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25 **ABSTRACT**

26 Synaptic plasticity in the motor cortex (M1) is associated with strength training and can be modified by  
27 transcranial direct current stimulation (tDCS). The M1 responses to strength training increase when anodal-tDCS  
28 is applied during training due to gating. An additional approach to improve the M1 responses to strength training,  
29 which has not been explored, is to use anodal-tDCS to prime the M1 before a bout of strength training. We  
30 examined the priming effects of anodal-tDCS of M1 on the acute corticospinal responses to strength training. In  
31 a randomized double-blinded cross-over design, changes in isometric strength, corticospinal-excitability and  
32 inhibition (assessed as area under the recruitment curve [AURC] using transcranial magnetic stimulation [TMS])  
33 were analysed in 13 adults exposed to 20-min of anodal and sham-tDCS followed by a strength training session  
34 of the right elbow-flexors. We observed a significant decrease in isometric elbow-flexor strength immediately  
35 following training (11-12%;  $P < 0.05$ ) which was not different between anodal-tDCS and sham-tDCS. TMS  
36 revealed a 24% increase in AURC for corticospinal-excitability following anodal-tDCS and strength training; this  
37 increase was not different between conditions. However, there was a 14% reduction in AURC for corticospinal-  
38 inhibition when anodal-tDCS was applied prior to strength training when compared to sham-tDCS and strength  
39 training (all  $P < 0.05$ ). Priming anodal-tDCS had a limited effect in facilitating corticospinal-excitability following  
40 an acute bout of strength training. Interestingly, the interaction of anodal-tDCS and strength training appears to  
41 affect the excitability of intracortical inhibitory circuits of the M1 via non-homeostatic mechanisms.

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44 **Key Words:** Corticospinal excitability, corticospinal silent period, neuroplasticity, strength exercise,  
45 transcranial direct current stimulation.

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## 51 **Introduction**

52           Strength training improves muscle strength, which can be broadly defined as the maximal force or torque  
53 that can be developed by the muscles performing a specific movement (8). Studies have demonstrated that muscle  
54 strength can be improved following a single session of strength training (9, 11, 21, 34). Adaptation within the  
55 central nervous system is believed to contribute to the increase in muscle force that is observed during the early  
56 phases of a strength training program. It is plausible that these adaptations are initiated over a very short time-  
57 span. For example, a single session of heavy-load elbow-flexion strength training increased MEPs evoked by  
58 single-pulse TMS (23). More recently, Latella et al. (21) reported increased MEP amplitude following a single  
59 session of both heavy-loaded and hypertrophy-based strength training. However, in contrast, Selvanayagam et al.  
60 (34) reported reduced MEP amplitude following a single session of strength training.

61

62           The acute effects of strength training on increasing corticospinal excitability appear inconclusive, but  
63 preliminary evidence shows that changes in the duration of the corticospinal silent period could be an important  
64 early neural adaptation to strength training. For example, the duration of the corticospinal silent period is reduced  
65 immediately following both heavy-load and hypertrophy-based strength training (21, 22); however, this is in  
66 conflict with earlier findings that suggested increases in corticospinal silent period duration throughout and  
67 immediately following a single session of strength training (33). Thus, there is a need to examine alternative  
68 techniques that may facilitate the early neural responses to strength training.

69

70           The use of transcranial direct current stimulation (tDCS) has gained popularity as a safe and non-invasive  
71 technique that can be utilized to induce plasticity in the primary motor cortex (M1) (28). tDCS utilizes weak direct  
72 currents that induce prolonged modulation of corticospinal excitability within the M1 (28). The procedure  
73 involves applying low level (1–2 mA) electrical currents to the M1 over the area of interest via saline-soaked  
74 electrodes (28). The orientation of the electrodes and direction of current flow determine the physiological effect  
75 of stimulation, with anodal stimulation (anodal-tDCS) increasing excitability of underlying cortical neurons, and  
76 cathodal stimulation (c-tDCS) decreasing excitability, both being associated with long-term potentiation and long-  
77 term depression (28). The immediate effects of tDCS are due to changes in membrane polarity which influence  
78 the likelihood of depolarization (25). In contrast, longer lasting changes in corticospinal excitability, which have  
79 been reported up to 90 min following stimulation, are attributed to changes in synaptic efficacy (25). Evidence

80 over the last 10-15 years has demonstrated that, in addition to the modulation of corticospinal excitability  
81 following anodal-tDCS, stimulation also appears to produce transient effects in motor performance (6).

82

83         There are two approaches to applying anodal-tDCS (before or during motor training) which have  
84 different proposed mechanisms of action. The concurrent application of tDCS during the performance of motor  
85 learning tasks (i.e., gating) has been shown to facilitate the motor performance (11, 36). Gating describes the  
86 influx of calcium ions to the targeted corticospinal neurons resulting in the release of inhibition from intracortical  
87 inhibitory circuits (39). More relevant to the current study is the principle of motor priming whereby the resting  
88 state of corticospinal neurons is altered (increased/decreased level of excitability following a low/high level of  
89 synaptic activity) due to changes in postsynaptic glutamate receptor activity (39). Given that anodal-tDCS has  
90 been shown to modulate N-methyl-D-aspartate (NMDA) receptors, and subsequently produce a shift in the resting  
91 membrane potential (28), it is possible that anodal-tDCS could be used as a priming tool to increase synaptic  
92 activity prior to a single bout of strength training to further enhance the acute corticospinal responses to strength  
93 training. Understanding the interaction between the priming effects of anodal-tDCS and strength training has  
94 important implications for strength training program design, as the effects of anodal-tDCS could depend on the  
95 timing of its application relative to the timing of the strength training intervention. To the best of our knowledge,  
96 no study has compared the corticospinal responses to strength training when the training is performed following  
97 anodal-tDCS.

98         Therefore, the aim of this study was to examine the effect of priming the M1 using anodal-tDCS prior to  
99 a single bout of strength training to determine if the early corticospinal responses to strength training are facilitated  
100 compared to sham-tDCS and strength training alone. It was hypothesised that the application of anodal-tDCS prior  
101 to a single bout of strength training would increase corticospinal excitability (motor-evoked potential amplitudes)  
102 and reduce corticospinal inhibition (silent period duration) compared to the application of sham-tDCS prior to a  
103 bout of strength training.

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106

107 **Methods**

108 *Experimental Approach to the Problem*

109 All participants completed two experiments as outlined in Figure 1A-B. After obtaining consent,  
110 participants completed a familiarization session one week prior to the study that involved performing a one-  
111 repetition maximum (1RM) strength test of the right elbow flexors (to establish training load) and were exposed  
112 to single-pulse TMS. In a double-blinded cross-over design, all participants were exposed to two conditions in  
113 Experiment 1. Each participant was exposed to 20 min of anodal and sham tDCS followed by a single strength  
114 training session of the right elbow flexors (anodal tDCS + ST and sham tDCS + ST, respectively). The order of  
115 the conditions was counterbalanced and randomized between participants, with a wash-out period of one week  
116 between each condition (37). All participants underwent TMS and isometric strength testing (maximum voluntary  
117 isometric contraction [MVC]) of the right elbow flexors prior to and following the tDCS and strength training  
118 intervention (see Figure 1A).

119 To determine the effects of anodal tDCS without strength training on corticospinal excitability and  
120 corticospinal inhibition, participants also completed Experiment 2. Each participant was exposed to 20 min of  
121 anodal and sham tDCS with a wash-out period of one week between each condition (37). Prior to and following  
122 the tDCS intervention, 20 single-pulse TMS stimuli were collected at 150% and 170% active motor threshold  
123 (AMT) (see Figure 1B).

