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Title: Priming the Motor Cortex With Anodal Transcranial Direct Current Stimulation Affects the Acute Inhibitory Corticospinal Responses to Strength Training

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1 **Priming the motor cortex with anodal tDCS affects the acute inhibitory corticospinal responses to**

2 **strength training.**

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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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Introduction

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

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

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

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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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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 ± 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 ± 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).

Voluntary Strength Testing

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

Isometric Strength Testing

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

Strength Training Protocol

Participants completed a supervised strength-training session following the anodal and sham tDCS intervention (Experiment 1). Using the same set-up as the 1RM, participants completed flexion-extension 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 200^2 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 µV. 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 µs) 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^2; cathode 35 cm^2; current density 0.08 mA/cm^2)

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^2. 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 ± 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 µV, averaged and normalized to the M_{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 ± 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 cursored, 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 ± SE.

269

270   **Results**

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

272   Table 1 presents the mean (± 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 ± 0.5, 3.2 ± 0.5, 2.8 ±

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 γ-aminobutyric acid (GABA$_B$) 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$_B$ 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 coricopsinal 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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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. $^\wedge$ 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 (± 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 (± 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 (± SE) for AMT stimulus intensity, M_{MAX} and single-pulse TMS pre-stimulus

605 *rms*EMG prior to and following sham tDCS + ST and anodal tDCS + ST.

	Sham tDCS + ST		Anodal tDCS + ST		
	Pre	Post	Pre	Post	*P* value
AMT SI (%)	42.85 ± 2.40	42.08 ± 2.36	44.31 ± 1.87	43.37 ± 2.32	0.78
M_{MAX} (mV)	9.41 ± 1.31	9.53 ± 1.42	8.92 ± 0.79	8.96 ± 0.79	0.40
SP *rms*EMG (% *rms*EMG$_{MAX}$)	4.26 ± 0.59	4.65 ± 0.78	3.78 ± 0.63	3.91 ± 0.52	0.64

618 AMT SI: active motor threshold stimulus intensity. Single-pulse (SP) *rms*EMG 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_{MAX} and single-pulse TMS pre-stimulus *rms*EMG.

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 (± SE) changes in MVIC strength of the right Biceps Brachii muscle for 13 participants

635 following anodal-tDCS + ST and sham-tDCS + ST. ˆ 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

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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-

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658 anodal and sham-tDCS (Experiment 2) for 13 participants. [*] indicates significant to sham tDCS.

