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

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Abstract

Frazer, AK, Howatson, G, Ahtiainen, JP, Avela, J, Rantalainen, T, and Kidgell, DJ. Priming the motor cortex with anodal transcranial direct current stimulation affects the acute inhibitory corticospinal responses to strength training. *J Strength Cond Res* 33(2): 307–317, 2019—Synaptic plasticity in the motor cortex (M1) is associated with strength training (ST) and can be modified by transcranial direct current stimulation (tDCS). The M1 responses to ST increase when anodal tDCS is applied during training due to gating. An additional approach to improve the M1 responses to ST, which has not been explored, is to use anodal tDCS to prime the M1 before a bout of ST. We examined the priming effects of anodal tDCS of M1 on the acute corticospinal responses to ST. 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) were analyzed in 13 adults exposed to 20 minutes of anodal tDCS and sham tDCS followed by a ST session of the right elbow flexors. We observed a significant decrease in isometric elbow-flexor strength immediately after training (11–12%; $p < 0.05$), which was not different between anodal tDCS and sham tDCS. Transcranial magnetic stimulation revealed a 24% increase in AURC for corticospinal excitability after anodal tDCS and ST; this increase was not different between conditions. However, there was a 14% reduction in AURC for corticospinal inhibition when anodal tDCS was applied before ST when compared with sham tDCS and ST (all $p < 0.05$). Priming anodal tDCS had a limited effect in facilitating corticospinal excitability after an acute bout of ST. Interestingly, the interaction of anodal tDCS and ST seems to affect the excitability of intracortical inhibitory circuits of the M1 through nonhomeostatic mechanisms.

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

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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 after a single session of strength training (ST) (9,11,20,33). 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 ST 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 ST increased motor-evoked potentials (MEPs) evoked by single-pulse transcranial magnetic stimulation (TMS) (22). More recently, Latella et al. (20) reported increased MEP amplitude after a single session of both heavy-loaded and hypertrophy-based ST. However, by contrast, Selvanayagam et al. (33) reported reduced MEP amplitude after a single session of ST.

