THE INTERACTION BETWEEN METAPLASTIC NEUROMODULATION AND FATIGUE
DURING SINGLE-JOINT EXERCISE

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ABSTRACT

Fatigue is a multifaceted phenomenon involving neural, physiological, and psychological changes that result in a decrease in force output during exercise, leading to impairments in physical and cognitive performance in healthy individuals. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique which exhibits potential for attenuating fatigue through modulation of mechanisms that contribute to fatigability such as corticospinal excitability. The high inter- and intra-individual variability is an obstacle that limits its efficacy as a treatment option, however this may be mitigated by utilising homeostatic metaplasticity mechanisms to enhance the outcomes of tDCS. We explored the effects of priming with cathodal tDCS (ctDCS) to boost the effects of anodal tDCS (atDCS) modulation of corticospinal excitability and fatigue in a young, healthy population. 5 subjects completed a fatiguing exercise with concurrent application of atDCS that was primed by either sham (stDCS) or ctDCS stimulation to the motor cortex. We assessed changes to motor evoked potential (MEP) and maximal voluntary contraction force (MVC) over time. There was a main effect of time on corticospinal excitability (P < 0.05) however, there was no interaction between neuromodulation and time (P = 0.41), suggesting a possible non-homeostatic response in younger adults. There was a significant main effect of time and an interaction between time and neuromodulation on fatigue (P < 0.05). There was recovery in MVC force post-exercise only in the stDCS-atDCS condition. These findings provide important insight for optimising tDCS protocols to target fatigue more effectively in a healthy population.
INTRODUCTION

Neuromuscular fatigue is a complex process involving both central and peripheral mechanisms that contribute to an exercise-dependant decrease in force output from the muscle\textsuperscript{1}. Fatigability can be influenced by a reduction in neural drive from the cortex leading to insufficient maximal activation of muscle or processes occurring at or distal to the neuromuscular junction. The extent of fatigue is dependent on numerous factors such as the muscle group involved or the type of exercise (intermittent vs. continuous)\textsuperscript{2-4}.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method involving the delivery of low-intensity current through surface electrodes on the scalp to modulate cortical excitability and produce inhibitory and excitatory effects in targeted motor regions\textsuperscript{5-7}. tDCS has polarity-specific effects on neuron membrane potential; anodal tDCS (atDCS) causes membrane depolarization, thus increasing cortical excitability, and cathodal tDCS (ctDCS) hyperpolarises the membrane, leading to a decrease in cortical excitability\textsuperscript{5,8}. Previous studies have also suggested that tDCS-induced increases and decreases in excitability are mediated by long-term potentiation (LTP) and long-term depression (LTD) mechanisms\textsuperscript{9,10}.

The relationship between tDCS and cortical excitability has been explored in healthy populations, however studies concerning the application of tDCS to the motor cortex to modulate fatigue have yielded mixed results\textsuperscript{11}. Certain studies have reported increases in corticospinal excitability and endurance time, and reduction in the magnitude of fatigue through atDCS\textsuperscript{6,12,13}, whereas other studies have reported no improvements to corticospinal responsiveness, exercise performance or muscle activity and large inter-subject variability\textsuperscript{11,14,15}. A potential avenue for optimising tDCS protocols to circumvent this variability is by taking into account the subject’s previous neuronal activity and the ongoing homeostatic regulation of the targeted cortical region when applying neuromodulation\textsuperscript{16,17}. 
Homeostatic regulation is present in all neural activity to avoid destabilisation of neuronal function. Metaplasticity refers to the regulation of the synaptic modification threshold at which LTP or LTD occurs, based on past synaptic history. In other words, prior induction of LTP shifts the threshold to make further induction of LTP more difficult and LTD more likely to occur, and vice versa\(^{18,19}\). This input-mediated shift in threshold, detailed by the Bienenstock-Cooper-Munro (BCM) model\(^{20}\), can be manipulated by the application of a separate period of priming tDCS. By applying ctDCS priming to reduce the depolarisation threshold before applying atDCS, it is possible to boost the effects of the subsequent corticospinal excitability changes and improve functional changes\(^6, 21, 22\).