124 **Insert Figure 1A-B**

125 *Subjects*

126 Thirteen participants (five women, eight men [ $25.2 \pm 5.8$  yr]) volunteered to participate. All volunteers  
127 provided written informed consent prior to participation in the study, which was approved by the La Trobe  
128 University Human Research Ethics Committee (2013-231) in accordance with the standards by the Declaration  
129 of Helsinki. All subjects were informed of the benefits and risks of the investigation prior to signing the approved  
130 informed consent document to participate in the study. All participants were right-hand dominant as determined  
131 by the Edinburgh Handedness Inventory (30) with a Laterality Quotient score of  $86 \pm 5$ , had not participated in  
132 strength training for at least 12 months, but were recreationally active, and were free from any known history of  
133 peripheral or neurological impairment. Prior to the experiment, all participants completed the adult safety-  
134 screening questionnaire to determine their suitability for TMS and tDCS (12).

135 *Voluntary Strength Testing*

136 To determine maximal voluntary dynamic force, participants completed a one-repetition maximum  
137 (1RM) test of the right-elbow flexor muscles. As described by Kidgell et al. (16) participants stood against a wall  
138 with the dumbbell held in their right hand and their left arm placed behind their back to prevent excessive body  
139 movement. The starting position involved the participant holding the weight in their right hand with their elbow  
140 in full extension and forearm supinated. The participant was then instructed to flex their arm and lift the dumbbell.  
141 If the lift was successful, the weight was increased until the participant could no longer perform one repetition.  
142 Between each trial, 3-min rest was given to minimise muscular fatigue. The last successful trial was recorded as  
143 their 1RM strength and was used to determine individual training load and was only measure at baseline (16). On  
144 average, it took three trials for each participant to obtain their 1RM. Importantly, the researcher who administered  
145 the voluntary strength testing was blinded to the tDCS condition.

146

147 *Isometric Strength Testing*

148 Maximal voluntary isometric contraction (MVC) force was measured using handheld dynamometry  
149 (Microfet2, Salt Lake City, USA). Participants were instructed to stand against a wall (gluteal and shoulder  
150 contact) with the elbow flexed at 90°, as measured by an electronic goniometer (ADInstruments, Bella Vista,  
151 Australia), and with their hand in a supinated position. The dynamometer was positioned on the participant's  
152 forearm at the level of the wrist. The participant was then instructed to flex the elbow against the dynamometer  
153 as forcefully as possible for 3 sec. Three attempts, with a 2-min rest between each attempt were performed. The  
154 standard criteria for measurement of MVCs were fulfilled and included a period of familiarization (prior to data  
155 collection), verbal encouragement provided by the investigators, and the rejection of a trial in the case the  
156 participant felt it was not a maximal effort. We have previously reported that this testing procedure is reliable,  
157 with a coefficient of variation of 1.1% ( $P = 0.54$ ,  $r = 0.99$ ) (31). Again, the researcher who administered the  
158 isometric strength testing pre and post was blinded to the tDCS condition.

159

160 *Strength Training Protocol*

161 Participants completed a supervised strength-training session following the anodal and sham tDCS  
162 intervention (Experiment 1). Using the same set-up as the 1RM, participants completed flexion-extension  
163 movements of the right elbow with the forearm supinated (biceps curl). Participants completed 4 sets of 6-8

164 repetitions at 80% 1RM with 3-min recovery between sets (16). A repetition timing of 3 sec concentric and 4 sec  
165 for the eccentric phase was maintained using an electronic metronome (16). The use of an automated timing device  
166 was selected as previous research has shown that controlled-velocity strength training facilitates greater neural  
167 adaptations compared to self-paced training (23, 24).

168

### 169 *Surface Electromyography*

170 The area of electrode placement was shaved to remove fine hair, rubbed with an abrasive skin gel to  
171 remove dead skin, and then cleaned with 70% isopropyl alcohol. Surface electromyography (sEMG) was recorded  
172 from the right biceps brachii muscle using bipolar Ag-AgCl electrodes. The site of measurement was determined  
173 by marking the skin two thirds of the distance between the acromion and the lateral epicondyle, while the  
174 participant stood relaxed in the anatomical position (31). This mark was then extended to the most anterior point  
175 of the muscle bulk, and the electrodes were placed 2 cm apart over the mid-belly of the bicep brachii, with a  
176 ground electrode secured on the lateral epicondyle of the humerus. sEMG signals were amplified (x1000), band  
177 pass filtered (high pass at 13 Hz, low pass at 1000 Hz), digitized online at 2 kHz, recorded (1 sec), and analyzed  
178 using Power Lab 4/35 (AD Instruments, Bella Vista, Australia).

179

### 180 *Transcranial Magnetic Stimulation*

181 TMS was delivered using a Magstim 200<sup>2</sup> stimulator (Magstim Co, Dyfed, UK) and a single figure-of-  
182 eight coil (external diameter of each loop 70 mm). Sites near the estimated center of the right biceps brachii area  
183 (motor hotspot) were explored to determine the site at which the largest motor evoked potential (MEP) amplitude  
184 was evoked and AMT was established as the intensity at which at least 5 of 10 stimuli produced MEP amplitudes  
185 of greater than 200  $\mu$ V. Following the tDCS and strength training intervention, AMT was re-tested and adjusted  
186 (increased or decreased) if required. To ensure all stimuli were delivered to the optimal motor hotspot throughout  
187 testing, participants wore a tight-fitting cap marked with a latitude-longitude matrix, positioned with reference to  
188 the nasion-inion and interaural lines.

189 Recruitment curves were constructed to determine corticospinal excitability (MEP amplitude) and  
190 corticospinal inhibition (silent period duration) pre and post intervention for Experiment 1. For a single stimulus-  
191 response curve, 10 stimuli were delivered at 90%, 110%, 130%, 150%, 170%, and 190% of AMT during a low-  
192 level isometric contraction of the right biceps brachii muscle. Participants were required to maintain an elbow



193 joint angle of 90° elbow flexion. Joint angle was measured with an electromagnetic goniometer (ADInstruments,  
194 Bella Vista, Australia), with visual feedback provided on a screen visible to both the participant and the researcher  
195 (13). This joint position equated to  $4 \pm 1\%$  of maximal root-mean squared electromyography (rmsEMG), with  
196 consistent muscle activation confirmed by recording pre-stimulus rmsEMG for the 100-ms epoch before the  
197 delivery of each stimulus (Table 1).

198

#### 199 *Maximum Compound Muscle Action Potential*

200 Direct muscle responses were obtained from the right biceps brachii muscle by supramaximal electrical  
201 stimulation (pulse width 200  $\mu$ s) of the brachial plexus at Erbs point (DS7A; Digitimer, Hertfordshire, United  
202 Kingdom). The stimuli were delivered while the participant sat in an upright position, with the elbow at 90°  
203 elbow flexion holding  $4 \pm 1\%$  of maximal rmsEMG. This low level of muscle activity was used to match the  
204 conditions under which TMS was delivered. An increase in current strength was applied to Erbs point until there  
205 was no further increase observed in the amplitude of the sEMG response ( $M_{MAX}$ ). To ensure maximal responses,  
206 the current was increased an additional 20% and the average  $M_{MAX}$  was obtained from five stimuli, with a period  
207 of 6–9 sec separating each stimulus.  $M_{MAX}$  was recorded at baseline and following the tDCS intervention to  
208 control for possible changes in peripheral muscle excitability that could influence MEP amplitude.

209

#### 210 *Transcranial Direct Current Stimulation*

211 In all tDCS conditions (Experiment 1 and 2), participants received 20 min of tDCS delivered by a battery-  
212 driven constant-current transcranial direct current stimulator (NeuroConn, Ilmenau, Germany). Stimulation was  
213 delivered by a pair of conductive rubber electrodes (anode 25 cm<sup>2</sup>; cathode 35 cm<sup>2</sup>; current density 0.08 mA/cm<sup>2</sup>)  
214 each soaked in saline solution (0.9% NaCl) and secured on the head with a rubber strap (28). Anodal tDCS  
215 involved 20-min at an intensity of 2 mA, with a current density of 0.08 mA/cm<sup>2</sup>. The anode was fixed over the  
216 optimal cortical representation of the right biceps brachii muscle, as identified by TMS over the left cortex, and  
217 the cathode was placed over the right contralateral supra orbital area. To ensure consistency of the site of  
218 stimulation, the participant's head was marked with a latitude-longitude matrix, positioned with reference to the  
219 nasion-inion and interaural lines. Both the experimenter and participant were blinded to the tDCS condition (i.e.,  
220 sham versus anodal tDCS) using codes on the tDCS machine. The sham protocol had the identical arrangement  
221 to the anodal tDCS condition, but the stimulation terminated after approximately 20 sec. This resulted in the

222 participant experiencing the initial sensation of tDCS, however, no experimental effects occurred. To obtain the  
223 participant's perception of discomfort throughout all tDCS conditions, discomfort (which included pain, itching,  
224 and tingling sensations) was assessed using a visual analogue scale (VAS) during the first 3 minutes of stimulation.  
225 The VAS ranged from 0 to 10 as visually described in cm units: 0 cm indicates "no discomfort" and 10 cm means  
226 "extremely uncomfortable".