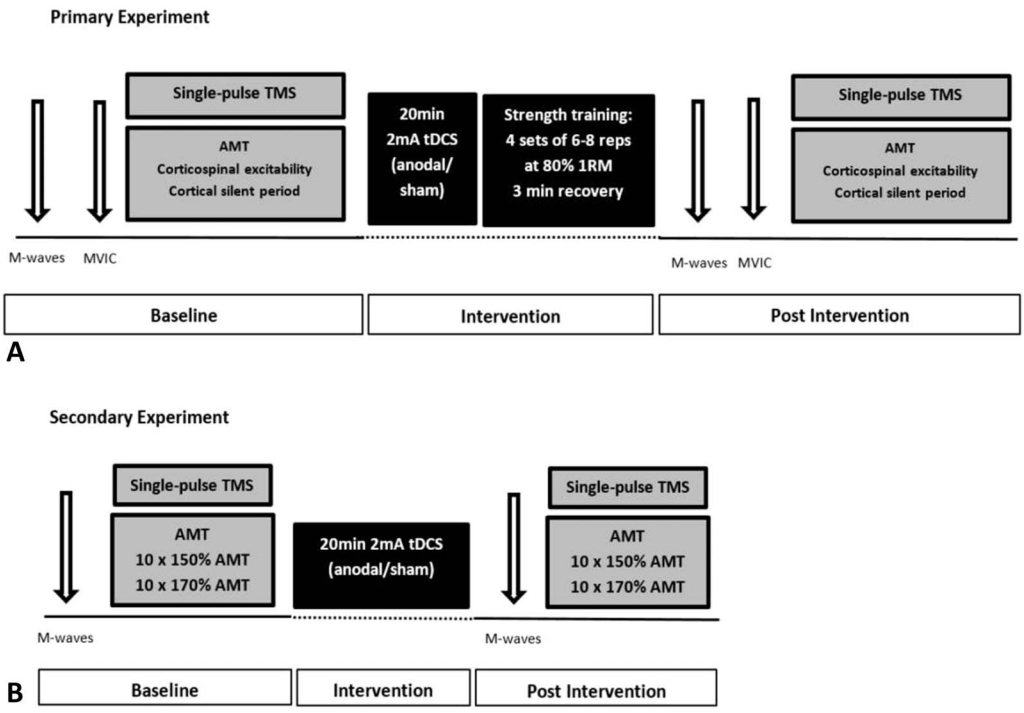

Figure 1. A) Schematic representation of the design of experiment 1 with measures obtained before and after 20 minutes of anodal and sham tDCS and ST. Pre- and post-measures included assessment of peripheral muscle excitability (M_{MAX}), corticospinal excitability and inhibition recruitment curves, and maximal voluntary isometric contraction (MVIC) strength test of the right biceps brachii muscle. There was a 1-week washout period between conditions. B) Schematic representation of the design of experiment 2 with measures obtained before and after 20 minutes of 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 1-week washout period between conditions. AMT = active motor threshold; tDCS = transcranial direct current stimulation; TMS = transcranial magnetic stimulation.

The acute effects of ST on increasing corticospinal excitability seem inconclusive, but preliminary evidence shows that changes in the duration of the corticospinal silent period could be an important early neural adaptation to ST. For example, the duration of the corticospinal silent period is reduced immediately after both heavy-load and hypertrophy-based ST (20,21); however, this is in conflict with earlier findings that suggested increases in corticospinal silent period duration throughout and immediately after a single session of ST (32). Thus, there is a need to examine alternative techniques that may facilitate the early neural responses to ST.

The use of transcranial direct current stimulation (tDCS) has gained popularity as a safe and noninvasive technique that can be used to induce plasticity in the primary motor cortex (M1) (27). Transcranial direct current stimulation uses weak direct currents that induce prolonged modulation of corticospinal excitability within the M1 (27). The procedure involves applying low-level (1–2 mA) electrical currents to the M1 over the area of interest through saline-soaked electrodes (27). 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 (27). The immediate effects of tDCS are due to changes in membrane polarity, which influence the likelihood of depolarization (24). By contrast, longer-lasting changes in corticospinal excitability, which have been reported up to 90 minutes after stimulation, are attributed to changes in synaptic efficacy (24). Evidence over the past 10–15 years has demonstrated that, in addition to the modulation of corticospinal excitability after anodal tDCS, stimulation also seems to produce transient effects in motor performance (6).

There are 2 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 (11,35). Gating describes the influx of calcium ions to the targeted corticospinal neurons resulting in the release of inhibition from intracortical inhibitory circuits (38). More relevant to

Table 1. Mean (±*SE*) for AMT stimulus intensity, M_{MAX}, and single-pulse TMS pre-stimulus *rms*EMG before and after sham tDCS + ST and anodal tDCS + ST.*†

	Sham tDCS + ST		Anodal tDCS + ST		
	Pre	Post	Pre	Post	*p*
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

*tDCS = transcranial direct current stimulation; AMT SI = active motor threshold stimulus intensity; TMS = transcranial magnetic stimulation.

†Single-pulse (SP) *rms*EMG was pooled across stimulus intensities. *p* values represent the 2 (conditions) × 2 (time) repeated-measures analysis of variance 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.

the current study is the principle of motor priming whereby the resting state of corticospinal neurons is altered (increased/decreased level of excitability after a low/high level of synaptic activity) due to changes in postsynaptic glutamate receptor activity (38). 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 (27), it is possible that anodal tDCS could be used as a priming tool to increase synaptic activity before a single bout of ST to further enhance the acute corticospinal responses to ST. Understanding the interaction between the priming effects of anodal tDCS and ST has important implications for ST program design because the effects of anodal tDCS could depend on the timing of its application relative to the timing of the ST intervention. To the best of our knowledge, no study has compared the corticospinal responses with ST when the training is performed after anodal tDCS.

Therefore, the aim of this study was to examine the effect of priming the M1 using anodal tDCS before a single bout of ST to determine whether the early corticospinal responses to ST are facilitated compared with sham tDCS and ST alone. It was hypothesized that the application of anodal tDCS before a single bout of ST would increase corticospinal excitability (MEP amplitudes) and reduce corticospinal inhibition (silent period duration) compared with the application of sham tDCS before a bout of ST.

