-evoked responses are regarded as indicators of cortical plasticity confined to the M1.  
172 Experimental evidence showed that strength training performed over three to four weeks either  
173 increased CSE (Griffin and Cafarelli 2007; Goodwill et al. 2012; Kidgell et al., 2010; Kidgell et al.,

174 2011; Weier et al. 2012; Pearce et al. 2013; Leung et al. 2015; Mason et al. 2017), decreased CSE  
175 (Carroll et al. 2002; Coombs et al. 2016; Jensen et al. 2005; Lee et al. 2009), and reduced the silent  
176 period duration (Kidgell and Pearce 2010; Coombs et al. 2016; Mason et al. 2017; Latella et al. 2012).  
177 Although these findings are mixed, a recent systematic review concluded that short-term strength  
178 training increases CSE, reduces the duration of the silent period and reduces SICI (Siddique et al. 2019).  
179 This suggest that use-dependent adaptations within the M1 support improvements in muscular strength.  
180 It is possible that the training-related responses following multiple weeks of strength training are simply  
181 the culmination of single training sessions. Hortobágyi et al. (2009) used TMS throughout a four-week  
182 strength training program to determine the effect of strength training on M1 plasticity. In this study,  
183 after every strength training session, real or sham repetitive transcranial magnetic stimulation (rTMS)  
184 was applied over the M1. Interestingly, when the M1 was disrupted via rTMS after each session,  
185 cumulative strength gains were diminished (Hortobágyi et al. 2009). Importantly, the diminished gain  
186 in strength was associated with reduced M1 plasticity. These data suggests that each individual strength  
187 training session plays a critical role in the process of acquiring strength, but also directly associates  
188 cortical plasticity with strength gains. Therefore, it is conceivable that a summation of the M1 responses  
189 could accrue from each session to the next; ultimately generating improvements in muscle  
190 strength. Therefore, the previously unexplored idea of tracking the cortical responses session by session  
191 might reveal a more detailed time-course of the neural adaptations to strength training.

192  
193 Theoretical frameworks for early and late phases of cortical plasticity have been established for the  
194 acquisition of motor skills (Dayan and Cohen 2011; Karni et al., 1998; Rosenkranz et al. 2007; Kleim  
195 et al. 2006; Floyer-Lea and Matthews 2005), which aid in the appropriate prescription and scheduling  
196 of skill-based training. However, no such frameworks are available for strength training. The  
197 establishment of similar frameworks identifying the cortical responses that shape the acquisition and  
198 consolidation of muscular strength would allow practitioners to prescribe training that directly and  
199 appropriately targets these underlying mechanisms in order to maintain and improve human health and  
200 performance. Therefore, the primary aim of this study was to track the progressive M1 responses prior  
201 to and following every strength-training session throughout a two-week strength-training period. It was  
202 hypothesised that as strength would increase throughout the training period, the acute excitatory and  
203 inhibitory responses (CSE, ICF, silent period, SICI and LICI) would accumulate within each session,  
204 leading to changes in M1 plasticity due mechanisms associated with use-dependent plasticity.

205

## 206 **Methods**

207

### 208 ***Study Design and Participants***

209 Participants were randomly allocated to a control or experimental group that completed supervised  
210 heavy-load strength training of the wrist flexors, three times per week for two-weeks (Figure 1). All

211 participants provided written informed consent prior to participation. Eighteen healthy individuals (8  
212 female, 10 male, aged  $23.45 \pm 4.2$ ) were selected on a voluntary basis and all experiments were  
213 conducted according to the standards established by the Declaration of Helsinki, and the project was  
214 approved by the Monash University Human Research Ethics Committee (MUHREC 11882). All  
215 participants were right handed according to the Edinburgh Handedness Inventory (Oldfield 1971) with a  
216 laterality quotient  $>85$ , were free from peripheral and neurological impairment, and had not participated  
217 in strength training for a period of twelve months prior to the commencement of the study. All  
218 participants were recruited from the University population and were required to complete an adult  
219 safety-screening questionnaire to determine their suitability for TMS (Keel et al. 2011).

220

### 221 *Experimental approach*

222 Participants attended a familiarisation session one-week prior to the commencement of baseline testing  
223 that involved one-repetition maximum strength testing (1-RM) of the wrist flexors, exposure to single-  
224 pulse and paired-pulse TMS, and peripheral nerve stimulation. Following randomisation, participants  
225 were allocated to either a strength-training group or a non-training control group. The experimental  
226 condition involved heavy-load isotonic strength-training of the right wrist flexors (dominant limb) six  
227 times over the course of two weeks, with at least 48 hours rest in between training sessions. Prior to  
228 and sixty seconds immediately after the cessation of each strength-training session, measures of motor  
229 cortical and corticospinal responses using TMS were obtained. A retention session including all  
230 assessments was completed  $\sim 72$  hours following the completion of the training intervention, and  
231 strength measurements were taken at baseline, following one week of training and following two weeks  
232 of training. The control group followed an identical protocol to the strength-training group, including  
233 frequency and volume of visits to the laboratory, pre- and post-session TMS testing, a retention session  
234 and strength testing. However, instead of heavy-load strength training, the control group sat quietly at  
235 rest for fifteen minutes.