To date, there are no studies that explore the impact of metaplastic neuromodulation on neuromuscular fatigue; particularly, priming tDCS and atDCS applied during exercise and the effect of this protocol on fatigue and corticospinal responsiveness. Maximal force reduction during an isometric maximal voluntary contraction (MVC) exercise is an accessible and feasible model to study fatigue and recovery\(^{23}\). Studying fatigue during a single-joint isometric exercise of the first dorsal interosseus (FDI) muscle is suitable as, firstly, it produces more robust responses due to its large representation in the human motor cortex\(^{24}\). The nature of the exercise also requires less movement compared to more dynamic exercises and therefore it is easier to collect consistent measurements.

The aim of this study was to investigate the interaction between metaplastic neuromodulation and fatigue during a single-joint exercise in a healthy, young population. We hypothesised that priming with ctDCS before the concurrent application of atDCS during fatiguing exercise would enhance corticospinal excitability and attenuate fatigue, compared to atDCS primed with sham stimulation (stDCS).
METHODS

Subjects

5 healthy, right-handed participants were recruited for the study (3 women and 2 men, mean age 21.4 ± 1.2). A questionnaire was used to screen for any contraindications to transcranial magnetic stimulation (TMS) such as pregnancy, metallic cranial implants, cardiac pacemaker and/or history of seizures/epilepsy. Subject were also not taking any medications at the time of participation such as selective serotonin reuptake inhibitors (SSRIs) that would affect the magnitude of tDCS effects. Procedures were approved by the University of Adelaide Human Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

Experimental Setup and Electromyography

Subjects abducted their index finger against a force transducer (MLP 100; Transducer Techniques, Temecula, CA) (Fig. 1). Their right forearm rested on a horizontal surface and the elbow was flexed at approximately 90°. The pronated wrist and forearm were held in place using custom restraints and subjects were instructed to refrain from moving the hand and arm extraneously. Surface electromyography (EMG) recorded responses evoked from the right first dorsal interosseus (FDI) muscle and right abductor digiti minimi (ADM) muscle: four cutaneous Ag-AgCl electrodes attached in a belly-tendon montage, and two grounding straps around the forearm.
Figure 1. Experimental Setup. tDCS electrodes are placed on the scalp in M1 contralateral-supraorbital montage and secured with a strap with red markings indicating TMS coil placement. The index finger of the right hand is positioned against a force transducer and the arm is restrained using custom manipulandum.

Experimental Protocol

Subjects participated in three sessions, held in the afternoon (at approximately the same time of day for each subject across sessions) to control for diurnal influences of cortisol on excitability. Sessions were separated by at least 48 hours to minimise carryover effects from the intervention. The tDCS polarities were pseudo-randomised across sessions by a second experimenter and the primary experimenter and subject were blind to the configuration.

To determine maximal voluntary contraction (MVC) force, the average force of three, approximately 5-second maximal FDI abduction tasks were calculated (Fig. 2A). Baseline corticospinal excitability measurements involved 15 single TMS pulses and 3 peripheral nerve stimulations (PNS) and then ctDCS or stDCS priming was applied while the subjects were rested. At
2 minutes and 8 minutes post priming the measurements (15 TMS and 3 PNS) were repeated to detect priming effects on corticospinal excitability (Fig. 2A). After 10 minutes had elapsed from the end of priming, the test stimulation (atDCS or stDCS) was applied. Measurements were repeated at 30 seconds following the application of test stimulation and then subjects performed the fatiguing exercise of 10 intermittent 30-second MVCs. Between the sets of fatiguing contractions measurements (5 TMS and 1 PNS) were also taken (Fig. 2B). Subjects were given verbal cues to start and stop contraction as well as verbal encouragement to perform at maximal capacity throughout the exercise. Force and EMG output were displayed on a screen to provide participants with visual feedback. Post-exercise measurements (15 TMS and 3 PNS) were taken immediately after completion of the fatiguing exercise and two ~5 second MVCs with 30-second rest between contractions were completed (Fig. 2C). These post exercises measurements and MVCs were repeated at 10 minutes and 20 minutes following the conclusion of the fatiguing exercise to monitor fatigue recovery and tDCS after-effects. Subjects also reported any sensations from the tDCS electrodes at the beginning, middle and end of both stimulation periods (priming and test tDCS). All corticospinal excitability measurements were taken while the subject contracted the muscle to 5% of maximum EMG to reduce the threshold for activation and produce more consistent motor evoked potentials (MEPs).
Figure 2. Experimental protocol schematic. (A) 3 maximal voluntary contractions (MVCs) and baseline measurements followed priming tDCS – either sham (stDCS) or cathodal (ctDCS) and post-priming measurements. (B) test tDCS, either stDCS or anodal tDCS (atDCS), during a fatiguing exercise of 10, 30s MVCs. Measurements are taken 30s after test tDCS application and between contractions. (C) recovery measurements at 0, 10- and 20-min post-exercise, including 2, 5 s MVCs at each time point.