Methods

Experimental Approach to the Problem

All participants completed 2 experiments as outlined in Figure 1A, B. After obtaining consent, participants completed a familiarization session 1 week before the study that involved performing a 1 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 2 conditions in experiment 1. Each participant was exposed to 20 minutes of anodal tDCS and sham tDCS followed by a single ST 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 washout period of 1 week between each condition (36). All participants underwent TMS and isometric strength testing (maximum voluntary isometric contraction [MVIC]) of the right elbow flexors before and after the tDCS and ST intervention (Figure 1A).

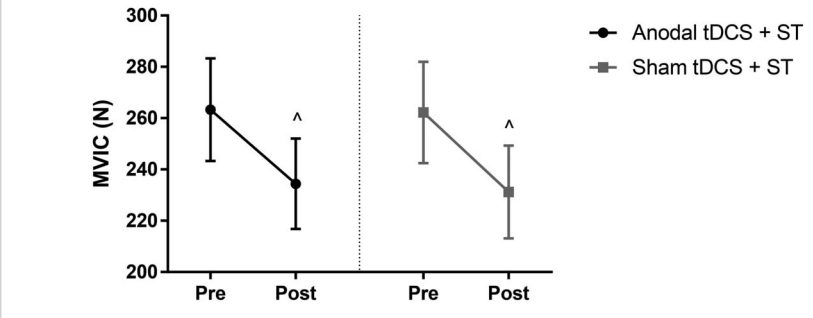

Figure 2. Mean (±*SE*) changes in MVIC strength of the right biceps brachii muscle for 13 participants after anodal tDCS + ST and sham tDCS + ST. ^ Indicates significant to baseline. tDCS = transcranial direct current stimulation.

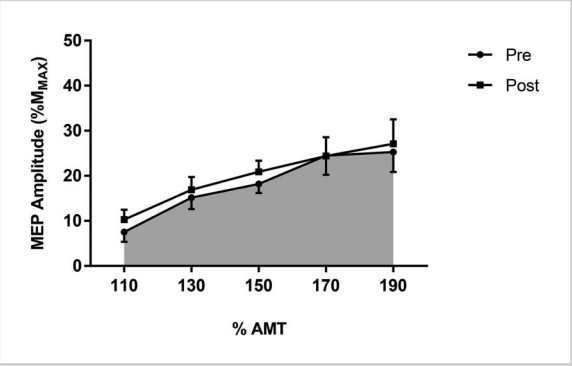

Figure 3. The AURC for corticospinal excitability was calculated using the method of trapezoidal integration for experiment 1. The AURC obtained before the sham tDCS + ST intervention is shaded in gray (pre). The additional area enclosed by the recruitment curve obtained after the sham tDCS + ST intervention is shaded in white (post). AMT = active motor threshold; AURC = area under the recruitment curve; MEP = motor-evoked potential; tDCS = transcranial direct current stimulation.

To determine the effects of anodal tDCS without ST on corticospinal excitability and corticospinal inhibition, participants also completed experiment 2. Each participant was exposed to 20 minutes of anodal tDCS and sham tDCS with a washout period of 1 week between each condition (36). Before and after the tDCS intervention, 20 single-pulse TMS stimuli were collected at 150 and 170% active motor threshold (AMT) (Figure 1B).

Subjects

Thirteen participants (5 women and 8 men [mean ± *SD*: 25.2 ± 5.8 years]) volunteered to participate. All volunteers provided written informed consent before 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 before signing the approved informed consent document to participate in the study. All participants were right-hand dominant as determined by the Edinburgh Handedness Inventory (29) with a Laterality Quotient score of 86 ± 5, had not participated in ST for at least 12 months, but were recreationally active, and were free from any known history of peripheral or neurological impairment. Before the experiment, all participants completed the adult safety-screening questionnaire to determine their suitability for TMS and tDCS (12).