659 **Figure. 8:** Mean (± 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

(a) Primary Experiment

(b) Secondary Experiment
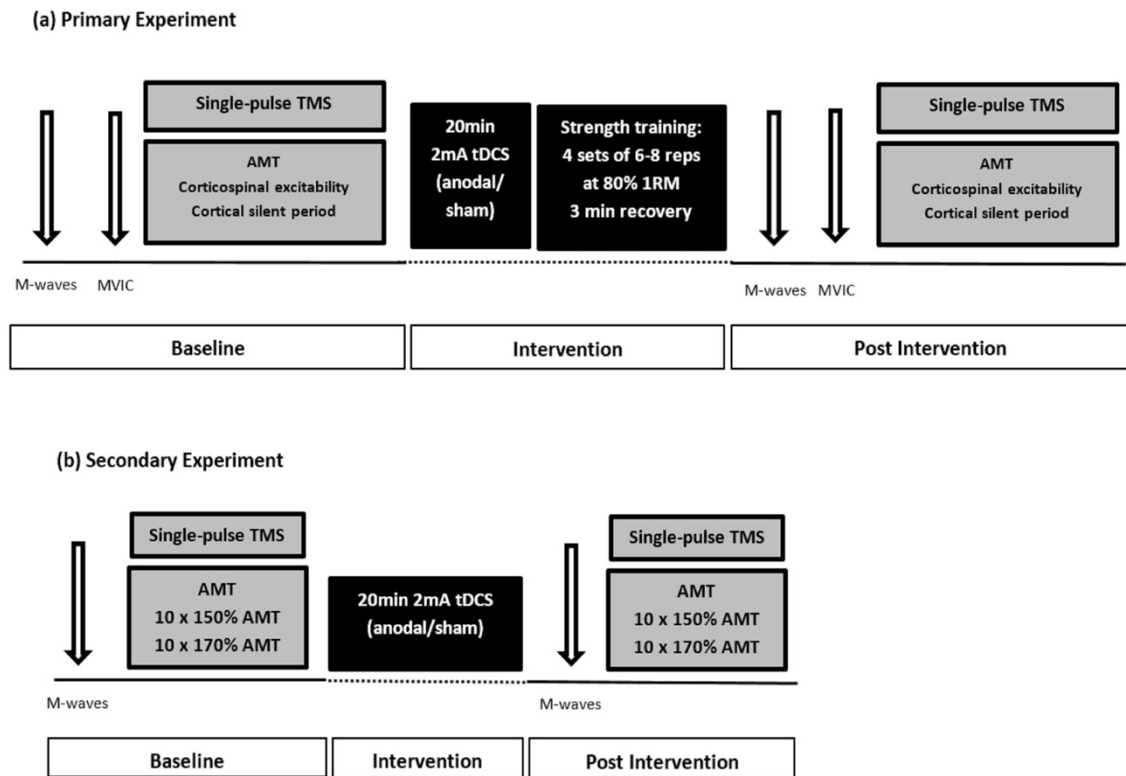
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667 **Figure 2**
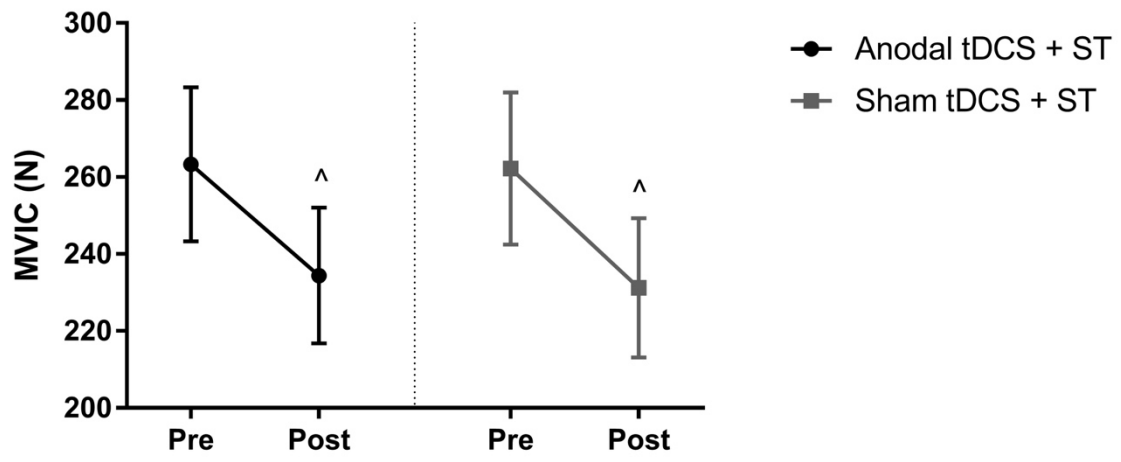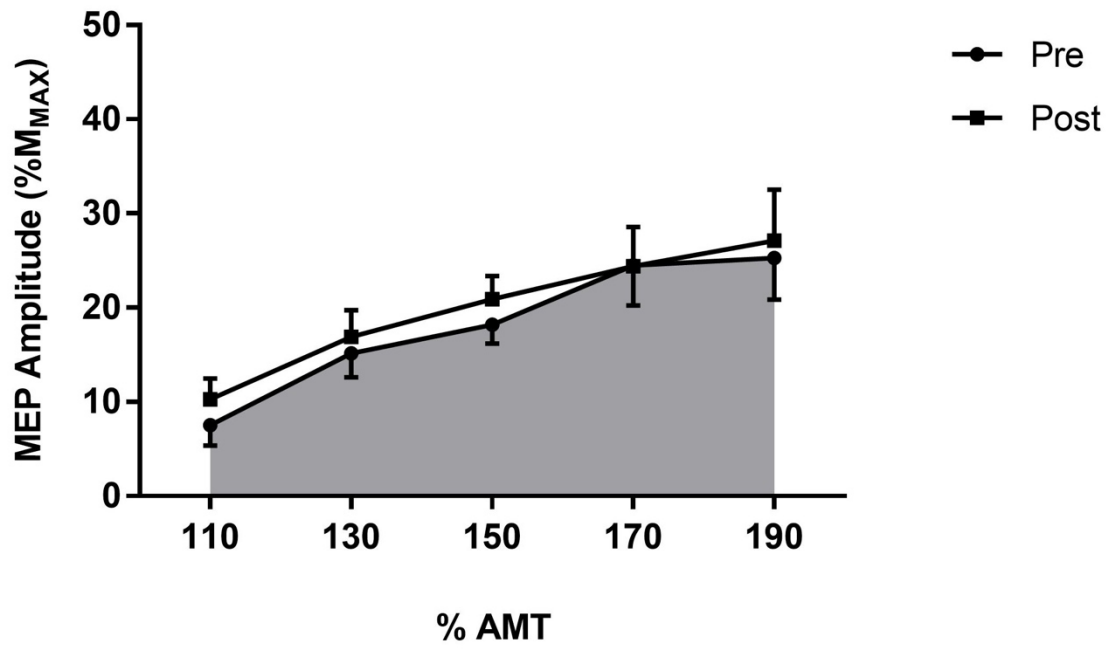

