Priming the motor cortex with anodal tDCS affects the acute inhibitory corticospinal responses to strength training.

Ashlyn K Frazer [1], Glyn Howatson [2,3], Juha P Ahtiainen [4], Janne Avela [4], Timo Rantalainen [4,5], and Dawson J Kidgell [1]

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

[2] Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle-upon-Tyne, UK

[3] Water Research Group, School of Biological Sciences, North West University, Potchefstroom, South Africa

[4] Neuromuscular Research Center, Biology and Physical Activity, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland.

[5] Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland.

Address for Corresponding author:

Dr Dawson J Kidgell

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

Email: dawson.kidgell@monash.edu

ABSTRACT

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

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

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

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

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

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

Methods

Experimental Approach to the Problem

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

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

Insert Figure 1A-B

Subjects

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

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

Surface Electromyography

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

Transcranial Magnetic Stimulation

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

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

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

Maximum Compound Muscle Action Potential

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

Transcranial Direct Current Stimulation

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

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

Data Analysis

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

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

Sample Size Calculations and Statistical Analyses

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

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

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

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

Results

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

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

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

Insert Table 1

Maximal Voluntary Isometric Contraction Force

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

Insert Figure 2

Corticospinal Excitability and Corticospinal Inhibition

Experiment 1

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

Figure 5 shows the AURC for corticospinal inhibition (silent period duration) obtained prior to and following the sham-tDCS + ST, whilst Figure 6 shows AURC for corticospinal inhibition (silent period duration) prior to and following the anodal-tDCS + ST intervention. The AURC was similar between conditions at baseline [$F_{(1, 12)} = 2.60$; $P = 0.99$]. 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

Discussion

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

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

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

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

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

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

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

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

Practical Applications

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

Acknowledgements

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

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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 (± SE) changes in MVIC strength of the right Biceps Brachii muscle for 13 participants
575 following anodal-tDCS + ST and sham-tDCS + ST. ^ 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

Table 1: Mean (± SE) for AMT stimulus intensity, M_{MAX} and single-pulse TMS pre-stimulus *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

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

FIGURE LEGENDS

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

Figure. 2: Mean (± SE) changes in MVIC strength of the right Biceps Brachii muscle for 13 participants following anodal-tDCS + ST and sham-tDCS + ST. ^ indicates significant to baseline.

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

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

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

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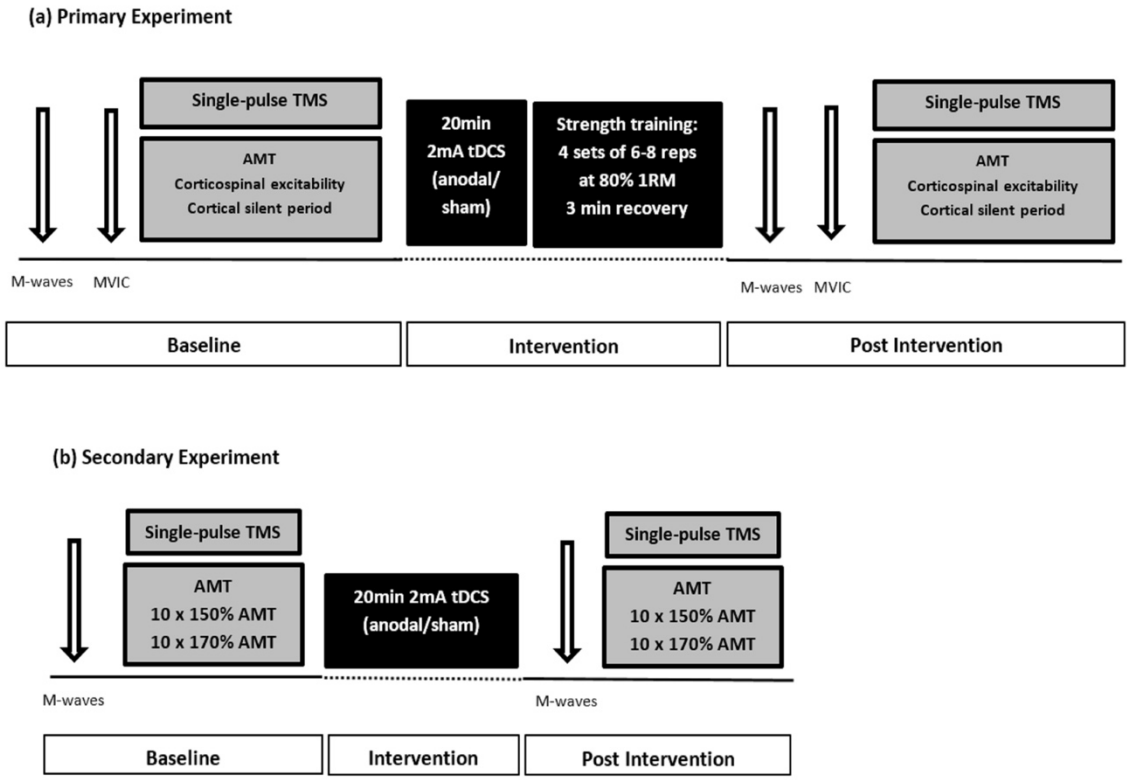
659 **Figure. 8:** Mean (± SE) changes in cortical silent period duration at 150% and 170% AMT before and
660 after 20 min of anodal and sham-tDCS (Experiment 2) for 13 participants. * indicates significant to
661 sham tDCS.