Procedures

Voluntary Strength Testing. To determine maximal voluntary dynamic force, participants completed a 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 1 repetition. Between each trial, a 3-minute rest was given to minimize muscular fatigue. The last successful trial was recorded as their 1RM strength and was used to determine individual training load and was only measured at baseline (16). On average, it took 3 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 (MVIC) force was measured using handheld dynamometry (Microfet2, Salt Lake City, UT, 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 (AD Instruments, Bella Vista, New South Wales, 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 seconds. Three attempts, with a 2-minute rest between each attempt, were performed. The standard criteria for measurement of MVICs were fulfilled and included a period of familiarization (before data collection), verbal encouragement provided by the investigators, and the rejection of a trial in 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% ($p = 0.54$, $r = 0.99$) (30). Again, the researcher who

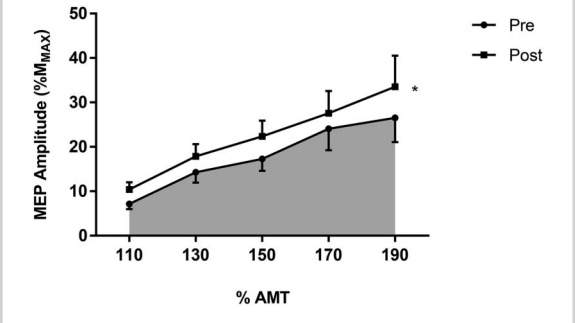

Figure 4. The AURC for corticospinal excitability was calculated using the method of trapezoidal integration for experiment 1. The AURC obtained before the anodal tDCS + ST intervention is shaded in gray (pre). The additional area enclosed by the recruitment curve obtained after the anodal tDCS + ST intervention is shaded in white (post). * Indicates significant within-condition effect. AMT = active motor threshold; AURC = area under the recruitment curve; MEP = motor-evoked potential; tDCS = transcranial direct current stimulation.

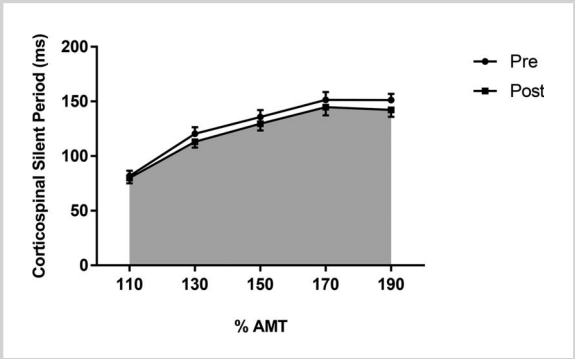

Figure 5. The AURC for corticospinal inhibition was calculated using the method of trapezoidal integration for experiment 1. The AURC obtained before sham tDCS + ST intervention is shaded in white. The additional area enclosed by the recruitment curve obtained after sham tDCS + ST is shaded in gray. 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. AMT = active motor threshold; AURC = area under the recruitment curve; tDCS = transcranial direct current stimulation.

administered the isometric strength testing before and after was blinded to the tDCS condition.

Strength Training Protocol. Participants completed a supervised ST session after the anodal tDCS and sham tDCS intervention (experiment 1). Using the same setup 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-minute recovery between sets (16). A repetition timing of 3 seconds for the concentric phase and 4 seconds for the eccentric phase was maintained using an electronic metronome (16). The use of an automated timing device was selected because previous research has shown that controlled-velocity ST facilitates greater neural adaptations compared with self-paced training (22,23).

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 (30). This mark was then extended to the most anterior point of the muscle bulk, and the electrodes were placed 2 cm apart over the midbelly of the bicep brachii, with a ground electrode secured on the lateral epicondyle of the humerus. Surface electromyography signals were amplified (×1000), band-pass filtered (high pass at 13 Hz, low pass at 1,000 Hz), digitized online at 2 kHz, recorded (1 second), and analyzed using Power Lab 4/35 (AD Instruments).

Transcranial Magnetic Stimulation. Transcranial magnetic stimulation was delivered using a Magstim 200^2 stimulator (Magstim Co, Dyfed, Whitland, United Kingdom) 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 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. After the tDCS and ST intervention, AMT was retested 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) before and after 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° elbow flexion. Joint angle was measured with an electromagnetic goniometer (AD Instruments), 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