227

### 228 *Data Analysis*

229 Pre-stimulus rmsEMG activity was determined in the right biceps brachii muscle 100 ms prior to each  
230 TMS stimulus during pre- and post-testing. Any trial in which pre-stimulus rmsEMG was greater than  $4 \pm 1$  % of  
231 maximal rmsEMG was discarded and the trial was repeated. The peak-to-peak amplitude of MEPs evoked because  
232 of stimulation was measured in the right biceps brachii muscle contralateral to the cortex being stimulated in the  
233 period 10-50 ms after stimulation. MEP amplitudes were analyzed (LabChart 8 software, ADInstruments, Bella  
234 Vista, NSW, Australia) after each stimulus was automatically flagged with a cursor, providing peak-to-peak  
235 values in  $\mu\text{V}$ , averaged and normalized to the  $M_{\text{MAX}}$ , and multiplied by 100.

236 To determine the input-output properties of the corticospinal tract, the total area under the recruitment  
237 curve (AURC) was calculated for Experiment 1 via the method of trapezoidal integration using the actual data  
238 collected during the construction of corticospinal excitability (MEP amplitude) and corticospinal inhibition (silent  
239 period duration) RC (4). The experimenter was blinded to each condition during all AURC analysis. Silent-period  
240 durations were obtained from single-pulse stimuli delivered during the construction of the RC (90-190% AMT  
241 for Experiment 1) and at 150% and 170% AMT during a light contraction ( $4 \pm 1$  % of maximal rmsEMG of the  
242 right biceps brachii muscle) for Experiment 2. For Experiments 1 and 2, corticospinal silent period durations were  
243 determined by examining the duration between the onset of the MEP and the resolution of background sEMG,  
244 which was visually inspected and manually cursoried, with the experimenter blinded to each condition. The  
245 average from ten stimuli was used to determine corticospinal silent period durations (26).

246

### 247 *Sample Size Calculations and Statistical Analyses*

248 The number of participants required was based upon power calculations for the expected changes in  
249 mean-rectified MEPs (sEMG recordings from the elbow flexor muscle) following a single session of strength  
250 training. Using previous data in healthy untrained adults (23), we estimated that 11 participants would provide at

251 least 80% power (95% confidence interval) to detect a 15% increase in mean-rectified MEPs assuming a SD of  
252 10–15% between conditions at  $P < 0.05$  (two-tailed).

253 All data were screened with the Shapiro-Wilk test and found to be normally distributed (all  $P > 0.05$ )  
254 and, thus, the assumptions of the ANOVA were not violated. Subsequently, for Experiment 1, a split-plot in time,  
255 repeated measure ANOVA was used to compare the effects of anodal tDCS + ST and sham tDCS + ST conditions  
256 on multiple dependent variables (MVC force, pre-stimulus EMG, AURC for corticospinal excitability and silent  
257 period duration) over two time points (pre-testing and post-testing). For all comparisons, effect sizes (ES) of 0.2,  
258 0.5, and 0.8 were established to indicate small, moderate and large comparative effects (Cohen's  $d$ ), respectively.

259 A sub-analysis was also conducted for Experiment 2 to determine if anodal tDCS without strength  
260 training had an effect on indices of corticospinal excitability and corticospinal inhibition. Again, a split-plot in  
261 time, repeated measure ANOVA was used to compare the effects of anodal tDCS and sham tDCS conditions on  
262 multiple dependent variables (corticospinal excitability and corticospinal silent period duration at 150% and 170%  
263 AMT) over two time points (pre-testing and post-testing). Again, for all comparisons, effect sizes (ES) of 0.2, 0.5,  
264 and 0.8 were established to indicate small, moderate and large comparative effects (Cohen's  $d$ ). In addition, paired  
265 t-tests were performed on VAS scales. Bonferroni correction for multiple comparisons was applied for each  
266 dependent variable where significant main effects and interactions were found. Prism 7 for Windows (Graphpad  
267 Software Inc, CA, USA) was used for all statistical analyses, with the level of significance set as  $P < 0.05$  for all  
268 testing. All data are presented as mean  $\pm$  SE.

269

## 270 **Results**

### 271 *Pre-stimulus rmsEMG, Maximal Compound Wave, and Visual Analogue Scale*

272 Table 1 presents the mean ( $\pm$  SE) for AMT stimulus intensity,  $M_{MAX}$  and single-pulse TMS pre-stimulus  
273 rmsEMG prior to and following anodal tDCS + ST and sham tDCS + ST. Pre-stimulus rmsEMG ( $P = 0.54$ ), AMT  
274 stimulus intensity ( $P = 0.23$ ) and  $M_{MAX}$  ( $P = 0.76$ ) were similar between the two conditions at baseline. Pre-  
275 stimulus rmsEMG did not vary between single-pulse trials, and there was no TIME or TIME x CONDITION  
276 interaction observed ( $P = 0.64$ ). Similarly, there was no TIME or TIME x CONDITION interaction detected for  
277 AMT stimulus intensity ( $P = 0.78$ ). Furthermore, there was no TIME or TIME x CONDITION interaction detected  
278 for  $M_{MAX}$  ( $P = 0.40$ ). VAS data were collected for each condition and there was no difference in the participants'

279 perception of discomfort between anodal tDCS + ST and sham tDCS + ST conditions ( $3.3 \pm 0.5$ ,  $3.2 \pm 0.5$ ,  $2.8 \pm$   
 280  $0.7$ , respectively;  $P = 0.48$ ).

281 **Insert Table 1**

282

283 *Maximal Voluntary Isometric Contraction Force*

284 Isometric strength was assessed for the right-elbow flexor muscles prior to and following the anodal-  
 285 tDCS + ST and sham-tDCS + ST intervention. Figure 2 shows the mean change in isometric strength for the right-  
 286 elbow flexor muscles. There were no differences in isometric strength at baseline between anodal-tDCS + ST and  
 287 sham tDCS + ST conditions [ $F(1, 12) = 0.19$ ;  $P = 0.66$ ]. Following the intervention, the ANOVA revealed only a  
 288 TIME effect for both the anodal-tDCS + ST (95% CI 14.02 to 43.72;  $d = 0.46$ ;  $P = 0.0006$ ) and sham-tDCS + ST  
 289 conditions (95% CI 16.14 to 45.3;  $d = 0.50$ ;  $P = 0.0004$ ). There was no TIME x CONDITION interaction detected  
 290 [ $F(1, 12) = 0.06$ ;  $P = 0.80$ ]. Isometric elbow flexor strength decreased by 11% following anodal-tDCS + ST and,  
 291 similarly, by 12% following sham-tDCS + ST.

292 **Insert Figure 2**

293 *Corticospinal Excitability and Corticospinal Inhibition*

294 *Experiment 1*

295 Figure 3 shows the AURC for corticospinal excitability obtained prior to and following the sham-tDCS  
 296 + ST, whilst Figure 4 shows AURC for corticospinal excitability prior to and following the anodal-tDCS + ST  
 297 intervention. The AURC was similar between conditions at baseline [ $F(1, 12) = 0.10$ ;  $P = 0.75$ ]. Following the  
 298 intervention, there was a main effect for TIME [ $F(1, 12) = 14.54$ ;  $P = 0.005$ ], but there was no TIME x  
 299 CONDITION interaction detected [ $F(1, 12) = 2.62$ ;  $P = 0.13$ ]. AURC increased in the anodal-tDCS + ST condition  
 300 by 24% (95% CI -581 to -109.2;  $d = 3.38$ ;  $P = 0.0056$ ) compared to a 9% increase following the sham-tDCS + ST  
 301 condition (95% CI -369.9 to 102;  $d = 1.31$ ;  $P = 0.34$ ).

