No effect of tDCS of the primary motor cortex on isometric exercise performance or perceived fatigue

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Abstract

Anodal transcranial direct current stimulation (tDCS) of the primary motor cortex has been reported to improve isometric exercise performance without changing corticospinal excitability. One possible cause for this may be the previous use of relatively high (2 mA) current intensities, which have inconsistent effects on corticospinal excitability. The present pre-registered study aimed to replicate previously reported ergogenic effects of 2 mA tDCS, and examine whether 1 mA anodal tDCS both improved isometric exercise performance and perceived fatigue, and more reliably altered corticospinal excitability. On three separate occasions, participants performed a sustained submaximal isometric knee extension until failure after receiving either 1 mA, 2 mA or sham anodal tDCS. Corticospinal excitability of the knee extensors was measured using transcranial magnetic stimulation immediately before and after tDCS. Rating of fatigue was recorded throughout the isometric exercise. Neither 1 nor 2 mA tDCS improved exercise performance, or reduced perceived fatigue, compared to sham stimulation. There was also no effect of tDCS on the corticospinal excitability of the knee extensors. We found no effect of tDCS on either exercise performance, perceived fatigue or corticospinal excitability. This study adds to the growing body of literature reporting no ergogenic effect of tDCS. Large preregistered replications of previously reported effects are now required before tDCS can be considered an effective method to improve exercise performance.

Introduction

Fatigue is a debilitating symptom experienced in many neurological diseases (Chaudhuri & Behan, 2004) and is also a contributing factor to the voluntary cessation of exercise (Kayser, 2003). During exercise, the symptom of fatigue arises from an interaction between an individual's performance fatigability and their perceived fatigue, i.e. from both the physiological demands of the exercise and subjective perceptions of those demands (Kluger *et al.*, 2013; Enoka & Duchateau, 2016). Both the descending cortical drive to the muscles, and the perception of fatigue, are dependent on motor cortex activity (for reviews, see Pageaux, 2016; Taylor *et al.*, 2016). Ergogenic aids that target motor cortex activity may thus alter descending cortical drive and perceived fatigue, and subsequently improve exercise performance (Angius *et al.*, 2017).

Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, may improve both exercise performance and perceived fatigue (Angius *et al.*, 2017; Edward *et al.*, 2017). tDCS of the primary motor cortex has been reported to improve the performance of fatiguing upper and lower limb isometric exercise (Cogiamanian *et al.*, 2007; Williams *et al.*, 2013; Abdelmoula *et al.*, 2016; Angius *et al.*, 2016). However, the mechanisms underpinning these effects are unclear. The primary physiological effect of tDCS is assumed to be a polarity-dependent modulation of neuronal excitability (Stagg & Nitsche, 2011). Anodal stimulation of the primary motor cortex is suggested to increase, and cathodal stimulation decrease, corticospinal excitability (Nitsche & Paulus, 2000, 2001). Interestingly, however, no changes in corticospinal excitability (i.e. alterations in the motor evoked potential; MEP) have been observed when isometric exercise performance was improved after anodal tDCS of the motor cortex (Abdelmoula *et al.*, 2016; Angius *et al.*, 2016). Despite this inconsistency, it was recently proposed that tDCS-induced alterations to corticospinal excitability reduces perceived fatigue and subsequently improves exercise performance (Angius *et al.*, 2017). This assumption is problematic because

the only measure of corticospinal excitability that tDCS appears to alter reliably is the MEP amplitude (Horvath *et al.*, 2014). Therefore, at present, it is not possible to conclude that improvements in exercise performance are due to changes to corticospinal excitability.