236

### 237 *Voluntary strength testing*

238 Participants performed a standard unilateral one-repetition maximum (1-RM) strength test for the right  
239 wrist flexor at baseline, after three training sessions and following six training sessions and at retention  
240 (72 h following the sixth training session). Participants were seated in the isokinetic dynamometer,  
241 shoulders relaxed and elbow flexed at 90 degrees, with the forearm supinated and fastened firmly on  
242 the arm rest. The dynamometer attachment was removed and a weighted dumbbell was used to allow  
243 for a more sensitive and functional measure of dynamic strength. The wrist was positioned such that  
244 the styloid process sat just beyond the edge of the arm rest, and the relaxed hand hung free. The  
245 researcher placed the dumbbell in each participant's hand and instructed them to grasp the dumbbell  
246 and completely flex the wrist, moving the hand upward. The exact same procedures were used for TMS

247 positions, the strength training protocol, and for strength testing of the ECR, however, the forearm was  
248 pronated in the case of the latter. Following a warm-up, participants were asked what they considered  
249 their 1-RM to be, and this weight served as the starting point for 1-RM establishment. If the trial was  
250 successful, the weight of the dumbbell was increased accordingly (0.25-0.5 kg increments). This  
251 procedure continued until the subject could no longer complete one repetition, and their prior successful  
252 trial served as their 1-RM wrist flexor and extensor strength (Kidgell et al. 2011) and was subsequently  
253 used to calculate the intensity for subsequent training. Following each trial, subjects were given 3-mins  
254 recovery to minimise the development of muscular fatigue (Kidgell et al. 2011), and typically needed  
255 three to five trials to achieve their 1-RM strength.

256

### 257 ***Strength training protocol***

258 Participants performed supervised, loaded unilateral wrist flexion and extension through 20 degrees,  
259 with 0 degrees being the anatomical position, of the dominant arm monitored by a metronome (2 s  
260 concentric; 4 s eccentric; Kidgell et al. 2011) and electromagnetic goniometer (ADIInstruments, Bella  
261 Vista, Australia). Participants completed four sets of 6-8 repetitions at 80% of their 1-RM, with 2.5 min  
262 rest between sets. The principle of progressive overload was employed throughout the training period  
263 to maximise the training response. Specifically, when participants could complete four sets of eight  
264 repetitions, at the beginning of the next training session, the training weight (kg) was increased by  
265 0.5kg. Control participants sat quietly at rest for 15 minutes, matching the time for strength-training  
266 completion in the intervention group.

267

### 268 ***Surface electromyography (sEMG)***

269 The area of electrode placement was shaven to remove fine hair, rubbed with an abrasive skin gel to  
270 remove dead skin, and then cleaned with 70% isopropyl alcohol. Surface electromyography (sEMG)  
271 was recorded from the right flexor carpi radialis (FCR) muscle using bipolar Ag-AgCl electrodes. As  
272 described by Selveanayagam et al. (2011) the electrodes for the FCR were positioned 9 cm from the  
273 medial epicondyle of the humerus with an inter-electrode distance (center to center) of 2 cm. As  
274 antagonist co-activation data was also collected, extensor carpi radialis (ECR) electrodes were  
275 positioned at 45% of the distance from the medial epicondyle of the humerus to the radial styloid  
276 process with an inter-electrode distance of 2 cm. A grounding strap was placed around the wrist as the  
277 common reference point for all electrodes. sEMG signals were amplified ( $\times 1,000$ ), band pass filtered  
278 (high pass at 13 Hz, low pass at 1,000 Hz), digitized online at 2 kHz, recorded (1 s), and analyzed using  
279 Power Lab 4/35 (ADIInstruments, Bella Vista, Australia). The sEMG was used to record the test and  
280 conditioned MEPs obtained during TMS prior to and following each training session throughout the  
281 two-week period and at retention 72 h following the intervention. sEMG was also used during the  
282 strength-training bout to provide an estimation of antagonist co-contraction.

283

284 ***Transcranial magnetic stimulation***

285 During each testing session, TMS was delivered using two Magstim 200<sup>2</sup> stimulators (Magstim Co.,  
286 UK) to produce motor evoked potentials (MEPs) in the active FCR via a figure-8 coil. The motor  
287 hotspot for the FCR (with posterior-to-anterior-induced current flow in the cortex) was determined and  
288 resting motor threshold (RMT) and active motor threshold (AMT) were then established as the stimulus  
289 intensity at which at least five of ten stimuli produced MEP amplitudes of greater than 50  $\mu$ V for RMT  
290 and greater than 200  $\mu$ V for AMT (Rossini et al. 1999). Prior to and following each session throughout  
291 the strength-training intervention, AMT and RMT were retested and adjusted if required. To ensure that  
292 all stimuli were delivered to the optimal motor hotspots throughout testing, participants wore a tight-  
293 fitting cap marked with a latitude–longitude matrix, positioned with reference to the nasion–inion and  
294 interaural lines.

295 All single- and paired-pulse stimuli were delivered during a low-level isometric contraction of the right  
296 FCR. Participants were required to maintain a wrist joint angle of 20° wrist flexion in a position of  
297 supination. Joint angle was measured with an electromagnetic goniometer (ADInstruments, Bella Vista,  
298 Australia), with visual feedback provided on a screen visible to both the participant and the researcher  
299 (Hendy and Kidgell 2013). Holding the hand in this joint position equated to  $5 \pm 1\%$  of the maximal  
300 root-mean squared electromyography (rmsEMG). Because this position resulted in a low level of  
301 muscle activity, and to ensure that background muscle activity was consistent between TMS stimuli,  
302 rmsEMG was recorded 100 ms before the delivery of each TMS pulse. During the TMS trials, visual  
303 feedback was presented to the volunteer to display an upper limit of 5% rmsEMG; participants were  
304 instructed to maintain their muscle activation levels below this upper limit. The stimulus delivery  
305 software (LabChart 8 software, ADInstruments, Bella Vista, NSW, Australia) was set so that stimuli  
306 were not delivered if the rmsEMG value, 100 ms immediately prior to the stimulus, exceeded  $5 \pm 1\%$   
307 (Table 1).