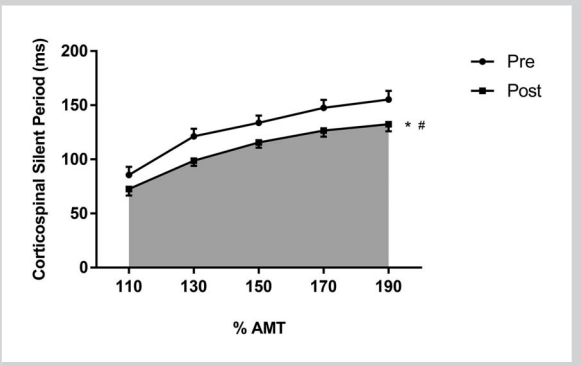

Figure 6. The AURC for corticospinal inhibition was calculated using the method of trapezoidal integration for experiment 1. The AURC obtained before anodal tDCS + ST intervention is shaded in white. The additional area enclosed by the recruitment curve obtained after anodal tDCS + ST is shaded in gray. The AURC calculated from corticospinal inhibition curves for 13 participants in the anodal tDCS + ST condition whereby MEP amplitude was plotted against stimulus intensity.
* Indicates significant within-condition effect. # Indicates significant difference to sham + ST (between-condition effect). AMT = active motor threshold; AURC = area under the recruitment curve; MEP = motor-evoked potential; tDCS = transcranial direct current stimulation.

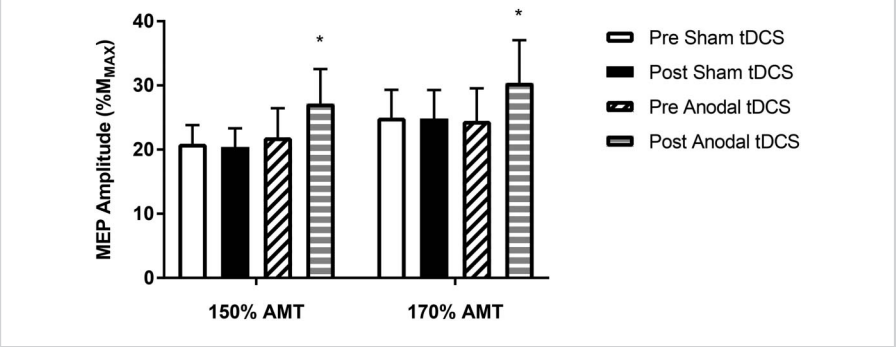

Figure 7. Mean (±*SE*) changes in MEP amplitude at 150% and 170% AMT before and after 20 minutes of anodal and sham tDCS (experiment 2) for 13 participants. * Indicates significant to sham tDCS. AMT = active motor threshold; MEP = motor-evoked potential; tDCS = transcranial direct current stimulation.

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° 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 5 stimuli, with a period of 6–9 seconds separating each stimulus. M_{MAX} was recorded at baseline and after 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 (experiments 1 and 2), participants received 20 minutes 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 (27). Anodal tDCS involved 20 minutes 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 tDCS 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 seconds. 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."

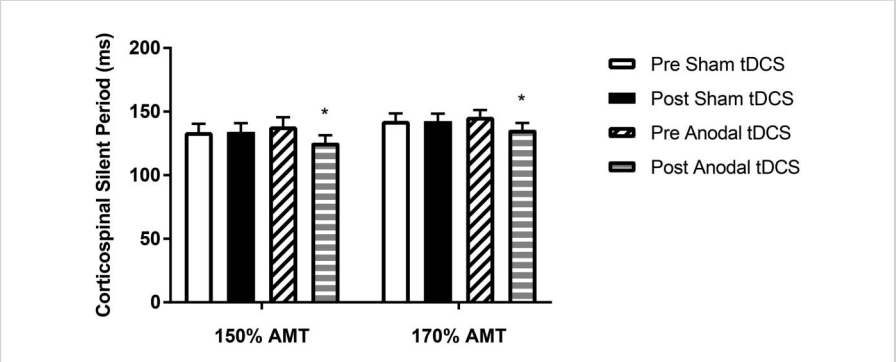

Figure 8. Mean (±*SE*) changes in cortical silent period duration at 150% and 170% AMT before and after 20 minutes of anodal and sham tDCS (experiment 2) for 13 participants. * Indicates significant to sham tDCS. AMT = active motor threshold; tDCS = transcranial direct current stimulation.