302 Figure 5 shows the AURC for corticospinal inhibition (silent period duration) obtained prior to and  
 303 following the sham-tDCS + ST, whilst Figure 6 shows AURC for corticospinal inhibition (silent period duration)  
 304 prior to and following the anodal-tDCS + ST intervention. The AURC was similar between conditions at baseline  
 305 [ $F(1, 12) = 2.60$ ;  $P = 0.99$ ]. Following the intervention, there was a main effect for TIME and a TIME x

306 CONDITION interaction detected [ $F(1, 12) = 7.61; P = 0.017$ ]. Post hoc analysis showed that anodal-tDCS + ST  
307 decreased the total AURC by 14% (95% CI -882.2 to 2296;  $d = 1.02; P = 0.002$ ) compared to 5% following the  
308 sham-tDCS + ST condition (95% CI -195.3 to 1218;  $d = 0.08; P = 0.173$ ).

309 **Insert Figure 3 and 4**

310 **Insert Figure 5 and 6**

311

### 312 *Experiment 2*

313 The MEP amplitudes were similar between sham and anodal-tDCS conditions at baseline for each  
314 stimulus intensity [150% AMT,  $F(1, 12) = 0.007; P = 0.99$ ; 170% AMT,  $F(1, 12) = 0.074; P = 0.99$ ]. Following the  
315 anodal-tDCS intervention, there was a main effect for TIME [150% AMT;  $F(1, 12) = 11.63; P = 0.005$ ; 170%  
316 AMT;  $F(1, 12) = 5.23; P = 0.047$ ] and a TIME x CONDITION interaction [ $F(1, 12) = 5.53; P = 0.041$ ] detected at  
317 150% and 170% of AMT (see Figures 7 and 8). Post hoc analysis of MEPs at 150% and 170% of AMT showed  
318 that anodal-tDCS increased MEP amplitudes by 24% for both 150% AMT (95% CI -10.04 to -0.045;  $d = 2.80; P$   
319  $= 0.002$ ) and 170% AMT (95% CI -581 to -109.2;  $d = 1.96; P = 0.003$ ) compared to 1% and 2% following sham-  
320 tDCS (150% AMT, 95% CI -7.717 to 2.281;  $d = 0.23; P = 0.37$ ; 170% AMT, 95% CI -7.936 to 4.222;  $d = 0.11$ ;  
321  $P = 0.89$ ).

322 **Insert Figure 7 and 8.**

323 Corticospinal silent period durations were similar between sham and anodal-tDCS conditions at baseline  
324 for each stimulus intensity [150% AMT,  $F(1, 12) = 3.81; P = 0.074$ ; 170% AMT,  $F(1, 12) = 3.334; P = 0.098$ ].  
325 Following the tDCS intervention, there was a main effect for TIME [150% AMT,  $F(1, 12) = 21.6; P = 0.0006$ ;  
326 170% AMT,  $F(1, 12) = 29.08; P = 0.0002$ ] and a TIME x CONDITION interaction [150% AMT,  $F(1, 12) = 5.29$ ;  
327  $P = 0.041$ ; 170% AMT,  $F(1, 12) = 6.22; P = 0.028$ ] (see Figure 8). Post hoc analysis showed that anodal-tDCS  
328 decreased corticospinal silent period duration by 7% at 150% AMT (95% CI -8.749 to 27.59;  $d = 0.90; P = 0.0007$ )  
329 and by 9% at 170% AMT (95% CI 10.58 to 31.17;  $d = 0.95; P = 0.0005$ ) compared to an average of 1% following  
330 sham-tDCS (150% AMT, 95% CI -3.225 to 15.62;  $d = 0.17; P = 0.236$ ; 170% AMT, 95% CI -3.611 to 16.98;  $d$   
331  $= 0.23; P = 0.244$ ).

332

## 333 Discussion

334 The primary objective of this research was to determine if priming the M1 by anodal-tDCS, prior to a  
335 single bout of strength training, would facilitate the corticospinal responses to strength training. The main findings  
336 from **Experiment 1** were: (i) MVC of the elbow flexors declined in both groups (sham-tDCS + ST and anodal-  
337 tDCS + ST) to a similar magnitude following a single bout of strength training, suggesting that priming the M1  
338 with anodal-tDCS does not attenuate the loss of muscle strength; (ii) The application of anodal-tDCS prior to a  
339 single bout of strength training (anodal tDCS + ST) reduced corticospinal inhibition, but had no effect on  
340 corticospinal excitability. The main findings for **Experiment 2** were: (i) The application of anodal-tDCS increased  
341 corticospinal excitability and decreased corticospinal silent period duration showing that priming the M1  
342 modulates the corticospinal responses to tDCS.

343

### 344 *Priming the M1 with Anodal-tDCS Increases Corticospinal Excitability and Reduces Corticospinal Inhibition*

345 The first important finding of this study was the observed increase in corticospinal excitability and decreased  
346 corticospinal silent period duration following the application of anodal-tDCS only (Experiment 2). Anodal-tDCS  
347 has been shown previously to increase corticospinal excitability for up to 90 min post stimulation (15, 28) and  
348 decrease corticospinal inhibition (15, 29), with the changes in synaptic strength attributed to modulation of the  
349 NMDA receptor (27, 29, 32). Pharmacological interventions have further highlighted the importance of the  
350 NMDA receptor by using a NMDA receptor antagonist (i.e., dextromethorphan) to block the after-effects of tDCS  
351 (25, 29, 38). Importantly, these results confirmed the theoretical basis for using anodal-tDCS as a priming method  
352 to the M1 prior to a single bout of strength training to potentially further enhance or accelerate the acute  
353 corticospinal responses to strength training (24).

354

### 355 *Anodal-tDCS Prior to Strength Training Affects Corticospinal Inhibition, Not Corticospinal Excitability*

356 At present, there are conflicting results regarding the effect of using anodal-tDCS to prime the M1 prior to a  
357 motor-training task (1). Visuo-motor tracking performance has been shown to improve following 10-15 min of  
358 anodal-tDCS at 1 mA prior to training (1, 35), with retention lasting up to 24 hours (35). In direct contrast, Stagg  
359 et al. (36) found that anodal-tDCS applied to the M1 prior to a reaction-time task had a negative effect on motor  
360 learning. Currently, no study has investigated the effect of priming the M1 using anodal-tDCS prior to a single

361 bout of strength training to determine the effects of this on modulating corticospinal excitability and inhibition.  
362 Hendy and Kidgell (11) conducted the only study that has examined the effect of anodal-tDCS and strength  
363 training; however, they applied the tDCS during strength training, exploiting the principle of gating and reported  
364 a 15-25% increase in corticospinal excitability, 18% decrease in corticospinal inhibition (silent period duration)  
365 and a 15% increase in MVC force. Here, we sought to examine the effects of priming as the benefits of tDCS and  
366 strength training may lie within the timing of application (i.e., before or during training). However, prior synaptic  
367 activity induced by anodal-tDCS had a limited effect on corticospinal excitability following strength training,  
368 which is consistent with the principles of homeostatic plasticity (18). Because priming the M1 with anodal-tDCS  
369 increased neuronal plasticity prior to strength training, the excitability-enhancing effects of the strength training  
370 intervention were blocked, due to homeostatic plasticity. Overall, this likely led to a more persistent increase in  
371 corticospinal excitability that was not further affected by the subsequent strength training bout (36). This  
372 interpretation is supported by Experiment 2 where there was also a 24% increase in corticospinal excitability  
373 following anodal-tDCS only.