308 Recruitment curves for the FCR were constructed to determine CSE (MEP amplitude) and silent period  
309 duration before and after each heavy-load strength-training bout. For a single stimulus-response curve,  
310 10 stimuli were delivered at 130, 150 and 170% of AMT during a low-level isometric contraction of  
311 the FCR. Recruitment curves were also collected for the control group prior to and following 15 minutes  
312 of quiet sitting. This was repeated for each strength training session and at retention 72 h after the sixth  
313 training session.

314 To quantify short-interval intracortical inhibition (SICI), 10 single-pulse stimuli and 10 short-interval  
315 paired-pulse stimuli were delivered in a random order. The stimulator output intensity was set at 120%  
316 AMT, which was determined during familiarization and adjusted if there was a change following each  
317 strength training session. The conditioning stimulus for paired-pulse stimulation was set at 80% AMT,



318 the inter-stimulus interval was 3 ms, and subsequent posterior to anterior current flow was used. To  
319 quantify intracortical facilitation (ICF), 10 single-pulse stimuli and 10 paired-pulse stimuli were  
320 delivered in a random order. The stimulator output intensity was set at 120% AMT and the inter-  
321 stimulus interval was adjusted to 10 ms. Long-interval intracortical inhibition (LICI) was determined  
322 by a conditioning stimulus of 120% AMT followed by a test stimulus at 120% AMT with an inter-  
323 stimulus interval of 100 ms.

#### 324 ***Maximal compound muscle action potential***

325 Direct muscle responses were obtained from the FCR muscle by supramaximal electrical stimulation  
326 (pulse width 200  $\mu$ s) of the Brachial plexus (Erbs point) during light background muscle activity  
327 (DS7A, Digitimer, UK). An increase in current strength was applied to Erbs point until there was no  
328 further increase observed in the amplitude of the EMG response ( $M_{MAX}$ ). To ensure maximal responses,  
329 the current was increased an additional 20% and the average  $M_{MAX}$  was obtained from five stimuli,  
330 with a period of 6-9 s separating each stimulus.  $M_{MAX}$  was recorded at baseline, prior to and following  
331 each training session and then at retention 72 h following the intervention to ensure that there were no  
332 changes in peripheral muscle excitability that could influence MEP amplitude.

333

#### 334 ***Data analysis:***

335 Pre-stimulus rmsEMG activity was determined in the FCR muscle 100 ms before each TMS stimulus  
336 during pre- and post-testing. Trials were discarded when the pre-stimulus rmsEMG was greater than  
337  $5 \pm 1\%$  of maximal rmsEMG and then the trial was repeated. The peak-to-peak amplitude of MEPs  
338 was measured in the dominant right FCR muscle. MEPs were analyzed (LabChart 8 software; AD  
339 Instruments) after each stimulus and flagged automatically with a cursor, providing peak-to-peak  
340 values in mV, averaged and normalized to the  $M_{MAX}$ , and multiplied by 100. The total area under the  
341 recruitment curve (AURC) was calculated via the method of trapezoidal integration using the actual  
342 data collected during the construction of corticospinal excitability (MEP amplitude) and corticospinal  
343 inhibition (silent period duration) recruitment curves for the FCR before and after every strength-  
344 training session. The experimenter was blinded to each condition during all AURC analyses. Silent  
345 period durations were obtained from single-pulse stimuli delivered during the construction of the  
346 recruitment curve (130–170% AMT) and silent period durations were determined by examining the  
347 duration between the onset of the MEP and the resolution of background sEMG, which was visually  
348 inspected and manually cursoried. The average from 10 stimuli was used to determine silent period  
349 durations. SICI and ICF were expressed as a percentage of the unconditioned single-pulse MEP  
350 amplitude, while LICI was calculated and expressed as a percentage of the test to conditioning MEP  
351 amplitude for each individual paired stimuli. In regards to the changes in SICI, when the SICI  
352 percentage change increased following the strength-training sessions and the two-week intervention,  
353 this signified a decrease in cortical inhibition and when the SICI percentage change decreased

354 following training this signified an increase in cortical inhibition. The same percentage changes also  
355 applied to LICI.

356

357 The extent of co-activation of antagonists was determined by calculating the percentage of the maximal  
358 ECR and FCR rmsEMG recorded during wrist flexion 1-RM strength testing, compared to the maximal  
359 ECR rmsEMG recording during wrist extension 1-RM testing.

$$360 \text{ Co-activation} = (\text{ECR}/\text{ECR}_{\text{MAX}})/(\text{ECR}/\text{FCR}) \times 100$$

361 Peak rmsEMG of the ECR was recorded during wrist extension 1-RM testing; the peak rmsEMG for  
362 the ECR was also recorded during wrist flexion 1-RM testing. In a similar manner, peak rmsEMG for  
363 the FCR was recorded during wrist flexion 1-RM tests; and during wrist extension testing. For all  
364 testing conditions, the rmsEMG max was obtained during the 1-RM tests and was calculated from a 1  
365 s segment that occurred during the peak of the surface EMG trace. The ECR/ECR<sub>MAX</sub> ratio, expressed  
366 as a percentage of total activation was then used to correctly interpret the extent of ECR/FCR ratio.