662

663 Figure 1



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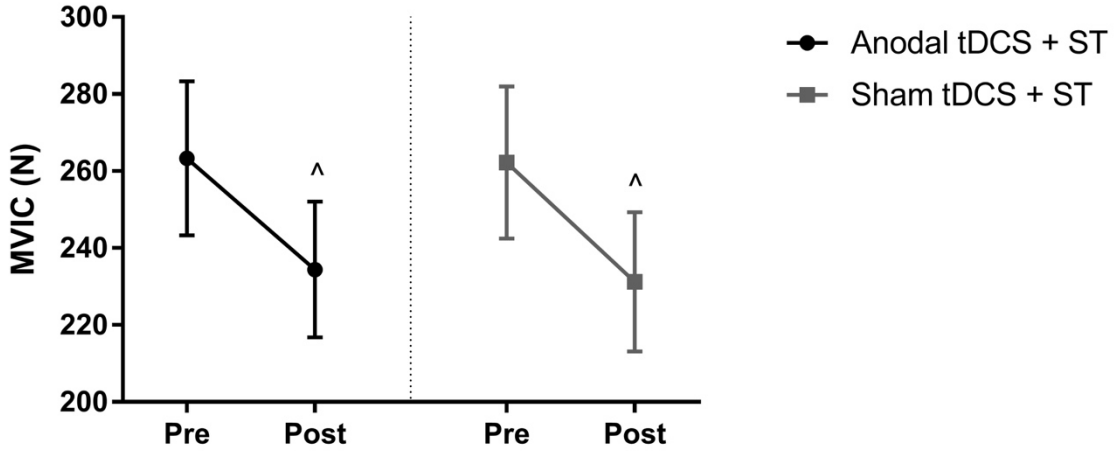
667 **Figure 2**