Data Analysis. Pre-stimulus rmsEMG activity was determined in the right biceps brachii muscle 100 ms before 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. Motor-evoked potential amplitudes were analyzed (LabChart 8 software; AD Instruments) 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 analyses. 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 10 stimuli was used to determine corticospinal silent period durations (25).

Statistical Analyses

The number of participants required was based on power calculations for the expected changes in mean-rectified MEPs (sEMG recordings from the elbow-flexor muscle) after a single session of ST. Using previous data in healthy untrained adults (22), we estimated that 11 participants would provide at least 80% power (95% confidence interval [CI]) to detect a 15% increase in mean-rectified MEPs assuming an *SD* of 10–15% between conditions at $p \leq 0.05$ (2-tailed).

All data were screened using the Shapiro-Wilk test and found to be normally distributed (all $p > 0.05$) and, thus, the assumptions of the analysis of variance (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 (MVIC force, pre-stimulus EMG, AURC for corticospinal excitability, and silent period duration) over 2 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 subanalysis was also conducted for experiment 2 to determine whether anodal tDCS without ST 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 2 time points (pre-testing and post-testing). Again, for all comparisons, ES of 0.2, 0.5, and 0.8 were established to indicate small, moderate, and large comparative effects (Cohen's *d*), respectively. In addition, paired *t*-tests were performed on VAS. 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, La Jolla, CA, USA) was used for all statistical analyses, with the level of significance set as $p \leq 0.05$ 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 before and after 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 2 conditions at baseline. Pre-stimulus rmsEMG did not vary between single-pulse trials, and there was no TIME or TIME × CONDITION interaction observed ($p = 0.64$). Similarly, there was no TIME or TIME × CONDITION interaction detected for AMT stimulus intensity ($p = 0.78$). Furthermore, there was no TIME or TIME × CONDITION interaction detected for M_{MAX} ($p = 0.40$). Visual analogue scale 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; $p = 0.48$).

Maximal Voluntary Isometric Contraction Force

Isometric strength was assessed for the right elbow-flexor muscles before and after 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 ($F_{(1, 12)} = 0.19$; $p = 0.66$). After the intervention, the ANOVA revealed only a TIME effect for both the anodal tDCS + ST (95% CI 14.02–43.72; $d = 0.46$; $p = 0.0006$) and sham tDCS + ST conditions (95% CI 16.14–45.3; $d = 0.50$; $p = 0.0004$). There was no TIME × CONDITION interaction detected ($F_{(1, 12)} = 0.06$; $p = 0.80$). Isometric elbow-flexor strength decreased by 11% after anodal tDCS + ST and, similarly, by 12% after sham tDCS + ST.

Corticospinal Excitability and Corticospinal Inhibition

Experiment 1. Figure 3 shows the AURC for corticospinal excitability obtained before and after the sham tDCS + ST, whereas Figure 4 shows the AURC for corticospinal

excitability before and after the anodal tDCS + ST intervention. The AURC was similar between conditions at baseline ($F_{(1, 12)} = 0.10$; $p = 0.75$). After the intervention, there was a main effect for TIME ($F_{(1, 12)} = 14.54$; $p = 0.005$), but there was no TIME × CONDITION interaction detected ($F_{(1, 12)} = 2.62$; $p = 0.13$). The AURC increased in the anodal tDCS + ST condition by 24% (95% CI −581 to −109.2; $d = 3.38$; $p = 0.0056$) compared with a 9% increase after 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 before and after the sham tDCS + ST, whereas Figure 6 shows the AURC for corticospinal inhibition (silent period duration) before and after the anodal tDCS + ST intervention. The AURC was similar between conditions at baseline ($F_{(1, 12)} = 2.60$; $p = 0.99$]. After the intervention, there was a main effect for TIME and a TIME × CONDITION interaction detected ($F_{(1, 12)} = 7.61$; $p = 0.017$). Post hoc analysis showed that anodal tDCS + ST decreased the total AURC by 14% (95% CI −882.2 to 2,296; $d = 1.02$; $p = 0.002$) compared with 5% after the sham tDCS + ST condition (95% CI −195.3 to 1,218; $d = 0.08$; $p = 0.173$).