367

### 368 *Statistical analysis*

369

370 All data were screened with Shapiro–Wilk and Kolmogorov–Smirnov tests and were found to be  
371 normally distributed (all  $P > 0.05$ ). A  $2 \times 7$  repeated measures analysis of variance (ANOVA) with  
372 factors CONDITION (Control and Training) and TIME (Pre, post session 1, post session 2, post  
373 session 3, post session 4, post session 5, post session 6 and post session 7) were used to compare  
374 changes in pre-stimulus rmsEMG, M-waves, CSE, ICF, silent period, SICI and LICI between  
375 conditions and across time. In order to determine the effect of strength training on dynamic muscle  
376 strength, a two-way ANOVA was used to compare group (trained vs. control) by week (week 1 vs.  
377 week 2) on the pooled changes in strength. For all ANOVAs, if significant main effects were found, a  
378 Bonferroni post hoc test was used to analyze the percentage change comparing condition interaction  
379 (Control and Training) by time. For all comparisons, effect sizes (ES) of 0.2, 0.5, and 0.8 were  
380 established to indicate small, moderate, and large comparative effects (Cohen's  $d$ ), respectively. Prism  
381 8 for Windows (GraphPad Software Inc, La Jolla, CA, USA) was used for all statistical analyses, with  
382 the level of significance set as  $P < 0.05$  for all testing. All data are presented as mean  $\pm$  95% CI in  
383 text, whilst mean  $\pm$  SD is presented in Tables and Figures.

384

## 385 **Results**

386

### 387 *Pre-stimulus rmsEMG, maximal compound waves and motor thresholds*

388 Pooled weekly summary data for measures of electrophysiology is reported in Table 1. In summary,  
389 there were no significant differences between groups in M-waves, pre-stimulus rmsEMG, RMT or  
390 AMT at baseline and no main effects for TIME or TIME  $\times$  CONDITION interactions in any measure  
391 (All  $P > 0.05$ ; Table 1). Thus, in both the strength-training and control group, there were no changes in

392 any of the aforementioned measures within any single session during the training program. Further, no  
393 changes were observed compared to baseline 72 h following the cessation of the training period in both  
394 the strength-training and control group (All  $P > 0.05$ ; Table 1).

395

### 396 ***Changes in Muscle Strength***

397 The percentage change in the dominant trained wrist flexor following strength-training or no training  
398 (control) is presented in Figure 2. Following strength training, there was a main effect for TIME [ $(F_{2, 32}$   
399  $= 32.7, P < 0.0001]$  and a GROUP  $\times$  TIME interaction [ $(F_{2, 32} = 20.5, P < 0.0001)$ ]. Post hoc analysis  
400 revealed by the end of the first week of strength-training, the strength-training group increased their 1-  
401 RM strength of the wrist flexor by  $6.3 \pm 4.5\%$  (CI -9.80 to -0.0995,  $P = 0.04, d = 1.24$ ) compared to a  
402  $1.4 \pm 3.5\%$  increase in the control group (Table 1). Post hoc analysis also showed after two-weeks of  
403 strength-training, the strength-training group increased their 1-RM strength by  $15.5 \pm 7.6\%$  (CI -18.5  
404 to -8.76,  $P < 0.001, d = 2.20$ ) compared to a  $1.8 \pm 3.5\%$  increase in the control group.

405

406

## INSERT FIGURE 2

407

### 408 ***TMS Measurements***

409 The primary aim of the TMS measurements were to investigate both the short-term and long-term  
410 adaptations to strength-training. Because none of the control group measurements showed any  
411 significant changes across testing sessions or training weeks (i.e., within group main effects, see Table  
412 2), the data presented in the short-term and long term responses to strength-training only include the  
413 main interaction effects between the strength-training and control groups.

414

415 ***Short-term MEP responses to strength training:*** Figure 3A illustrates the percentage change following  
416 each strength-training session across the two-week intervention for the strength-training group only.  
417 There was a significant main effect for increased CSE following the first session (CI -93.1 to -22.9,  $P$   
418  $< 0.001, d = 1.82$ ), second session (CI -91.8 to -21.5,  $P > 0.001, d = 1.89$ ), third session (CI -77.3 to -  
419 7.11,  $P = 0.008, d = 1.17$ ), fourth session (CI -79.8 to -9.58,  $P = 0.004, d = 1.68$ ), fifth session (CI -81.9  
420 to -11.7,  $P = 0.002, d = 1.42$ ), sixth session (CI -80.0 to -9.77,  $P = 0.004, d = 1.45$ ) and 72 h after the  
421 last strength training session [session 7, retention] (CI -78.3 to -8.10,  $P = 0.006, d = 2.12$ ) compared to  
422 the control group. There were no differences in CSE between sessions for the strength-training group,  
423 thus the short-term effects of training seemed to be largest in response to the first training session and  
424 then sustained across subsequent training sessions (Figure 3A).

425

426 ***Longer-term MEP responses to strength training:*** The longer-term adaptations to training are defined  
427 as the differences that occur when comparing the pre-training values obtained in the baseline test, the  
428 one-week test (session 3), the two-week test (session 6) and the retention test (session 7). These

429 responses are illustrated in Figure 3B. For the strength-training group, AURC for CSE increased by 53  
430  $\pm$  43% (CI 35.7 to 68.9,  $P < 0.0001$ ,  $d=1.67$ ) compared to the  $0.5 \pm 4.5\%$  increase in the control group  
431 at the end of training week 1, and by  $45 \pm 39\%$  (CI 30.4 to 60.5,  $P < 0.001$ ,  $d=1.60$ ) compared to the  
432  $0.2 \pm 2.6\%$  increase in the control group at the end of training week 2. The AURC for CSE was also  
433 increased from baseline 72 h following the strength-training intervention by  $44 \pm 27\%$  (CI 23.6 to 62.8,  
434  $P < 0.001$ ,  $d=2.13$ ) compared to the control group (Figure 3B).