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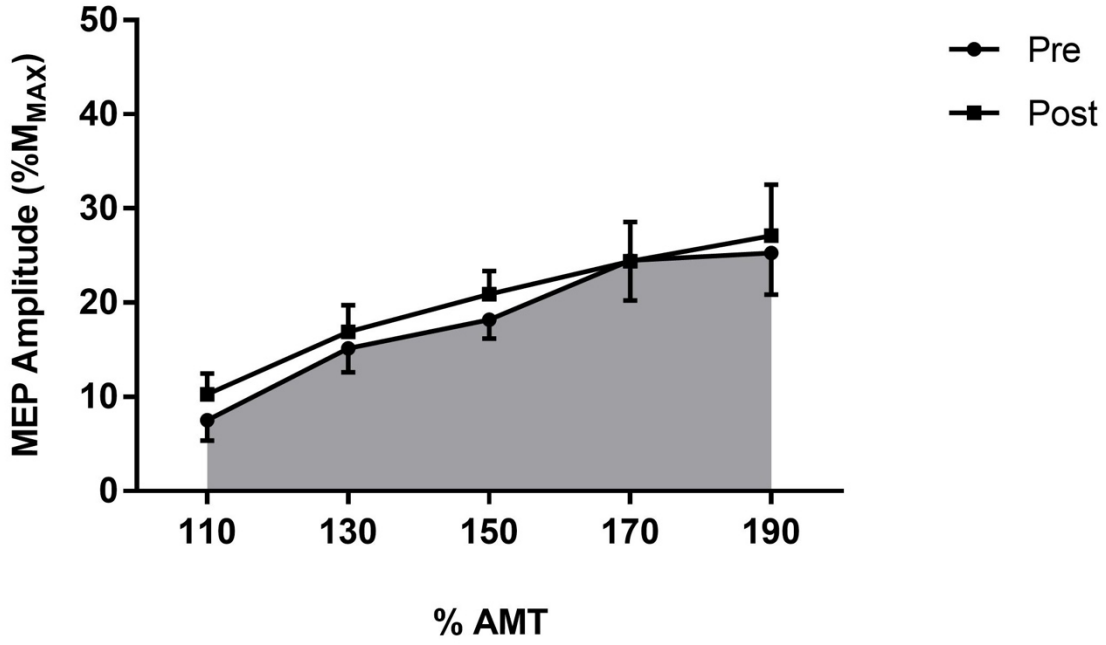
670 Figure 3



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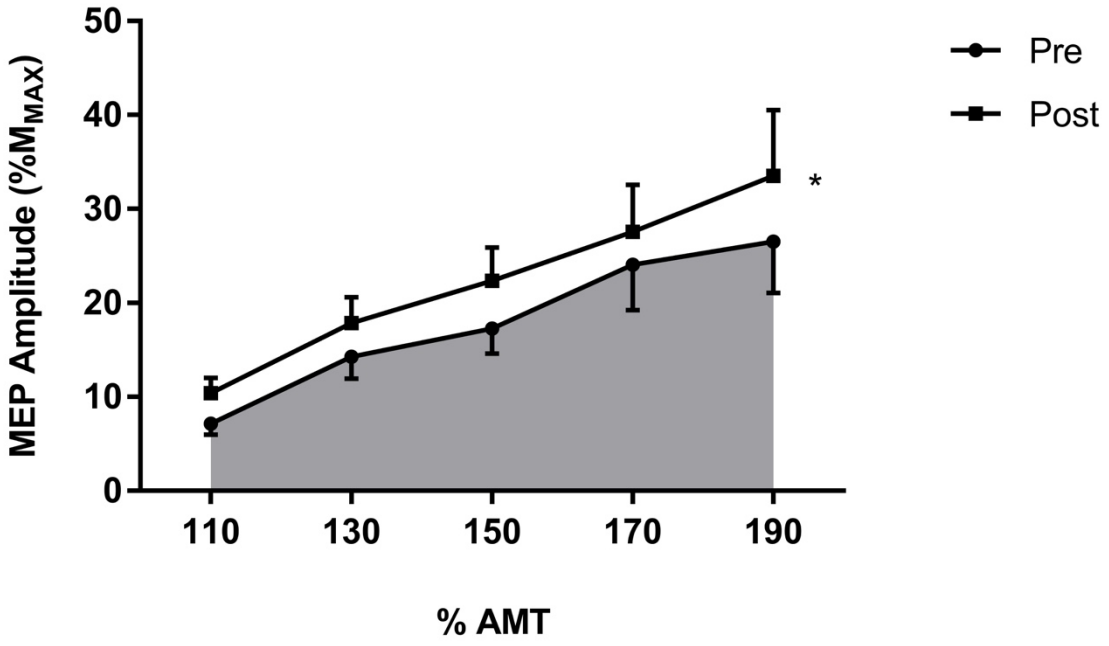