374

375 The current findings further extend the working hypothesis that anodal-tDCS + ST modulates  
376 corticospinal connections (i.e., improved synaptic efficacy) by exhibiting a decrease in the duration of the  
377 corticospinal silent period. Importantly, the data shows that the change in inhibition is due to non-homeostatic  
378 mechanisms, which is likely due to the effect of strength training post tDCS, specifically targeting the inhibitory  
379 neurons that use  $\gamma$ -aminobutyric acid (GABA<sub>B</sub>) as their neurotransmitter. Because sham-tDCS and strength  
380 training had no effect on corticospinal inhibition, and since priming induced homeostatic plasticity in the  
381 excitatory circuits of the M1, it seems that there is an interaction between priming the M1, strength training and  
382 the inhibitory motor circuits. At a minimum, priming affected corticospinal excitability leading to homeostatic  
383 plasticity, which resulted in strength training having a greater effect on modulating the inhibitory cortical circuits  
384 via non-homeostatic mechanisms. However, a caveat to this interpretation is that the exact inhibitory circuit within  
385 the M1 was not determined as only single-pulse TMS was employed. For example, initially, the duration of the  
386 corticospinal silent period is due to spinal cord refractoriness; however, the latter part is a result of cortical  
387 inhibition, which represents the overall strength of inhibition within the corticospinal tract (16). It appears that the  
388 interaction of anodal-tDCS + ST specifically targets neural circuits that use GABA<sub>B</sub> as their neurotransmitter,  
389 resulting in the release of corticospinal neurons from inhibition when compared to sham-tDCS+ ST. With respect  
390 to the input-output relationship between stimulus intensity and corticospinal silent period duration, a decrease in

391 total AURC was shown. This finding highlights that priming the M1 with anodal-tDCS prior to strength training  
392 reduced GABA-mediated inhibitory projections, which resulted in enhanced synaptic efficacy. The results also  
393 show that strength training further decreased inhibition. Changes in intracortical inhibition appear to be important  
394 for muscle strength, with studies of immobilization showing increased inhibition, whilst strength training studies  
395 show reduced inhibition (31). The observed immediate decrease in corticospinal inhibition may represent  
396 acquiring the skill of producing high levels of muscular force in response to the initial training exposure. An  
397 immediate reduction in the excitability of the inhibitory motor pathway may serve to increase ‘motor focus’, and  
398 therefore facilitate an increase in drive to muscle representations producing the intended movement (14).

399

400 Interestingly, this reduction in corticospinal silent period duration was similar to the reductions observed  
401 following 2-4 weeks of strength training (5, 7, 10, 13, 19, 26) and is consistent with recent findings by Latella et  
402 al. (21). Therefore, similar to motor learning, a reduction in cortical inhibition seems to be an important early  
403 neural response to strength training (13). This early neural response is also supported by a recent systematic review  
404 and meta-analysis which observed that strength training had a greater overall effect on corticospinal inhibition,  
405 rather than corticospinal excitability (14). Even though priming the M1 before a bout of strength training reduced  
406 corticospinal inhibition, the precise role of reduced corticospinal inhibition in the current study remains unclear  
407 as priming did not attenuate the loss in muscle force following training; therefore, the functional significance of  
408 this reduction remains unresolved. It is possible that the paced nature of the strength training task induced some  
409 form of peripheral fatigue that was not detectable by sEMG or by measuring m-waves post training.

410

411 There are several limitations that need to be considered when interpreting these data. First, if the  
412 fundamental purpose of strength training is to increase strength, then the central nervous system must adjust by  
413 increasing the activation of the spinal motor neuron pool that contributes to strength development. To this end, a  
414 limitation within the current study was the recording of MEPs from only the agonist muscle. It is well accepted  
415 that changes in the activation of the agonist and antagonist contribute to the net increase in force production  
416 following strength training (3). Although we have previously reported that the corticospinal responses to a single  
417 bout of strength training predominantly occur at the level of the M1 (23) and, supported by other recent work (20,  
418 21, 22), a limitation to this interpretation was that no spinal cord measures were obtained, in particular cervico-  
419 medullary motor-evoked potentials. This must be considered as a limitation because MEPs are influenced by  
420 changes in spinal excitability (2). Another consideration with the present study is that the functional role of the



421 early corticospinal responses to strength remain unclear. Although we show for the first time that priming the M1  
422 before strength training affects the corticospinal responses to strength training, how these responses specifically  
423 relate to the generation of muscle force remains unclear given that anodal-tDCS did not attenuate the decline in  
424 muscle force post-training. Despite these limitations, the findings from this study add new knowledge by showing  
425 that the corticospinal responses to strength training are affected by priming the M1 with anodal-tDCS prior to a  
426 bout of strength training.

427

### 428 **Practical Applications**

429 Overall, the findings from this study indicate that priming the M1 with anodal-tDCS prior to a single  
430 bout of strength training altered the corticospinal responses to strength training, through non-homeostatic  
431 mechanisms. Interestingly, priming the M1 with tDCS did not attenuate the loss in muscle force following  
432 training, suggesting that tDCS has little effect on preserving muscle strength. Although the current data do not  
433 provide conclusive evidence that the changes in corticospinal inhibition observed following anodal-tDCS and  
434 strength training is causally related to strength gain, the finding that the corticospinal responses to acute strength  
435 training are affected by anodal-tDCS may have important applications in understanding the long-term adaptations  
436 following a strength training program. Importantly, our findings show that priming the M1 with anodal-tDCS  
437 prior to strength training reduces neural inhibition, which is important for the development of muscular strength  
438 following short-term strength training (14).

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444

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564 **FIGURE LEGENDS**

565 **Figure. 1A-B:** (A) Schematic representation of the design of Experiment 1 with measures obtained  
566 prior to and following 20 min anodal and sham-tDCS and strength training. Pre- and post-measures  
567 included assessment of peripheral muscle excitability ( $M_{MAX}$ ), corticospinal excitability and inhibition  
568 recruitment curves and maximal voluntary isometric contraction (MVIC) strength test of the right  
569 Biceps Brachii muscle. There was a one-week wash-out period between conditions. (B) Schematic  
570 representation of the design of Experiment 2 with measures obtained prior to and following 20 min  
571 anodal and sham-tDCS. Pre- and post- measures included assessment of peripheral muscle excitability  
572 ( $M_{MAX}$ ), corticospinal excitability and inhibition at 150% and 170% AMT. Again, there was a one-week  
573 wash-out period between conditions.

574 **Figure. 2:** Mean ( $\pm$  SE) changes in MVIC strength of the right Biceps Brachii muscle for 13 participants  
575 following anodal-tDCS + ST and sham-tDCS + ST.  $\hat{\wedge}$  indicates significant to baseline.

576 **Figure 3:** The AURC for corticospinal excitability was calculated using the method of trapezoidal  
577 integration for Experiment 1. The AURC obtained prior to the sham-tDCS + ST intervention is shaded  
578 in grey (pre). The additional area enclosed by the recruitment curve obtained following the sham-tDCS  
579 + ST intervention is shaded in white (post).

580 **Figure 4:** The AURC for corticospinal excitability was calculated using the method of trapezoidal  
581 integration for Experiment 1. The AURC obtained prior to the anodal-tDCS + ST intervention is shaded  
582 in grey (pre). The additional area enclosed by the recruitment curve obtained following the anodal-  
583 tDCS + ST intervention is shaded in white (post). \* indicates significant within-condition-effect.

584 **Figure 5:** The AURC for corticospinal inhibition was calculated using the method of trapezoidal  
585 integration for Experiment 1. The AURC obtained prior to sham-tDCS + ST intervention is shaded in  
586 in white. The additional area enclosed by the recruitment curve obtained following sham-tDCS + ST is  
587 shaded in grey. The AURC calculated from corticospinal inhibition recruitment curves for 13  
588 participants in the sham-tDCS + ST condition whereby corticospinal silent period (ms) was plotted  
589 against stimulus intensity.