Experiment 2. The MEP amplitudes were similar between sham and anodal tDCS conditions at baseline for each stimulus intensity (150% AMT, $F_{(1, 12)} = 0.007$; $p = 0.99$; 170% AMT, $F_{(1, 12)} = 0.074$; $p = 0.99$). After the anodal tDCS intervention, there was a main effect for TIME (150% AMT; $F_{(1, 12)} = 11.63$; $p = 0.005$; 170% AMT; $F_{(1, 12)} = 5.23$; $p = 0.047$) and a TIME × CONDITION interaction ($F_{(1, 12)} = 5.53$; $p = 0.041$) detected at 150 and 170% of AMT (Figures 7 and 8). Post hoc analysis of MEPs at 150 and 170% of AMT showed that anodal tDCS increased MEP amplitudes by 24% for both 150% AMT (95% CI −10.04 to −0.045; $d = 2.80$; $p = 0.002$) and 170% AMT (95% CI −581 to −109.2; $d = 1.96$; $p = 0.003$) compared with 1 and 2% after sham 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; $d = 0.11$; $p = 0.89$).

Corticospinal silent period durations were similar between sham and anodal tDCS conditions at baseline for each stimulus intensity (150% AMT, $F_{(1, 12)} = 3.81$; $p = 0.074$; 170% AMT, $F_{(1, 12)} = 3.334$; $p = 0.098$). After the tDCS intervention, there was a main effect for TIME (150% AMT, $F_{(1, 12)} = 21.6$; $p = 0.0006$; 170% AMT, $F_{(1, 12)} = 29.08$; $p = 0.0002$) and a TIME × CONDITION interaction (150% AMT, $F_{(1, 12)} = 5.29$; $p = 0.041$; 170% AMT, $F_{(1, 12)} = 6.22$; $p = 0.028$) (Figure 8). Post hoc analysis showed that anodal tDCS decreased corticospinal silent period duration by 7% at 150% AMT (95% CI −8.749 to 27.59; $d = 0.90$; $p = 0.0007$) and by 9% at 170% AMT (95% CI 10.58–31.17; $d = 0.95$; $p = 0.0005$) compared with an average of 1% after 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; $d = 0.23$; $p = 0.244$).

Discussion

The primary objective of this research was to determine whether priming the M1 by anodal tDCS, before a single bout of ST, would facilitate the corticospinal responses to ST. The main findings from experiment 1 were: (a) MVIC of the elbow flexors declined in both groups (sham tDCS + ST and anodal tDCS + ST) to a similar magnitude after a single bout of ST, suggesting that priming the M1 with anodal tDCS does not attenuate the loss of muscle strength; and (b) the application of anodal tDCS before a single bout of ST (anodal tDCS + ST) reduced corticospinal inhibition, but had no effect on corticospinal excitability. The main findings for experiment 2 were: (a) 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.

The first important finding of this study was the observed increase in corticospinal excitability and decreased corticospinal silent period duration after the application of anodal tDCS only (experiment 2). Anodal tDCS has been shown previously to increase corticospinal excitability for up to 90 minutes after stimulation (15,27) and decrease corticospinal inhibition (15,28), with the changes in synaptic strength attributed to modulation of the NMDA receptor (26,28,31). Pharmacological interventions have further highlighted the importance of the NMDA receptor by using a NMDA receptor antagonist (i.e., dextromethorphan) to block the aftereffects of tDCS (24,28,37). Importantly, these results confirmed the theoretical basis for using anodal tDCS as a priming method to the M1 before a single bout of ST to potentially further enhance or accelerate the acute corticospinal responses to ST (23).

At present, there are conflicting results regarding the effect of using anodal tDCS to prime the M1 before a motor-training task (1). Visuomotor tracking performance has been shown to improve after 10–15 minutes of anodal tDCS at 1 mA before training (1,34), with retention lasting up to 24 hours (34). In direct contrast, Stagg et al. (35) found that anodal tDCS applied to the M1 before 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 before a single bout of ST 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 ST; however, they applied the tDCS during ST, 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 MVIC force. Here, we sought to examine the effects of priming because the benefits of tDCS and ST 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 after ST, which is consistent with