Transcranial Direct Current Stimulation

TDCS was delivered using a battery-powered direct current stimulator (NeuroConn DC Stimulator Plus, DE) via two 35cm² saline-soaked, sponge electrodes. The sponges were arranged in an M1 contralateral supraorbital montage with the active electrode centred on the representational field of the right FDI and reference electrode on the contralateral supraorbital region. The current was set to 1 mA intensity and ctDCs was delivered for 15 minutes, atDCS delivered for 12 minutes and
stDCS delivered for 10 seconds (with an 8-second ramp-up and ramp-down for all stimulation conditions). Three combinations of priming and test tDCS were applied in separate sessions for all subjects (stDCS-stDCS, stDCS-atDCS and ctDCS-atDCS).

**Transcranial Magnetic Stimulation**

Corticospinal excitability was evaluated by measuring the peak to peak amplitude of motor evoked potentials (MEPs) elicited by the delivery of single-pulse TMS. A figure-of-eight coil connected to a monophasic Magstim 200² magnetic stimulator (Magstim, Whitland, UK) delivered the stimuli to the left motor cortex representation of the left FDI. The coil was angled over the scalp at 45° to the sagittal plane, with the handle positioned to produce a posterior-anterior current flow. Subjects maintained a 5% EMG contraction (established during baseline MVC trials) when receiving stimulations for practical ease to reduce the threshold for activation so that a lower stimulator intensity was required to elicit MEPs. The motor hotspot was established by mapping for the location on the motor cortex that produced the largest amplitude MEP (at 60% of maximum stimulator output). The coil position was marked with permanent marker on tDCS electrodes and strap to ensure positioning consistency. This positioning was monitored throughout the protocol to ensure TMS was consistently applied on the same spot. The active motor threshold (AMT) was then determined by finding the lowest stimulus intensity required to elicit an MEP distinguishable from background EMG signal in 5 of 10 trials. TMS intensity was set to 120% of AMT across all measurements (69.52 ± 15 % of maximum stimulator output).

**Peripheral Nerve Stimulation**

A constant-current stimulator (DS7A; Digitimer, Hertfordshire, UK) was used to stimulate the ulnar nerve. A bipolar bar electrode probe was affixed over the ulnar nerve at the wrist with the cathodal end angled distally. To determine the nerve hotspot the current was first set to 10 mA and stimulations were delivered to locate the site which produced the greatest compound muscle action.
potential (M-wave) in resting FDI. The electrode was then secured and to establish the maximum M-wave response (Mmax) the stimulation intensity was increased by increments of 5 mA until the amplitude of M-wave did not increase further. Test intensity was set to 120% of Mmax intensity (17.2 ± 4.3 mA).

**Electromyography**

Four Ag-AgCl electrodes were attached to the skin in a belly-tendon montage (two electrodes on the FDI muscle and two on the ADM muscle) to record muscle activity. A reference electrode was placed on the ulnar styloid process. EMG signals were amplified 1000 times (CED 1902) and a high-pass filter of 20Hz and a low-pass filter of 1kHz were included. Signals were digitization with a 1401 interface (Cambridge Electronic Design, UK) at 2kHz. Data was stored offline. For all MVCs, the root mean squared EMG was calculated.

**Data Analysis**

All data was analysed offline. Individual MEP and Mmax amplitudes were measured peak to peak in millivolts using Spike2 software (Version 6.18). MEP and Mmax amplitudes at each time point were calculated as the average amplitude of the values in each measurement block across all trials. MEPs were normalised to Mmax to elucidate corticospinal excitability changes from muscle-dependant changes29.