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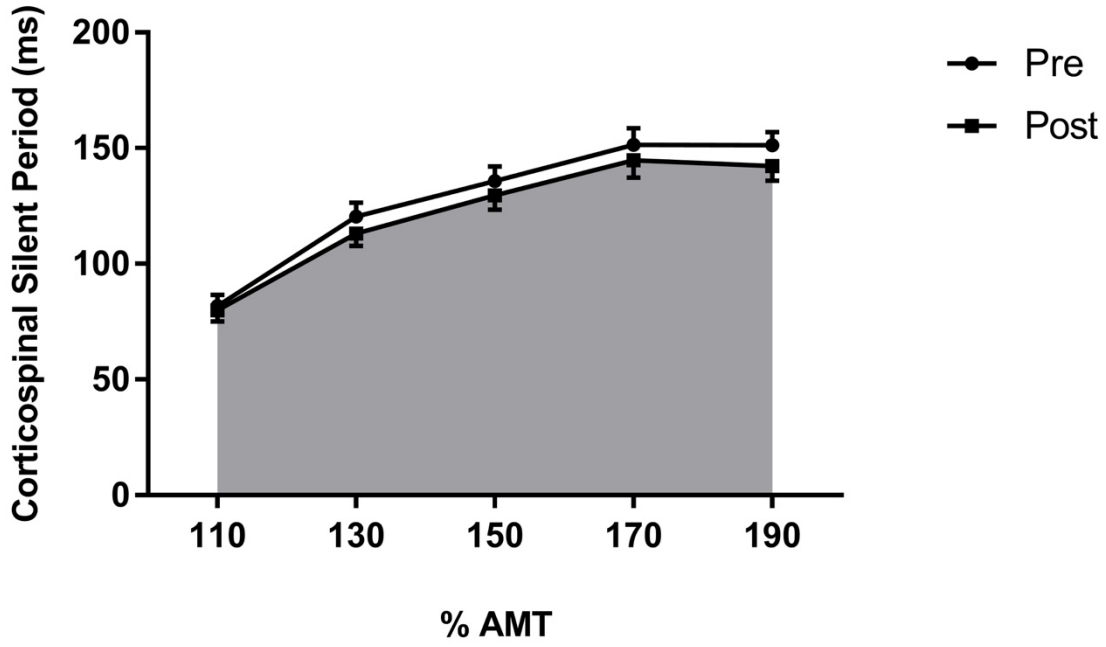
676 Figure 5



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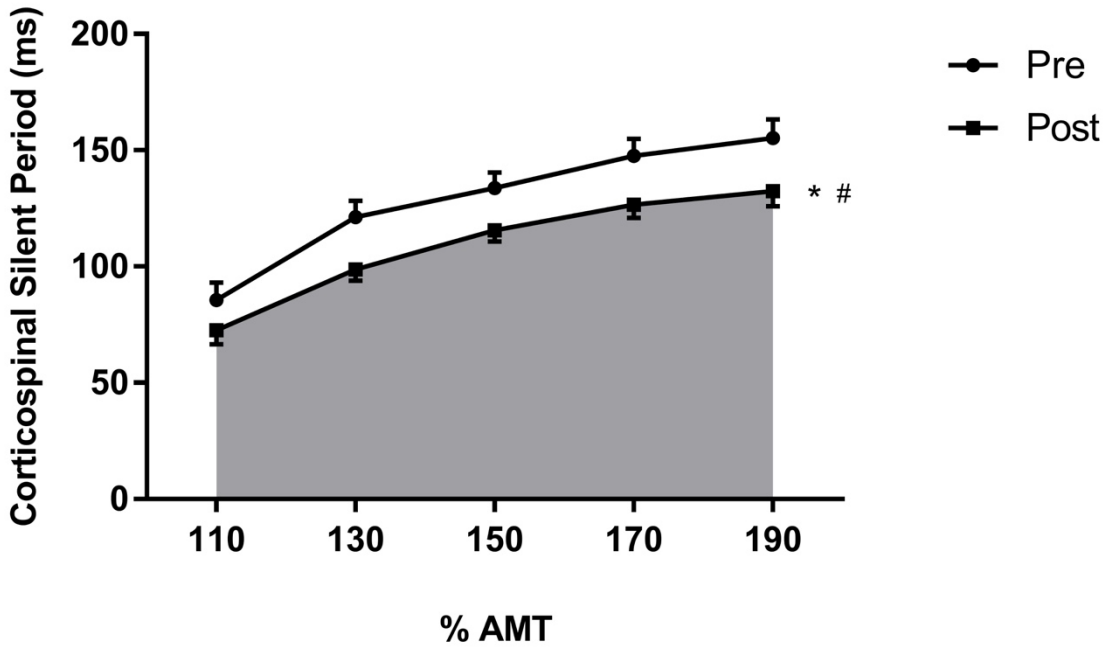
679 Figure 6