the principles of homeostatic plasticity (17). Because priming the M1 with anodal tDCS increased neuronal plasticity before ST, the excitability-enhancing effects of the ST 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 ST bout (35). This interpretation is supported by experiment 2 where there was also a 24% increase in corticospinal excitability after 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 show that the change in inhibition is due to nonhomeostatic mechanisms, which is likely due to the effect of ST after tDCS, specifically targeting the inhibitory neurons that use γ-aminobutyric acid ($GABA_B$) as their neurotransmitter. Because sham tDCS and ST had no effect on corticospinal inhibition, and because priming induced homeostatic plasticity in the excitatory circuits of the M1, it seems that there is an interaction between priming the M1, ST, and the inhibitory motor circuits. At a minimum, priming affected corticospinal excitability leading to homeostatic plasticity, which resulted in ST having a greater effect on modulating the inhibitory cortical circuits through nonhomeostatic mechanisms. However, a caveat to this interpretation is that the exact inhibitory circuit within the M1 was not determined because only single-pulse TMS was used. 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 seems 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 with sham tDCS + ST. With respect to the input-output relationship between stimulus intensity and corticospinal silent period duration, a decrease in total AURC was shown. This finding highlights that priming the M1 with anodal tDCS before ST reduced GABA-mediated inhibitory projections, which resulted in enhanced synaptic efficacy. The results also show that ST further decreased inhibition. Changes in intracortical inhibition seem to be important for muscle strength, with studies of immobilization showing increased inhibition, whereas ST studies show reduced inhibition (30). The observed immediate decrease in corticospinal inhibition may represent acquiring the skill of producing high levels of muscular force in response to the initial training exposure. An immediate reduction in the excitability of the inhibitory motor pathway may serve to increase "motor focus," and therefore facilitate an increase in drive to muscle representations producing the intended movement (14).

Interestingly, this reduction in corticospinal silent period duration was similar to the reductions observed after 2–4 weeks of ST (5,7,10,13,18,25) and is consistent with recent findings by Latella et al. (20). Therefore, similar to motor learning, a reduction in cortical inhibition seems to be an important early neural response to ST (13). This early neural response is also supported by a recent systematic review and meta-analysis, which observed that ST had a greater overall effect on corticospinal inhibition, rather than corticospinal excitability (14). Although priming the M1 before a bout of ST reduced corticospinal inhibition, the precise role of reduced corticospinal inhibition in the current study remains unclear because priming did not attenuate the loss in muscle force after training; therefore, the functional significance of this reduction remains unresolved. It is possible that the paced nature of the ST task induced some form of peripheral fatigue that was not detectable by sEMG or by measuring m-waves after training.

There are several limitations that need to be considered when interpreting these data. First, if the fundamental purpose of ST is to increase strength, then the central nervous system must adjust by increasing the activation of the spinal motor neuron pool that contributes to strength development. To this end, a limitation within the current study was the recording of MEPs from only the agonist muscle. It is well accepted that changes in the activation of the agonist and antagonist contribute to the net increase in force production after ST (3). Although we have previously reported that the corticospinal responses to a single bout of ST predominantly occur at the level of the M1 (22) and, supported by other recent work (19–21), a limitation to this interpretation was that no spinal cord measures were obtained, in particular cervicomedullary MEPs. This must be considered as a limitation because MEPs are influenced by changes in spinal excitability (2). Another consideration with this study is that the functional role of the early corticospinal responses to strength remains unclear. Although we show for the first time that priming the M1 before ST affects the corticospinal responses to ST, 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 after training. Despite these limitations, the findings from this study add new knowledge by showing that the corticospinal responses to ST are affected by priming the M1 with anodal tDCS before a bout of ST.

Practical Applications

Overall, the findings from this study indicate that priming the M1 with anodal tDCS before a single bout of ST altered the corticospinal responses to ST, through nonhomeostatic mechanisms. Interestingly, priming the M1 with tDCS did not attenuate the loss in muscle force after 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 after anodal tDCS and ST are causally related to strength gain, the finding that the corticospinal

responses to acute ST are affected by anodal tDCS may have important applications in understanding the long-term adaptations after a ST program. Importantly, our findings show that priming the M1 with anodal tDCS before ST reduces neural inhibition, which is important for the development of muscular strength after short-term ST (14).

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