MVC data was analysed using Spike2 software. Peak force amplitude of the MVCs was measured at baseline and post-exercise and averaged across trials for each time point. Mean force (from initial peak to end of contraction) was measured for each contraction during the fatiguing exercise across trials.
Statistical analysis

IBM SPSS Statistics software (Version 24) was used for all statistical analyses. Linear mixed model analyses with factors time and neuromodulation (stDCS-stDCS vs. stDCS-atDCS vs. ctDCS-atDCS) were used to determine main effects and interactions on MVC force and MEP peak to peak amplitude. For all comparisons, the normality of the data was first confirmed by visually assessing for equal variance in a spread-versus-level scatter plot of the residuals and predicted values and a confirming a normal distribution for the histogram of the residuals. Bonferroni’s correction for multiple comparisons was used to identify specific significant differences between groups. Two-sampled t-tests (equal variance) were used for determining group differences in demographic characteristics and one-way analyses of variance (ANOVA) were used for assessing differences in lab temperature and humidity between neuromodulation conditions. Data is expressed as mean ± standard deviation in tables and as mean ± confidence interval in figures. Significance was set at P < 0.05.

RESULTS

No adverse reactions to tDCS were reported and all sensations were tolerated by subjects. Subjects reported similar sensations during sham and real stimulation. The sensations described ranged from a warming sensation to mild itching/prickling to a mild to moderate burning sensation. Majority of the sensations were reported at the beginning of stimulation and subjects commonly reported feeling mild sensations in the middle and no sensations at the end of stimulation. There were no differences between neuromodulation conditions in lab temperature (22.2 ± 1.25°; P > 0.1) and humidity (36.8 ± 5.98%; P > 0.1).
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**Table 1.** Demographic characteristics of participants. Work, sport, and leisure time indices are subscales of the International Physical Activity Questionnaire

*Corticospinal Excitability*

There was a significant main effect of time (P < 0.01) but not neuromodulation (P = 0.08) nor interaction between time and neuromodulation (P = 0.41) on MEP (% Mmax) for FDI. There was no significant main effect of time (P = 0.41), neuromodulation (P = 0.07) nor interaction between time and neuromodulation (P = 0.65) on MEP (% Mmax) for ADM (i.e. non-target muscle). There were no main effects of time (P ≥ 0.2), neuromodulation (P ≥ 0.3) nor any significant interactions (P = 0.9), on background EMG activity during measurements for both FDI and ADM.
Figure 3. Mean MEP peak to peak amplitude for the FDI muscle normalised to Mmax as a percentage of baseline is displayed for each neuromodulation condition (stDCS-stDCS, stDCS-atDCS and ctDCS-atDCS) across time. Error bars indicate the mean ± confidence intervals. Horizontal green line represents baseline at 100%. * indicates significant main effect of time (P < 0.05). ** indicates significant differences from baseline (P < 0.05).
Figure 4. Mean MEP peak to peak amplitude for the ADM muscle normalised to Mmax as a percentage of baseline is displayed for each neuromodulation condition (stDCS-stDCS, stDCS-atDCS and ctDCS-atDCS) across time. Horizontal green line represents baseline at 100%. Error bars indicate the mean ± confidence intervals.

Fatigue

There was a significant main effect of time (P < 0.01) and a significant interaction between time x neuromodulation (P < 0.01; Fig. 5), but no significant main effect of neuromodulation (P = 0.87) on MVC force of the FDI. In the stDCS-stDCS condition MVC force declined significantly from baseline at each fatiguing contraction (P < 0.01) and remained significantly lower at 10 minutes and 20 minutes post exercise (P < 0.01). Similarly, in the stDCS-atDCS condition MVC force declined significantly from baseline at each fatiguing contraction (P < 0.01) however there were no significant differences from baseline at any time point post exercise (P ≥ 0.08). In the ctDCS-atDCS condition MVC force declined significantly from baseline at each fatiguing contraction and remained
significantly lower at all time point post exercise (P < 0.01). In the stDCS-atDCS condition MVC force was significantly higher at 20 minutes post exercise compared to stDCS-stDCS condition and the ctDCS-atDCS condition (P < 0.05). Finally, for RPE there was a significant main effect of time (P < 0.001; Fig. 6), but no significant effect of neuromodulation (P = 0.75) nor a significant interaction between time and neuromodulation (P = 0.76; Fig. 6).