435

436

#### INSERT FIGURE 3A-B

437

438 **Short-term corticospinal inhibitory responses to strength training:** Figure 4A illustrates the  
439 percentage change in silent period following each strength-training session across the two-week  
440 intervention for the strength-training group compared to the control group. In the strength-training  
441 group, there was a main effect for reduced silent period duration following the first session (CI 8.26 to  
442 20.3,  $P < 0.001$ ,  $d = 2.18$ ), second session (CI 7.74 to 19.8,  $P < 0.001$ ,  $d = 2.77$ ), third session (CI 4.92  
443 to 17.0,  $P < 0.001$ ,  $d = 1.73$ ), fourth session (CI 1.82 to 13.9,  $P = 0.002$ ,  $d = 1.72$ ), fifth session (CI -  
444 2.59 to 14.7,  $P = 0.0004$ ,  $d = 2.46$ ), sixth session (CI 1.73 to 13.8,  $P = 0.002$ ,  $d = 2.35$ ) and 72 h after  
445 the last strength-training session (CI 8.25 to 20.3,  $P < 0.001$ ,  $d = 1.96$ ) compared to the control group.  
446 There was a significant difference in the duration of the silent period between session 1 and session 4  
447 (CI -12.5 to -0.402,  $P = 0.025$ ,  $d = 0.92$ ) and session 1 and session 6 (CI -12.6 to -0.493,  $P = 0.021$ ,  $d$   
448  $= 1.20$ ) for the strength-training group. Corticospinal inhibition appears to reduce rapidly following the  
449 first training session and then steadily return towards baseline across subsequent strength-training  
450 sessions (Figure 4A).

451

452 **Longer-term corticospinal inhibitory responses to strength training:** The longer-term adaptations to  
453 training are defined as the differences that occur when comparing the pre training values obtained in  
454 the baseline test, the one-week test, the two-week test and the retention test. These responses are  
455 illustrated in Figure 4B. For the strength-training group, AURC for silent period reduced by  $13 \pm 6.3\%$   
456 (CI 6.69 to 19.6,  $P < 0.001$ ,  $d = 2.56$ ) compared to the  $0.1 \pm 2.5\%$  increase in the control group at the  
457 end of training week 1 and reduced by  $8\% \pm 3.9\%$  (CI 2.77 to 15.6,  $P < 0.002$ ,  $d = 2.26$ ) compared to  
458 the  $1.1 \pm 1.3\%$  increase in the control group at the end of training week 2. The AURC for corticospinal  
459 inhibition also reduced 72 h following the strength-training intervention by  $14 \pm 10\%$  (CI 9.33 to 22.2,  
460  $P < 0.001$ ,  $d=1.58$ , Figure 4B) compared to the control group.

461

462

#### INSERT FIGURE 4A-B

463

464 **Short-term SICI responses to strength training:** Figure 5A illustrates the percentage change in SICI  
465 following each strength-training session across the two-week intervention for the strength-training

466 group. In the strength-training group, there was a main effect for a release in SICI following the first  
467 session (CI -56.3 to -10.9,  $P = 0.002$ ,  $d = 1.33$ ), second session (CI -60.0 to -14.6,  $P < 0.001$ ,  $d = 1.43$ ),  
468 third session (CI -50.7 to -5.33,  $P < 0.003$ ,  $d = 1.55$ ), and 72 h after the last strength-training session  
469 (CI -58.3 to -13.0,  $P < 0.001$ ,  $d = 1.56$ ) compared to the control group. Interestingly, there were no  
470 differences in SICI release across strength-training sessions four, five and six for the strength-training  
471 group (all  $P > 0.05$ , Figure 5A).

472  
473 **Longer-term SICI responses to strength training:** Again, the longer-term adaptations to training are  
474 defined as the differences that occur when comparing the pre-training values obtained in the baseline  
475 test, the one-week test, the two-week test and the retention test. These responses are illustrated in Figure  
476 5B. For the strength-training group, SICI reduced by  $33 \pm 25\%$  (CI -52.6 to -12.5,  $P < 0.001$ ,  $d = 1.68$ )  
477 compared to the  $0.4 \pm 7.6\%$  increase in the control group at the end of training week 1. There were no  
478 differences in SICI release between the strength-training group and the control group at the end of week  
479 2 (CI -35.8 to 4.29,  $P = 0.163$ ,  $d = 2.26$ ), despite a large effect. However, SICI was reduced for the  
480 strength-training group at 72 h following the strength-training intervention by  $35 \pm 25\%$  (CI -54.7 to -  
481 14.6,  $P < 0.001$ ,  $d = 1.51$ ) compared to the control group.

482  
483 **INSERT FIGURE 5A-B**

484  
485 **Short-term and longer-term ICF responses to strength training:**

486 Figure 6A illustrates the percentage change in ICF following each strength-training session across the  
487 two-week intervention for the strength-training group. In the strength-training group, there was a main  
488 effect for increased ICF following the first session (CI -27.8 to -3.66,  $P = 0.001$ ,  $d = 1.48$ ) and second  
489 session (CI -25.2 to -0.231,  $P < 0.04$ ,  $d = 1.38$ ), compared to the control group. ICF also increased for  
490 the strength-training group following the fourth session (-24.5 to -0.396,  $P < 0.036$ ,  $d = 0.72$ ), but the  
491 magnitude of this change was not different to the control group. There were no differences in ICF across  
492 strength-training sessions three, five and six (all  $P > 0.05$ , Figure 6A) and at retention for the strength-  
493 training group compared to the control group. For the strength-training group, ICF increased by  $13 \pm$   
494  $10\%$  (CI -23.9 to -4.37,  $P = 0.002$ ,  $d = 1.86$ ) compared to the  $1.0 \pm 1.8\%$  decrease in the control group  
495 at the end of training week 1 and increased by  $12 \pm 11\%$  (CI -21.4 to -1.21,  $P = 0.023$ ,  $d = 1.57$ , Figure  
496 6B) compared to the  $0.7 \pm 1.7\%$  decrease in the control group after the end of training week two. There  
497 were no differences in ICF between the strength-training and control groups at retention (CI -17.9 to  
498 3.17,  $P = 0.245$ ).