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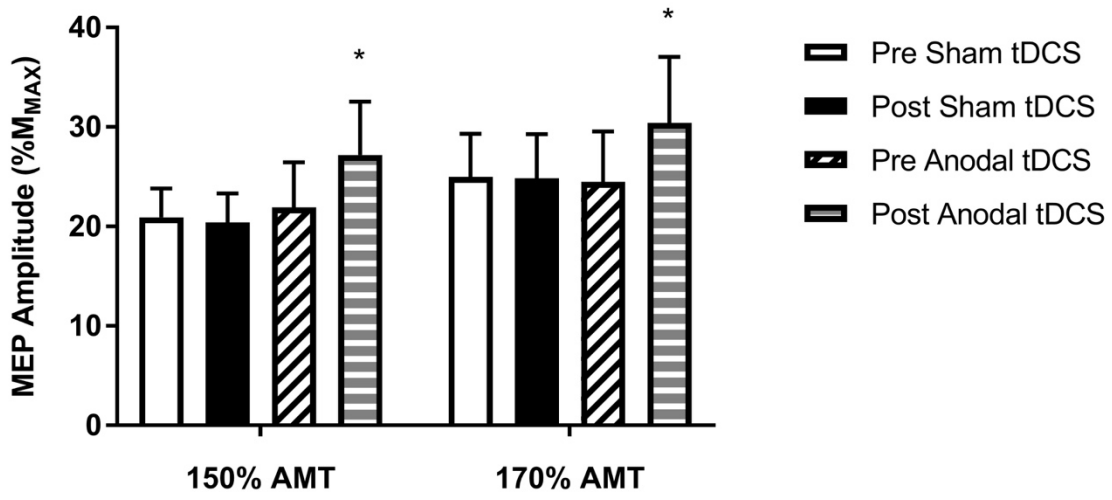
682 Figure 7



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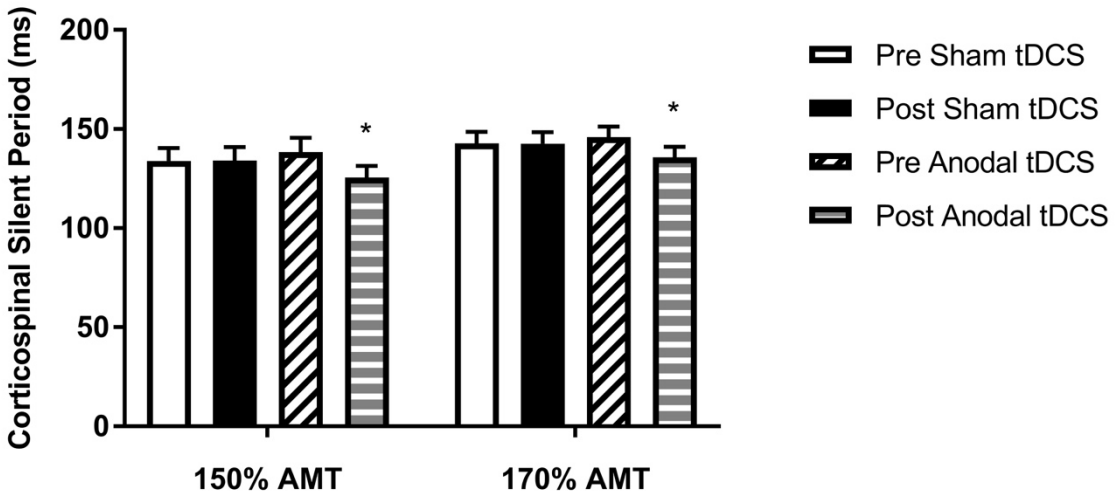
685 Figure 8



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