590 **Figure 6:** The AURC for corticospinal inhibition was calculated using the method of trapezoidal  
591 integration for Experiment 1. The AURC obtained prior to anodal-tDCS + ST intervention is shaded in  
592 white. The additional area enclosed by the recruitment curve obtained following anodal-tDCS + ST is  
593 shaded in grey. The AURC calculated from corticospinal inhibition curves for 13 participants in the  
594 anodal-tDCS + ST condition whereby MEP amplitude was plotted against stimulus intensity. \* indicates  
595 significant within-condition-effect. # Indicates significant difference to sham + ST (between-condition-  
596 effect).

597 **Figure 7:** Mean ( $\pm$  SE) changes in MEP amplitude at 150% and 170% AMT before and after 20 min of  
598 anodal and sham-tDCS (Experiment 2) for 13 participants. \* indicates significant to sham tDCS.

599 **Figure. 8:** Mean ( $\pm$  SE) changes in cortical silent period duration at 150% and 170% AMT before and  
600 after 20 min of anodal and sham-tDCS (Experiment 2) for 13 participants. \* indicates significant to  
601 sham tDCS.

602

603

604 **Table 1:** Mean ( $\pm$  SE) for AMT stimulus intensity,  $M_{\text{MAX}}$  and single-pulse TMS pre-stimulus  
 605 *rmsEMG* prior to and following sham tDCS + ST and anodal tDCS + ST.

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618 AMT SI: active motor threshold stimulus intensity. Single-pulse (SP) *rmsEMG* was pooled  
 619 across stimulus intensities. *P* values represent the 2 (conditions) x 2 (time) repeated measures  
 620 ANOVA used to determine any differences between conditions and time for the dependent  
 621 variables AMT stimulus intensity,  $M_{\text{MAX}}$  and single-pulse TMS pre-stimulus *rmsEMG*.

622

623

	Sham tDCS +		Anodal tDCS +		<i>P</i> value
	ST		ST		
	Pre	Post	Pre	Post	
<b>AMT SI (%)</b>	42.85	42.08	44.31	43.37	0.78
	$\pm 2.40$	$\pm 2.36$	$\pm 1.87$	$\pm 2.32$	
<b><math>M_{\text{MAX}}</math> (mV)</b>	9.41	9.53	8.92	8.96	0.40
	$\pm 1.31$	$\pm 1.42$	$\pm 0.79$	$\pm 0.79$	
<b>SP <i>rmsEMG</i></b>	4.26	4.65	3.78	3.91	0.64
<b>(% <i>rmsEMG</i><sub>MAX</sub>)</b>	$\pm 0.59$	$\pm 0.78$	$\pm 0.63$	$\pm 0.52$	



624 **FIGURE LEGENDS**

625 **Figure. 1A-B:** (A) Schematic representation of the design of Experiment 1 with measures obtained  
626 prior to and following 20 min anodal and sham-tDCS and strength training. Pre- and post-measures  
627 included assessment of peripheral muscle excitability ( $M_{MAX}$ ), corticospinal excitability and inhibition  
628 recruitment curves and maximal voluntary isometric contraction (MVIC) strength test of the right  
629 Biceps Brachii muscle. There was a one-week wash-out period between conditions. (B) Schematic  
630 representation of the design of Experiment 2 with measures obtained prior to and following 20 min  
631 anodal and sham-tDCS. Pre- and post- measures included assessment of peripheral muscle excitability  
632 ( $M_{MAX}$ ), corticospinal excitability and inhibition at 150% and 170% AMT. Again, there was a one-week  
633 wash-out period between conditions.

634 **Figure. 2:** Mean ( $\pm$  SE) changes in MVIC strength of the right Biceps Brachii muscle for 13 participants  
635 following anodal-tDCS + ST and sham-tDCS + ST.  $\hat{\wedge}$  indicates significant to baseline.

636 **Figure 3:** The AURC for corticospinal excitability was calculated using the method of trapezoidal  
637 integration for Experiment 1. The AURC obtained prior to the sham-tDCS + ST intervention is shaded  
638 in grey (pre). The additional area enclosed by the recruitment curve obtained following the sham-tDCS  
639 + ST intervention is shaded in white (post).

640 **Figure 4:** The AURC for corticospinal excitability was calculated using the method of trapezoidal  
641 integration for Experiment 1. The AURC obtained prior to the anodal-tDCS + ST intervention is shaded  
642 in grey (pre). The additional area enclosed by the recruitment curve obtained following the anodal-  
643 tDCS + ST intervention is shaded in white (post). \* indicates significant within-condition-effect.

644 **Figure 5:** The AURC for corticospinal inhibition was calculated using the method of trapezoidal  
645 integration for Experiment 1. The AURC obtained prior to sham-tDCS + ST intervention is shaded in  
646 in white. The additional area enclosed by the recruitment curve obtained following sham-tDCS + ST is  
647 shaded in grey. The AURC calculated from corticospinal inhibition recruitment curves for 13  
648 participants in the sham-tDCS + ST condition whereby corticospinal silent period (ms) was plotted  
649 against stimulus intensity.

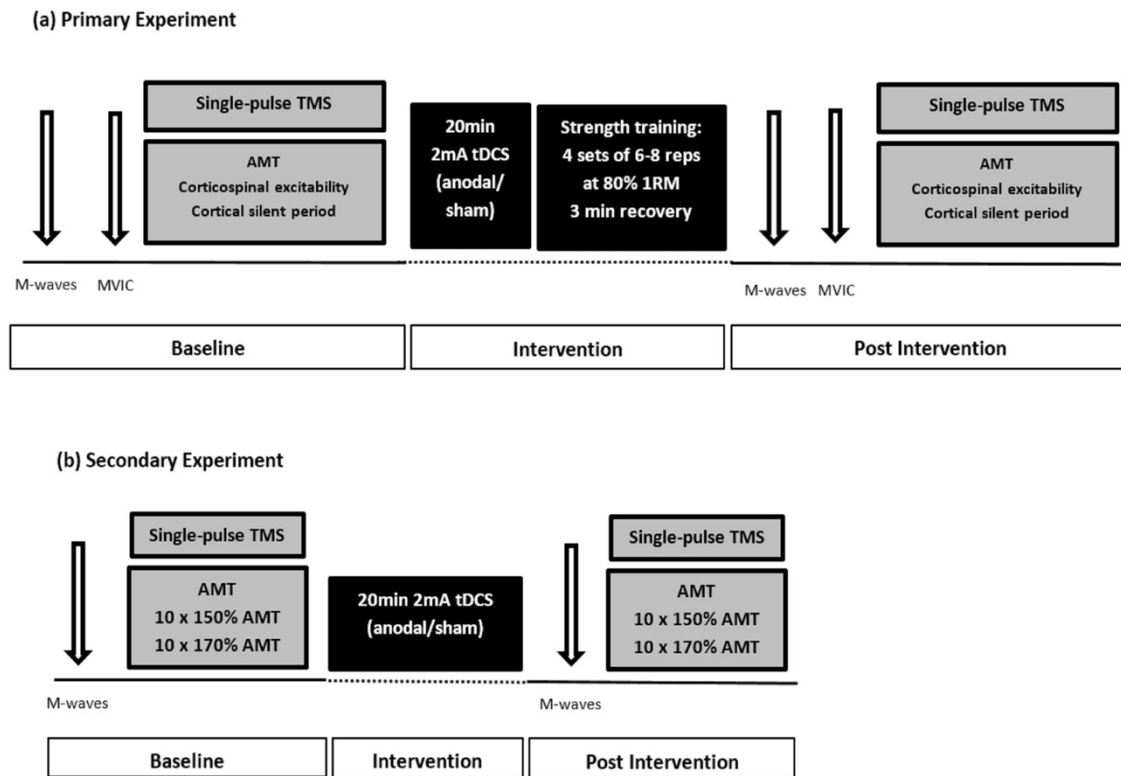
650 **Figure 6:** The AURC for corticospinal inhibition was calculated using the method of trapezoidal  
651 integration for Experiment 1. The AURC obtained prior to anodal-tDCS + ST intervention is shaded in  
652 white. The additional area enclosed by the recruitment curve obtained following anodal-tDCS + ST is  
653 shaded in grey. The AURC calculated from corticospinal inhibition curves for 13 participants in the  
654 anodal-tDCS + ST condition whereby MEP amplitude was plotted against stimulus intensity. \* indicates  
655 significant within-condition-effect. # Indicates significant difference to sham + ST (between-condition-  
656 effect).