**Figure 5.** Magnitude of fatigue. Mean MVC force is displayed for each neuromodulation conditions (stDCS-stDCS, stDCS-atDCS and ctDCS-atDCS) across time. Error bars indicate the mean ± confidence intervals. ** indicates significant differences from baseline (P < 0.05). # indicates significant difference compared to stDCS-stDCS and stDCS-atDCS (P < 0.05).
DISCUSSION

Main findings

To the best of our knowledge, this study is the first to examine the interaction between metaplastic neuromodulation and fatigue during single-joint exercise in a young, healthy population. It also provides novel insights on the effects of metaplastic neuromodulation on fatigue in a non-target muscle (ADM). Overall, there were no significant shifts in corticospinal excitability with ctDCS-atDCS nor stDCS-atDCS compared to the sham condition (stDCS-stDCS) for both FDI and ADM. Interestingly, even though no significant recovery of MVC force from baseline was observed...
in the ctDCS-atDCS and stDCS-stDCS conditions, there was significant recovery in the stDCS-atDCS condition. The negligible effects of cathodal priming on the patterns in corticospinal excitability shifts highlights a possible non-homeostatic interaction in healthy young adults which may warrant further exploration in future studies. There is, however, a potential link between corticospinal excitability changes during exercise and force recovery post-exercise. The correlation between the boost in excitability and the attenuation of force reduction post-exercise in the stDCS-atDCS condition indicates that excitability changes may augment force recovery.

*tdCS effects on corticospinal excitability*

The failure of atDCS primed with ctDCS to significantly enhance MEP compared to non-primed atDCS directly contrasts with our hypothesis that ctDCS priming will augment the effects of atDCS. As initially posited by the BCM model\(^{20}\), the previous synaptic activity of a neuron adjusts the modification threshold at which subsequent synaptic plasticity occurs as a way of mitigating destabilising increases in synaptic efficiency (i.e. homeostatic metaplasticity). Prior induction of LTD shifts the threshold to favour LTP over LTD, and vice versa\(^{19}\). There is ample evidence that atDCS and ctDCS induce lasting shifts in cortical excitability via LTP- and LTD-like processes\(^{9, 30}\), with atDCS depolarising the membrane and increasing excitability (LTP) and ctDCS hyperpolarising the membrane and decreasing excitability (LTD)\(^{5, 8}\). In line with the metaplasticity theory, it is expected that by reducing the synaptic modification threshold with a period ctDCS priming this will boost the efficacy of subsequent atDCS stimulation, leading to greater increase in cortical excitability than without priming. This boosting effect is not seen in our study but other metaplasticity-based tDCS studies have indicated that priming leads to an increase corticospinal excitability and MEP facilitation\(^{6, 8, 22}\), so our findings contradict this consensus. However, there is a visible latent shift (albeit non-significant) in MEP amplitude post-exercise favouring the ctDCS-atDCS condition that indicates there were possible delayed effects of priming. It is a possibility that due to the small sample
size of our study (n = 5) and the known inconsistencies in intra-subject response to tDCS\textsuperscript{11, 31} our study simply lacked the statistical power to reveal any overt effects of priming.

Priming with ctDCS also did not have an effect on corticospinal excitability in a non-target muscle (ADM) and when compared to the FDI, the ctDCS-atDCS condition for ADM appears to be least effective in MEP facilitation. The corticomotor representation of the ADM in the primary motor cortex is proximate to that of the FDI\textsuperscript{32} therefore it is possible that neuromodulation targeting the FDI could result in spill-over effects in the distal muscle. However, our results indicate minimal efficacy in a non-target muscle which indicates that the neuromodulatory effects of tDCS may be specific to the area being innervated. Studies have also shown that differential sodium conductance in motor axons of the FDI compared to the ADM combined with other discrepancies in axonal membrane properties may result in higher excitability in the FDI\textsuperscript{33, 34}. Therefore, while the effects of tDCS were strong enough to produce some excitability changes in the FDI it may not have been enough to affect the excitability of the ADM. It can be noted that there is a small (non-significant) shift in the ADM at 10 minutes and 20 minutes post recovery where ctDCS priming slightly increases MEP amplitude that, similarly to the FDI, might hint at possible delayed priming effects.

\textit{tDCS effects on fatigue}

MVC force declined similarly across all conditions during exercise, however post-exercise the stDCS-atDCS was the only condition in which force recovered to baseline. In both stDCS-stDCS and ctDCS-atDCS, there was a significant reduction in MVC force at 10- and 20-minutes post recovery. At 20 minutes post recovery there was a significantly higher MVC force output in the stDCS-atDCS condition compared to stDCS-stDCS and ctDCS-atDCS, indicating that atDCS with no priming was the most effective at attenuating fatigue. This suggests that simply applying anodal tDCS during exercise is more beneficial than preceding it with priming. Our results are in line with other studies involving anodal tDCS applied concurrently with exercise that have reported
improvement to motor performance in healthy individuals\textsuperscript{6, 35, 36} and motor function enhancement in stroke patients\textsuperscript{37, 38}.