499 **INSERT FIGURE 6A-B**

500  
501  
502

503 ***Short-term and long-term LICI responses to strength training:***

504 In the strength-training group, there were no main effects for a change in LICI from strength-training  
505 session 1 to strength-training session 6 ( $P = 0.463$ ) or following week 1 of training ( $P > 0.999$ ), week  
506 2 ( $P = 0.993$ ) or at retention ( $P = 0.99$ ) compared to the control group.

507

508 ***Changes in Co-Activation of Antagonists:***

509 Figure 7 illustrates the antagonist co-activation index obtained during the weekly 1-RM strength testing  
510 following week 1 and week 2 for the strength-training and control group. There was a significant main  
511 effect for a reduction in antagonist co-activation from week 1 to week 2 compared to the control group  
512 (CI -3.08 to -2.30,  $P = 0.02$ ,  $d = 1.80$ ).

513

514 **INSERT FIGURE 7**

515

516

517

518 **Discussion**

519

520 This study examined the time-course effects of strength-training on the formation of use-dependent  
521 cortical plasticity and how it contributed to improvements in muscular strength. The main findings are  
522 **1)** increases in strength were apparent after three sessions of strength-training, and further increases  
523 were observed following six sessions, **2)** following two-weeks of strength-training, CSE was increased  
524 with concurrent decreases in the duration of the silent period and SICI; however, **3)** the acute cortical  
525 responses to strength-training did not accumulate within each training session, rather **4)** the substantial  
526 and rapid responses to a single session of strength-training were either maintained (CSE), reduced  
527 (silent period) or abolished (ICF and SICI) during subsequent sessions, indicating that neural  
528 adaptations occurred between training sessions. Further, antagonist co-contraction during training was  
529 substantially reduced in week two compared to week one. These findings indicate that the M1 undergoes  
530 substantial use-dependent plasticity from the first strength-training session onwards alongside reduced  
531 co-contraction of antagonists in order to drive improvements in muscular strength. These adaptations  
532 are rapid, and beyond the immediate cellular response to the initial strength-training session (such as  
533 increases in synaptic efficacy), occur primarily between strength-training sessions, and culminate in  
534 longer-term functional changes (i.e., neurogenesis).

535

536 ***The time-course of strength development***

537

538 The current study provides insight into the temporal scale of strength improvement, with significant  
539 increases in strength following just three strength-training sessions, and further increases following six  
540 strength-training sessions. The time-course of strength improvement supports the findings of Griffin

541 and Cafarelli (2003) who observed strength increases following just two sessions of isometric strength  
542 training of the tibialis anterior, and further progressive increases throughout the rest of a four-week  
543 strength-training period. There are several lines of evidence suggesting that just one strength-training  
544 session can produce increases in strength upwards of 10% (Hood and Forward 1965; Christie and  
545 Kamen 2004; Nuzzo et al. 2019), and improvements in strength over a three-day strength-training  
546 period can be maintained three months following the cessation of training (Kroll 1963). The magnitude  
547 of strength gain following six sessions of training is comparatively large in reference to studies reporting  
548 improvements following longer strength-training periods (Ahtianen et al. 2003; Gomes et al. 2018;  
549 Serra et al. 2018). The difference is likely due to the subjects recruited in the current study being novices  
550 to any form of strength-training. Experimental evidence shows that inexperienced strength trainers  
551 obtain larger gains in strength across a multi-week training program when compared with subjects who  
552 are more experienced (Ahtianen et al. 2003). Further, discrepancies in the magnitude of strength  
553 improvements between studies might also be explained by the elements of the strength-training used in  
554 the current study, including heavy-load, dynamic contractions with external pacing (Leung et al. 2017;  
555 Kidgell et al. 2010; Mason et al. 2019). In summary, increases in strength begin very early after the  
556 onset of strength-training, and accumulate across training weeks, reinforcing the existing evidence that  
557 strength-training is an effective stimulus capable of producing rapid, lasting improvements in  
558 performance (Siddique et al. 2019).

559

560 ***The training-related corticospinal and M1 responses are similar to the short-term acute responses.***

561

562 Seventy-two hours following the final session, substantial changes in M1 plasticity were observed when  
563 compared to baseline and to the control group, which is consistent with the literature (see Siddique et  
564 al. 2019 for review). Similarly, the responses to the initial strength-training session were well-aligned  
565 with current evidence (see Mason et al. 2019 for review). With the exception of ICF, the corticospinal  
566 and M1 responses (or lack of, see LICI) to the initial strength-training session mirrored the responses  
567 measured at the retention period following the two-week strength-training period. The general  
568 alignment between the acute responses to the initial strength-training session and the retained responses  
569 following two-weeks of strength-training, provides the foundation for a simple and progressive  
570 accumulation of neural responses from session one onwards. However, from week one to week two,  
571 there appears to be no accumulation in the acute M1 and corticospinal responses to each individual  
572 strength training session as hypothesised. Rather, the M1 and corticospinal responses are substantially  
573 and rapidly enhanced from the first strength-training session and are maintained (CSE), reduced (silent  
574 period) or eventually eliminated (SICI and ICF) across the course of the sixth strength-training session.  
575 Combined, these results indicate that substantial neural adaptations between strength-training sessions  
576 could be influencing the corticospinal and M1 adaptations supporting the increase in strength  
577 throughout a training period.