657 **Figure 7:** Mean ( $\pm$  SE) changes in MEP amplitude at 150% and 170% AMT before and after 20 min of  
658 anodal and sham-tDCS (Experiment 2) for 13 participants. \* indicates significant to sham tDCS.

659 **Figure. 8:** Mean ( $\pm$  SE) changes in cortical silent period duration at 150% and 170% AMT before and  
660 after 20 min of anodal and sham-tDCS (Experiment 2) for 13 participants. \* indicates significant to  
661 sham tDCS.

662

663 Figure 1

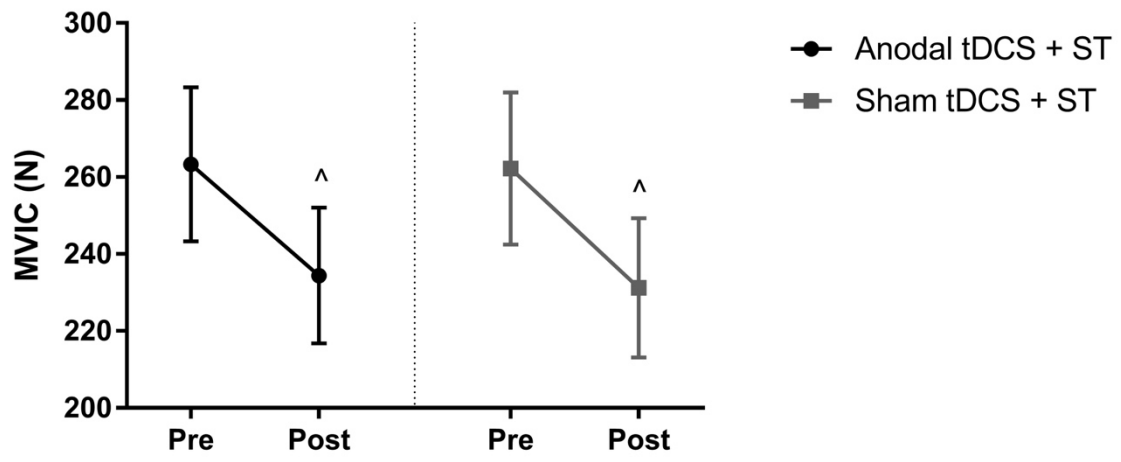


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667 **Figure 2**

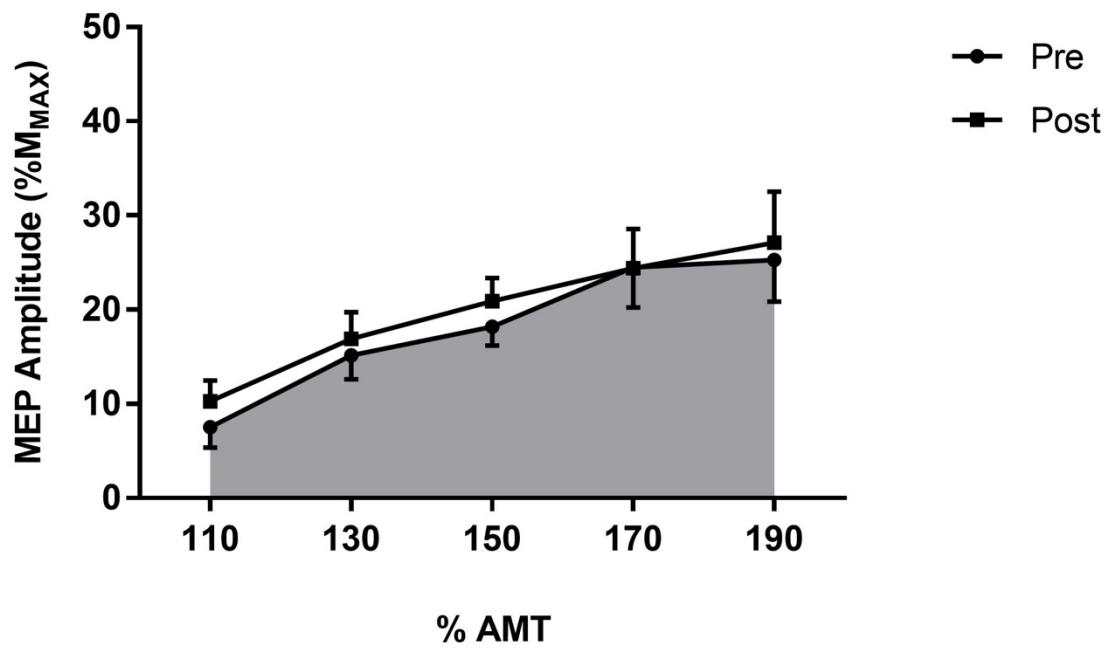