The effects of tDCS on isometric exercise performance are not consistent, and there are reports of no effect of stimulation on upper limb exercise (Kan *et al.*, 2013; Flood *et al.*, 2017; Radel *et al.*, 2017; see Holgado *et al.*, 2019 for a systematic review). The use of relatively high stimulation intensities may influence the effect of tDCS on the MEP (Parkin *et al.*, 2015). Early tDCS studies used a current intensity of 1 mA to alter corticospinal excitability (Nitsche and Paulus, 2000, 2001). However, in research examining the effects of tDCS on exercise and fatigue, current intensities are typically between 1.5-2 mA (Cogiamanian *et al.*, 2007; Williams *et al.*, 2013; Abdelmoula *et al.*, 2016; Angius *et al.*, 2016). The reasons for this choice are not entirely clear. It may be that it is assumed that higher current densities are required to activate the representation of the leg in the motor cortex, or that increased 'dose' will result in greater ergogenic effects though this is unlikely (see Parkin *et al.*, 2015, 2019). The relationship between current intensity and changes in corticospinal excitability is non-linear, and stimulation intensities over 1 mA may limit or even reverse the canonical polarity-dependent changes to the MEP (Batsikadze *et al.*, 2013; Wiethoff *et al.*, 2014). Therefore, previous studies may have failed to elicit group-wide changes to the MEP because they employed too high a current intensity. However, it is not clear whether using a current intensity of 1 mA, which may more reliably induce polarity-dependent shifts in corticospinal excitability (Batsikadze *et al.*, 2013), will improve exercise performance. Currently, the physiological mechanisms by which tDCS improves performance during fatiguing exercise remain speculative. For tDCS to be considered an efficacious intervention, it is essential to identify the physiological mechanisms by which it alters behaviour (Bestmann *et al.*, 2014).

The aims of the present study were to examine whether (i) both 1 mA and 2 mA anodal tDCS of the motor cortex improved performance of a fatiguing isometric exercise when compared to a placebo (sham stimulation); (ii) the effects of 1 mA and 2 mA anodal tDCS on exercise performance were accompanied by changes in corticospinal excitability. The study was preregistered on the Open Science Framework (https://osf.io/rh82g/files). Deviations from this registration are listed in the manuscript. It was hypothesized that 1) both 1 mA and 2 mA anodal tDCS would improve exercise performance, replicating previous reports (Abdelmoula *et al.*, 2016; Angius *et al.*, 2016) and 2) because the effect of tDCS on corticospinal excitability is variable following 2 mA stimulation, we also hypothesized that ergogenic effects of tDCS would be associated with changes in corticospinal excitability following 1 mA, but not 2 mA, tDCS.

Methods

The study was approved by the University of Calgary Conjoint Health Research Ethics Board (CHREB) and performed in accordance with the declaration of Helsinki.

Participants

When this study was preregistered, only two previous studies had reported standardized effect sizes for the effect of tDCS on isometric exercise performance (partial eta squared (ηp)=0.47; (Williams *et al.*, 2013) and ηp=0.49; (Angius *et al.*, 2016)). To address the primary research hypothesis (hypothesis 1) that tDCS would improve exercise performance, the present study was initially powered to detect the smallest of these two effect sizes. *A-priori* power analysis performed using the G*power software program (version 3.1, Faul *et al.*, 2007) revealed that 22 participants would be required (ηp=0.47, alpha = 0.01, beta = 0.10, Nonsphericity correction = 1, ANOVA with repeated measures within factors).

In our preregistered method, only right-handed healthy male participants were to be recruited. However, we altered this to include right-handed male and female participants to improve recruitment and ecological validity. The study protocol conformed to the Helsinki Declaration of Human Rights and received institutional ethical approval from the University of Calgary Research Ethics Board. Exclusion criteria included medical contra-indications to either tDCS or transcranial magnetic stimulation (TMS) (Poreisz *et al.*, 2007; Rossi *et al.*, 2009), which were determined using the rTMS screening questionnaire (Rossi *et al.*, 2011). Contra-indications to isometric exercise were assessed using a pre-exercise screening questionnaire. Handedness was assessed using the Edinburgh handedness inventory (Oldfield, 1971), which included a question about foot preference. Only participants who highlighted a preference for their right foot were included.