Both stDCS-atDCS and ctDCS-atDCS appear to have minimal effects on the participant’s perception of their level of exertion. Initially stDCS-atDCS stimulation is associated with lower RPE values however as the exercise progresses, the RPE values increase similarly across all conditions. Previous studies measuring RPE during exercise have also reported that tDCS was inadequate at modulating perception of effort during submaximal\textsuperscript{39, 40} and maximal exercise\textsuperscript{41}. Enoka & Stuart\textsuperscript{42} suggest that when motor neuron excitability is enhanced the resultant decrease in motor command has a proportional mitigatory effect on sense of exertion. This is somewhat reflected in our results as the increases in corticospinal excitability in the FDI for the stDCS-atDCS condition during exercise have corresponding lower RPE values compared to the other neuromodulation conditions. However, this correlation becomes more obscure by end of the exercise therefore it is difficult to delineate a clear relationship between increases in corticospinal excitability and attenuation of perceived exertion.

\textit{The interaction between neuromodulation and the magnitude of fatigue}

There is an interesting discrepancy between the shifts in corticospinal excitability (of the FDI) and the shifts in fatigue. Firstly, the pattern of excitability during the fatiguing exercise favours the stDCS-atDCS and ctDCS-atDCS conditions whereas when looking at fatigue during exercise there is a less noticeable difference between the three conditions. Similarly, when looking at post-exercise changes, fatigue recovery seems to be more strongly associated with stDCS-atDCS condition whereas excitability post-exercise is skewed more towards the ctDCS-atDCS condition. Recovery of fatigue in the stDCS-atDCS condition may be directly related the modulations in excitability induced during the exercise as the stDCS-atDCS condition is also where the greatest increase in excitability was observed during exercise. Another reason may be that, because the corticospinal excitability changes were non-significant between conditions, there was simply an
insufficient level of excitability to counteract the progressive reduction in central drive to the muscle and that is why the corticospinal excitability changes are not reflected in the pattern of fatigue recovery. Abdelmoula et al. and Williams et al. similarly observed that performance changes during submaximal contractions due to atDCS stimulation were not reflected in MEP changes, implying that perhaps fatigue development may occur somewhat independently of changes in corticospinal excitability.

Limitations and methodological considerations

There are some notable limitations of the present study. Firstly, the sample size of this study should be noted as there was insufficient statistical power due to the small number of participants (n = 5), caused by COVID-19 circumstances hindering the recruitment and testing of participants. Previous studies have noted the high inter-individual variability in response to tDCS due to factors such as dosage, sensitivity to TMS and sex. This variability may have had a substantial impact on such a small sample size, therefore, applying our results to a broader young, healthy population is difficult. Secondly, there was no ctDCS-stDCS condition included to observe the effects of priming by itself as this may have provided some important insight into whether the priming affects MEP modulation by atDCS or if priming influenced MEP facilitation related to exercise by itself. Different electrode sizes may also change the focal density of the current, affecting the performance of tDCS, therefore it could be worthwhile to investigate whether decreasing electrode size would enhance tDCS effects in future studies. A neuro-navigational system was also not available to guide TMS coil placement and this could have resulted in small changes to coil positioning when taking measurement, resulting in MEP variability. Finally, many of the studies involving tDCS and metaplastic neuromodulation have measured a resting muscle and therefore it is hard to draw direct comparisons with our study. This is somewhat reflected in our results as the
Conclusions and significance

This study provides some insights and data on metaplastic neuromodulation of corticospinal excitability and fatigue when applied during exercise in a young and healthy population. In contrast to our hypothesis and previous studies we observed that cathodal primed anodal tDCS did not influence corticospinal excitability compared to anodal tDCS with sham priming and it also did not attenuate fatigue post exercise. The distinct differences in outcomes for excitability compared to fatigue indicates that tDCS may modulate fatigue differentially to corticospinal changes and further studies exploring the interaction between these mechanisms may be needed to resolve this ambiguity. Understanding the relationship between metaplastic neuromodulation and fatigue has important implications for optimising tDCS protocols for fatigue reduction and corticospinal excitability enhancement in healthy populations that can also be extended to clinical settings.
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