578

579 *Identifying the neural mechanisms that accompany strength development*

580

581 Prior to discussing the mechanisms of cortical plasticity throughout the strength-training period, it may  
582 be useful to postulate what purpose cortical plasticity could serve. Alterations in corticospinal output  
583 during and following strength-training likely contributed to the development of strength through an  
584 influence on motor unit behaviour. The magnitude of muscle activation, and therefore the amount of  
585 force produced, is determined by the number of activated motor units (recruitment) and the rate at which  
586 the motoneurons are discharged (rate coding), with both being altered following strength-training  
587 (Farina et al. 2016). Recent evidence, using validated techniques previously unavailable (Farina et al  
588 2016), indicates that strength gains following four-weeks of isometric strength-training are driven by  
589 decreased motor unit recruitment thresholds and increased discharge rates (Del Vecchio et al. 2019).  
590 This aligns with earlier evidence whereby increases in strength are due to adaptations in motor unit  
591 recruitment and rate coding following isometric strength-training (Duchateau et al. 2006; Van Cutsem  
592 et al.1998; Vila-Cha et al. 2010; Kamen and Knight 2004). Given that motor units are controlled by  
593 input to the motoneurone pool from the corticospinal tract, alterations in motor unit behaviour likely  
594 involve adaptive changes in the corticospinal tract from the M1 to the spinal motoneurone pool. Of  
595 these potential sites, adaptations at a supraspinal level are a primary candidate (Siddique et al. 2019;  
596 Semmler and Enoka 2000; Schubert et al. 2008). Indeed, Del Vecchio and colleagues (2019) proposed  
597 that increased net excitatory synaptic input to the motoneurone pool was the likely mechanism driving  
598 motor unit adaptations as opposed to modification to the intrinsic motoneurone properties. This, paired  
599 with evidence that strength-training increases voluntary activation with no increase in cervicomedullary  
600 excitability (Nuzzo et al., 2017; Siddique et al. 2019), suggests that modulation at the level of the M1  
601 may be responsible for alterations in motor unit behaviour. Therefore, it is conceivable that in the  
602 current study, increases in CSE and decreases in inhibitory input to the motoneurone pool generated  
603 changes in motor unit recruitment and rate coding throughout the strength-training period, which  
604 ultimately underpinned the observed increases in strength. These corticospinal responses likely reflect  
605 an improved ability of the M1 to maximally recruit and discharge motor units, which is demonstrated  
606 by the increase in the input-output properties of the corticospinal tract following strength-training (i.e.  
607 change in AURC for CSE and silent period). However, a potential caveat to this line of inquiry is that  
608 there is evidence to suggest that the corticospinal tract is not the only descending motor pathway that  
609 provides synaptic input to the spinal motoneurone pool, which could alter motor unit behaviour (Riddle  
610 et al. 2009). For example, evidence shows that the reticulospinal tract is associated with force  
611 production (Baker and Perez 2017), therefore, it could be the case that the reticulospinal tract was also  
612 modulated as a result of the strength-training intervention. It is also likely that modulation in the  
613 reticulospinal tract, also contributed to the increase in force, presumably through enhanced direct and  
614 indirect synaptic input to the spinal motoneurone pool. The time-course of these adaptations also



615 supports this notion, as the increase in strength occurred rapidly and directly in line with the timeframes  
616 for alterations in motor unit behaviour (i.e. session by session, Christie and Kamen 2004). Further,  
617 reduced antagonist co-activation during the second week of strength-training is also consistent with  
618 existing evidence demonstrating rapid antagonist alterations following strength-training (Hight et al.  
619 2017). Thus, changes in antagonist behaviour, alongside the agonist corticospinal responses,  
620 collectively contribute to increases in strength (Mason et al. 2019).

621  
622 The timing of cortical plasticity within this study warrants further discussion, as it provides insight into  
623 how the rapid cellular responses ultimately develop into longer-lasting functional changes (i.e.,  
624 synaptogenesis) following two-weeks of strength training. The presence of substantial adaptations  
625 between training sessions and the formation of cortical plasticity across the strength-training program  
626 add to the consistent comparisons between the development of strength and the acquisition of a motor  
627 skill (Leung et al. 2015; Leung et al. 2017; Jensen et al. 2005; Mason et al. 2019). In fact, it seems that  
628 strength-training induces neurogenesis that occurs between training sessions. Although there are no  
629 strength-training studies that have examined this notion alongside the time-dependent adaptations to  
630 strength-training, the use of skill acquisition frameworks may aid in the interpretation of the current  
631 result and the notion that strength-training induces neurogenesis.

632  
633 Diminishing responses to individual sessions and significant adaptations between strength-training  
634 sessions may be indicative of early and late phases of cortical plasticity supporting strength acquisition,  
635 resembling the distinct early and later phases of skill acquisition identified by imaging, behavioural and  
636 TMS studies (Karni et al. 1998; Rosenkranz et al. 2007; Kleim et al. 2006; Floyer-Lea and Matthews  
637 2005). Early responses to skill training are commonly attributed to changes in existing synaptic strength,  
638 and later responses attributed to distinct functional processes such as synaptogenesis or neurogenesis  
639 (Rosenkranz et al. 2007; Kleim et al. 2006). Therefore, the early phase of strength development might  
640 also be characterised by changes in existing synaptic efficacy, which may occur both during training  
641 and at rest, whereas later changes may reflect structural changes that occur between training sessions.  
642 This idea is supported by the acute inhibitory responses to early training sessions, as a reduction in  
643 GABA-mediated inhibition is necessary for the early enhancement of synaptic efficacy (Hess et al.  
644 1996; Hess and Donoghue 1994) and is associated with the acquisition of novel motor tasks (Stagg et  
645 al. 2011; Floyer-Lea et al. 2006; Butefisch et al., 2000; Kida et al. 2016; Mooney et al. 2019). Further,  
646 a lack of acute online inhibitory responses later in training is compatible with evidence that longer-term  
647 structural plasticity occurs between training sessions, not within training sessions (Mednick et al. 2011),  
648 and that synaptogenesis does not directly contribute to initial acquisition, but occurs later in the learning  
649 process underpinning consolidation and retention of a skill (Kleim et al. 2004). However, the role of  
650 synaptogenesis and the functional reorganisation of M1 in strength development remains to be  
651 determined, despite evidence from animal models that unlike skill training, strength-training is

652 incapable of inducing changes in motor map representations regardless of training stage (Remple et al.  
653 2001). This is despite evidence of increased volume of excitable synapses onto motoneurons following  
654 strength-training (Adkins et al. 2006).