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Figure 3

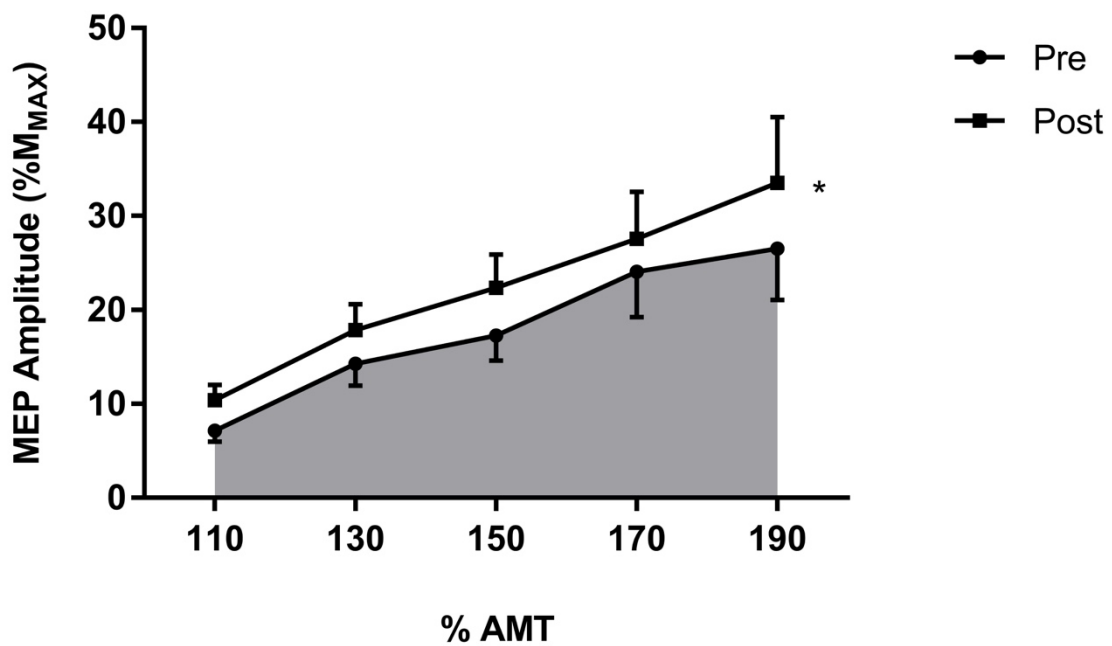


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Figure 4

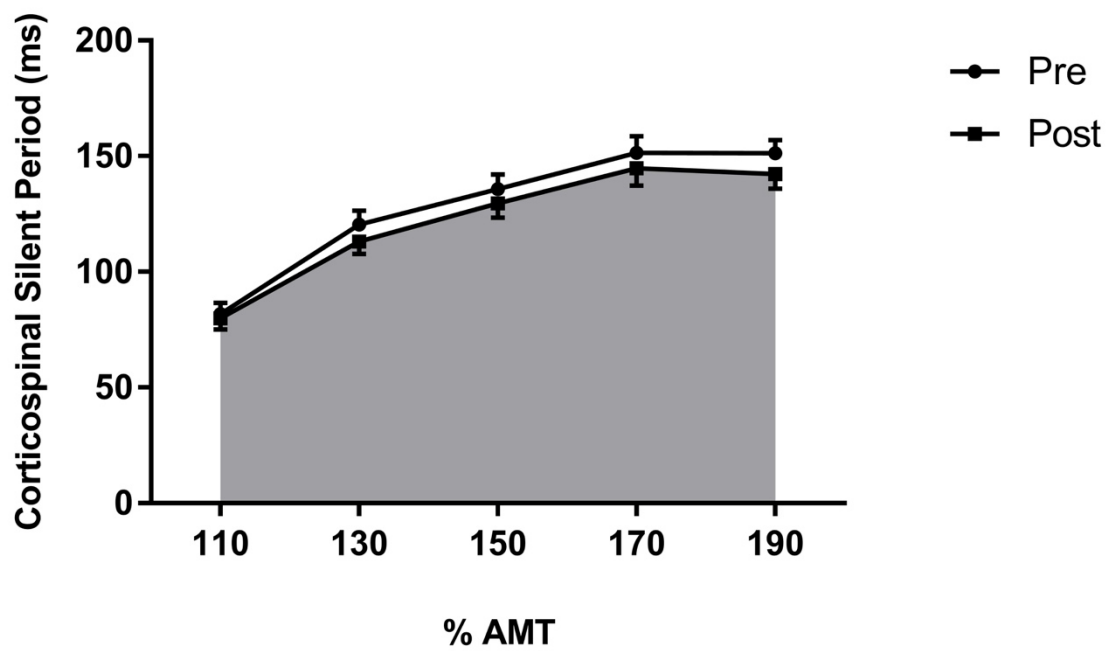


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Figure 5

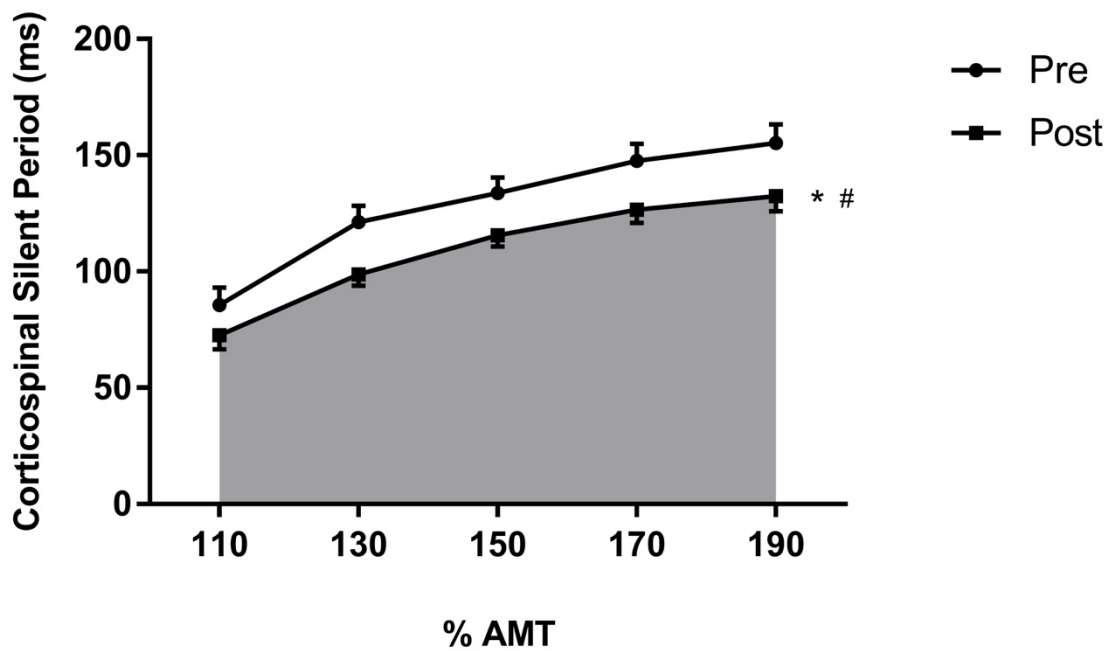


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Figure 6



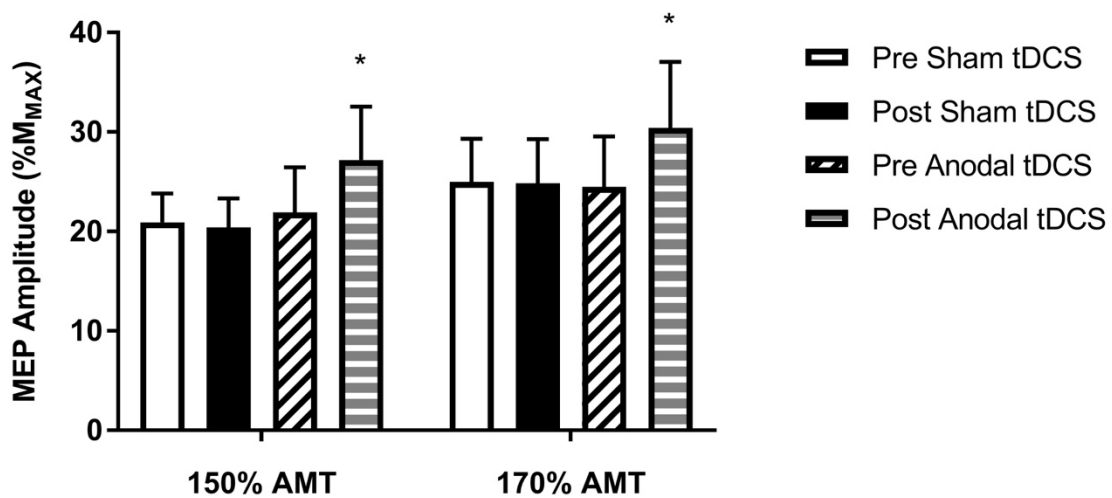
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Figure 7

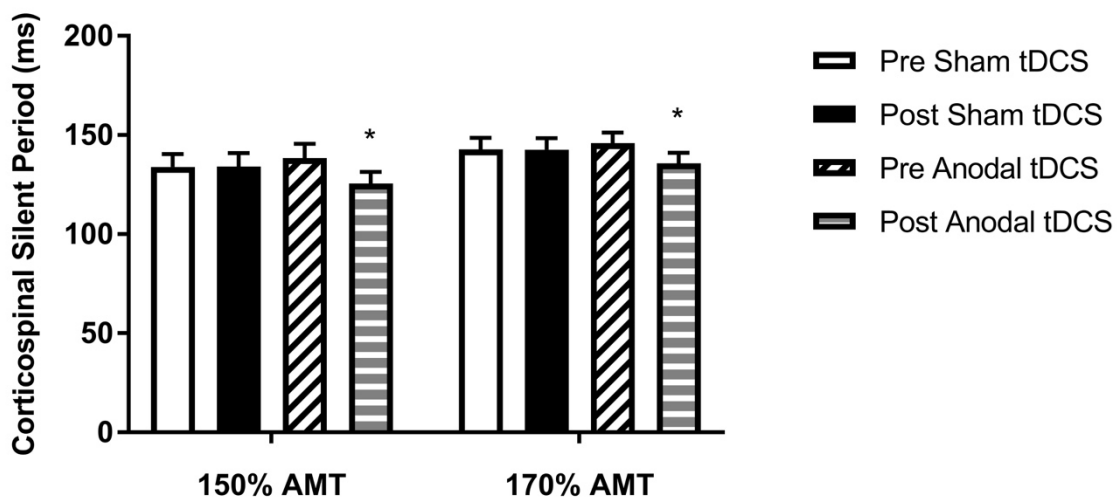


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Figure 8



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