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670 Figure 3

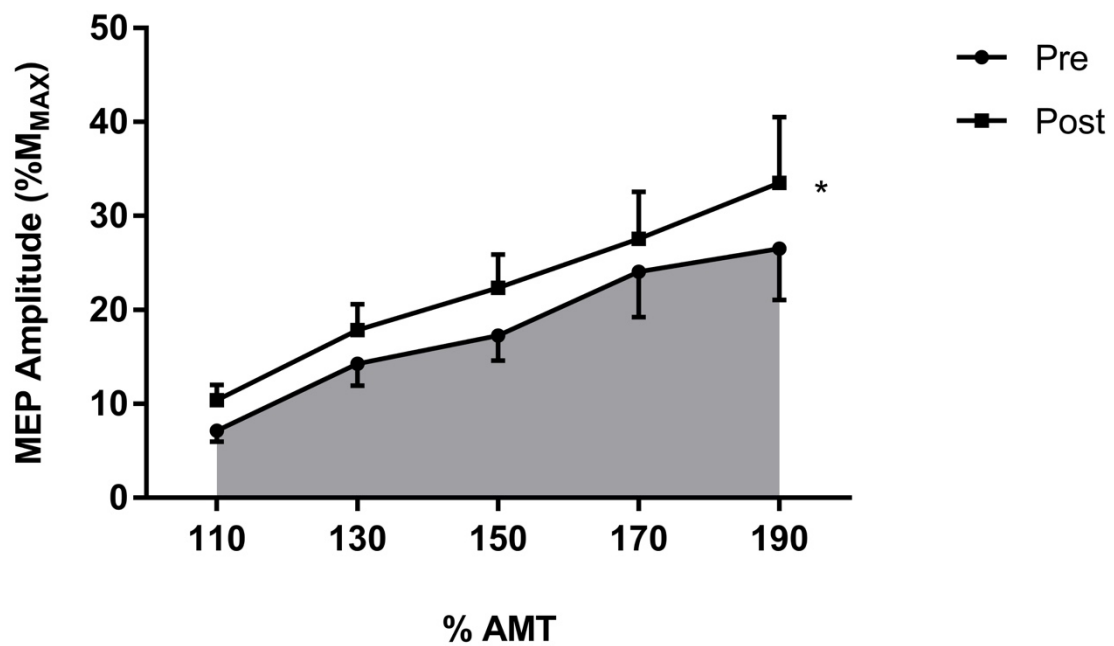
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673   