655

656 It must be noted in contrast to the skill training literature (Kleim et al. 2006; Rosenkrantz et al. 2007),  
657 CSE remained substantially modulated by each strength-training session, despite all other indicators of  
658 cortical plasticity diminishing across the strength-training period. An increase in CSE immediately  
659 following a single session of strength-training appears to be an important factor for cortical plasticity  
660 underpinning strength development, as its abolishment via rTMS following strength-training reduces  
661 strength improvements considerably (Hortobágyi et al. 2009). Collectively, this suggested that CSE  
662 could contribute to both early cellular and later structural plasticity (i.e. neurogenesis) serving increases  
663 in strength, despite a lack of correlation between gains in strength and increased CSE following several  
664 weeks of strength-training (Jensen et al. 2005; Mason et al. 2017). The lack of correlation is likely due  
665 to other neural structures and systems being involved in strength development, especially the intrinsic  
666 spinal circuitry (Siddique et al. 2019). Thus, there is a need to examine multiple sites within the CNS  
667 in order to provide a greater understanding of which systems in the CNS are most related to changes in  
668 strength. However, CSE is not just an indicator of corticospinal plasticity, it is also thought to increase  
669 as a function of fatigue (Mason et al. 2019; Latella et al. 2017), representing a point of difference  
670 between strength-training and the typically low-fatiguing paradigms used in skill training. Whilst it is  
671 possible that repeated acute modulation of CSE through strength-training is sufficient to trigger  
672 mechanisms of structural plasticity (synaptogenesis) between strength-training sessions, conclusions  
673 regarding the functional consequences of increased CSE are preliminary in this context (Bestmann and  
674 Krakauer 2015).

675

676 The current study has a number of limitations that must be considered when interpreting the findings.  
677 Firstly, a more precise temporal scale of strength improvements would have been generated through  
678 testing strength alongside every TMS testing day. However, this is logistically difficult, given the ability  
679 of even one maximum testing session to influence subsequent neuromuscular responses and  
680 performance (Nuzzo et al. 2019). Secondly, strength-training studies typically use more precise  
681 measurements of strength testing than 1-RM testing, such as maximal isometric voluntary contractions  
682 (MVIC) (Kidgell et al. 2017). However, previous strength-training studies have identified using  
683 different testing and training apparatus or techniques as a limitation. Indeed, adaptations are typically  
684 specific to the training involved (Brownstein et al. 2018), and are therefore better assessed by identical  
685 protocols. Additional limitations include a lack of a more comprehensive assessment protocol to assess  
686 spinal excitability, such as volitional waves and cervicomedullary evoked potentials. Future studies  
687 should seek to track the responses to both skill and strength-training across an entire training period to  
688 discern differences. Importantly, beyond the assessment of peripheral excitability, the current study was

689 unable to determine the contribution of fatigue to the single session responses. Therefore, similar  
690 upcoming studies should include techniques (such as cortical voluntary activation) to discern the role  
691 of both peripheral and central fatigue in mediating the acute and short-term responses to strength  
692 training and, how they relate to the process of acquiring muscular strength.

693

694 In summary, this study provides new insight into how the rapid responses to a single bout of strength-  
695 training evolve into longer-term cortical plasticity that accompanies the increases in muscle strength  
696 following a two-week strength-training period. These results add to the notion that the repeated stimulus  
697 of strength-training is sufficient to induce long-lasting changes in muscle strength and cortical  
698 plasticity. Combined, the findings provide evidence for early and late phases of strength development,  
699 mediated by distinct cortical mechanisms similar to the frameworks observed for the development of  
700 motor skills. Importantly, the alterations in CSE and inhibition across the strength-training program  
701 occur acutely and between training sessions, conceivably to drive the changes in motor unit behaviour,  
702 which ultimately seem responsible, at least in part, for improvements in force production.  
703 Understanding the time-course and location of neural adaptation to heavy-load strength-training will  
704 allow practitioners to design more efficient training programs to develop and preserve skeletal muscle  
705 strength for maintenance of health and improve human performance. Finally, Kleim and Jones (2008)  
706 suggested that cortical plasticity underlying improvements in motor skill is perhaps best considered a  
707 process rather than a single measurable event, as it involves a cascade of events at the molecular,  
708 cellular and structural levels (Kandel 2001). The same must be considered for the adaptations  
709 underpinning improvements in strength. Thus, the relationship between corticospinal and M1 plasticity  
710 and strength development is an area ripe for further exploration.

711 **Author contributions** JM, AF, and DJK conceived and designed the study. JM, AF, GH and DJK  
712 conducted experiments, analyzed data, and drafted the first version of the manuscript. AJP, JA critically  
713 revised the manuscript. All authors read and approved the manuscript.

714

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717

718 **Compliance with ethical standards**

719

720 **Conflict of interest** None of the authors have potential conflicts of interest to be disclosed.

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