Figure 4
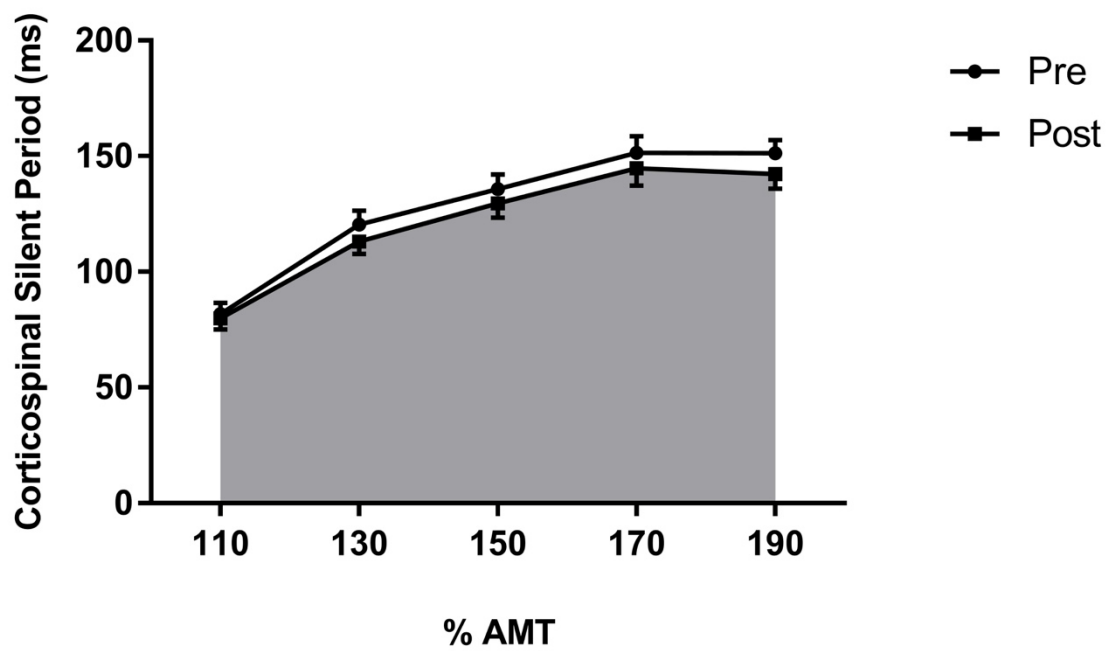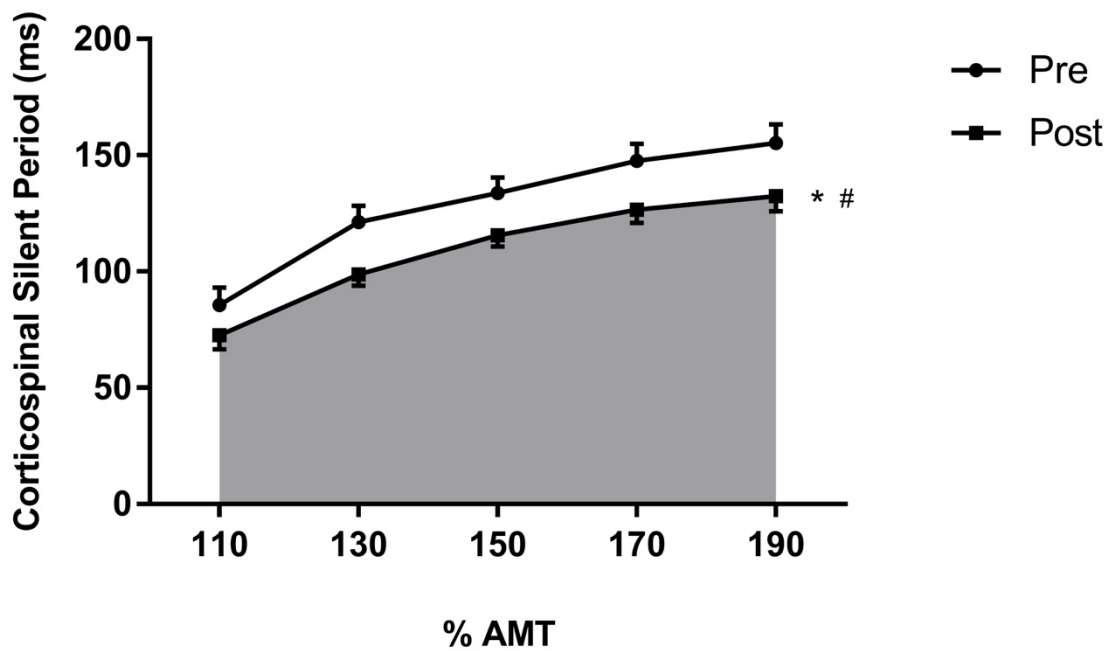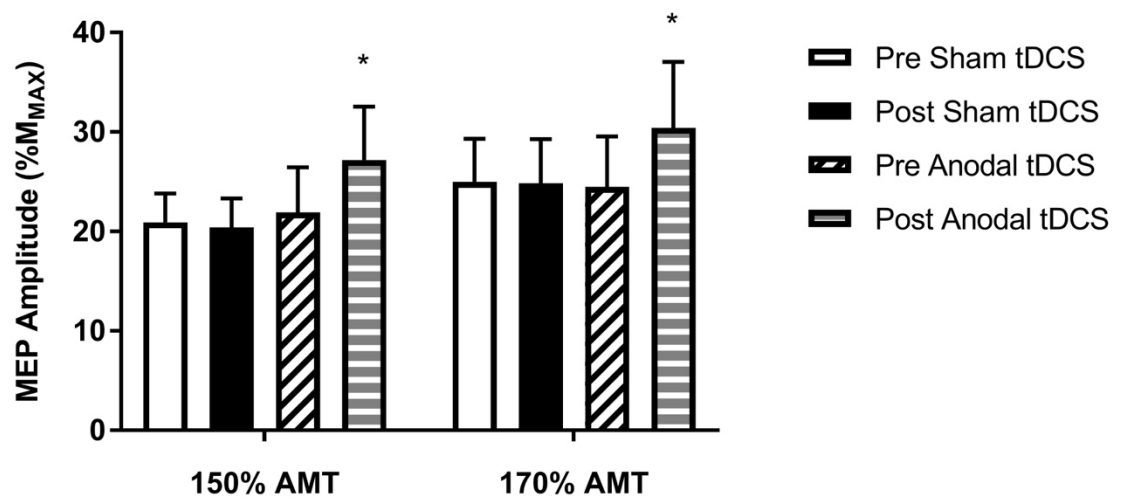

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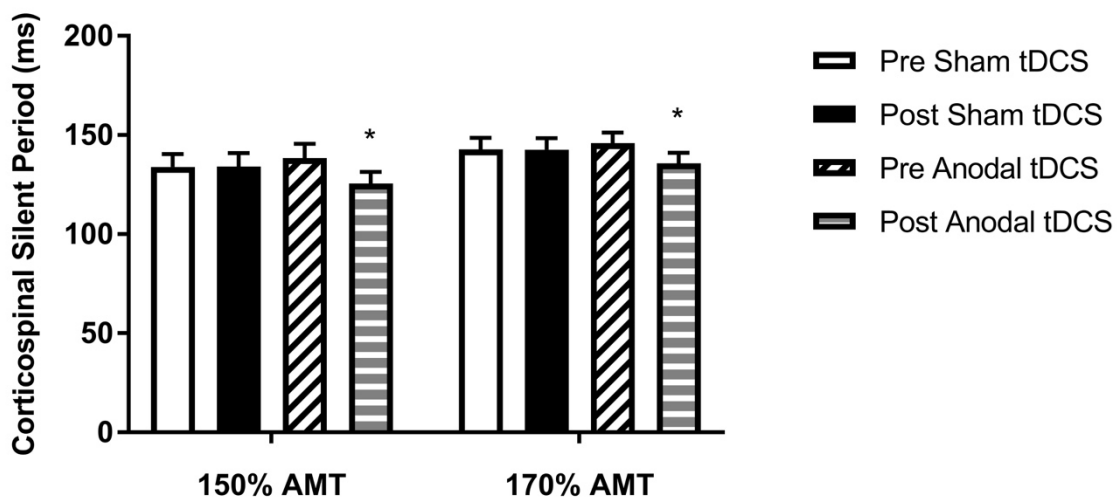676   Figure 5

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