Of the 22 participants recruited, two did not finish the study. One participant withdrew with no reason given. Another completed two of the three trials, but was uncomfortable during the 2 mA tDCS condition and withdrew before the trial was completed. Although their data is not included in this analysis, it is available in the online supplementary material (https://osf.io/rh82g/files). Twenty participants completed the study (11 males, mean+SD age: 23.8+4.7 years, height: 168.2+6.8 cm, body mass: 64.8+9.8 Kg). Compromised power to detect the effect size of interest, calculated using G*power, was 0.88.

Procedure

The experiment was a double-blind, repeated-measures, crossover design. Participants visited the laboratory on four occasions. During the preliminary visit, following familiarization to TMS and sham tDCS, the maximum force produced during an isometric contraction of the right knee extensors (MVC) was determined (see ‘Knee-Extensor Force’). Participants then performed an isometric contraction of the right knee extensors at a target force of 20% of MVC (20%MVC). Participants were asked to maintain 20%MVC until task failure (defined as a drop-in force to below

15% of MVC for 3 s). A figure summarizing the protocol is available in the supplementary material (Figure 5).

Subsequently, participants visited the laboratory for three experimental trials. Participants received either 1 mA anodal, 2 mA anodal or 2 mA sham tDCS to the left motor cortex for 10 minutes. Stimulation order was randomized using an online software program (Research Randomizer version 4). Immediately before and after tDCS, corticospinal excitability was measured using TMS. It has previously been demonstrated that tDCS does not alter the ability to produce maximal force (Cogiamanian *et al.*, 2007). However, to ensure the tDCS protocol used in this study did not result in an (unanticipated) alteration to maximal force, which may otherwise alter time to task failure, participants performed an MVC immediately after the TMS protocol, both pre- and post-tDCS. Participants were then required to perform 20%MVC to failure. The target force for each trial was 20% of the MVC force recorded at baseline.

Measures

Knee-Extensor Force

Force during the MVC and 20%MVC was measured using a custom-built chair with an attached calibrated load cell (LC101-2K, Omegadyne, Sunbury, OH) positioned directly behind the point of applied force and connected to a noncompliant cuff attached around the participant's right leg, 1-2 cm superior to the ankle malleoli. Chair position was altered so that participants' knees and hips were flexed at 90 degrees. Force values were recorded using a data acquisition system and analyzed offline using custom-made macro-instructions (PowerLab 16/35 and LabChart V8, ADInstruments Ltd, Oxford, UK).

For the determination of maximal force during the MVC, following a set of preparatory contractions (2 × 50%, 75% and 100% of maximum effort), three contractions of 3-5 s at maximum voluntary effort were performed, with 1-minute rest between contractions. Participants were given strong

verbal encouragement and visual feedback of force. MVC was determined as the highest force produced during a 500 ms plateau in any of the three contractions. During 20%MVC, visual feedback of force production and a guideline for the value equal to 20% of MVC was displayed on a computer monitor positioned directly in front of the participant. Participants were not aware of elapsed time during 20%MVC and were instructed to maintain force at the 20% guideline for as long as possible. Participants were informed that the task was terminated once force dropped below 15% of MVC (i.e. a drop of 5%) for 3 s. During 20%MVC, verbal encouragement timing and phrases were standardized across all trials.

Transcranial Direct Current Stimulation

tDCS was delivered through two saline-soaked sponge surface electrodes (secured to the scalp using an elasticated cap) using a programmable direct current stimulator (HDCkit, Newronika, Milan, Italy). The active and reference electrodes were both 35 cm^2 in size. To blind both participant and experimenter to stimulation type, the stimulation condition (1 mA anodal, 2 mA anodal or sham) was pre-programmed by researchers not involved with data collection or analysis. The active electrode was positioned over the hotspot for the contralateral (right) vastus lateralis (VL) muscle identified using TMS (see 'Transcranial Magnetic Stimulation,' below). In a deviation from our pre-registered method, the reference electrode was placed over the left deltoid as this set-up has been reported to alter the corticospinal excitability of the knee-extensors (Angius *et al.*, 2018). In the anodal stimulation conditions, the current density under the active electrode was either 0.029 mA/cm^2 (1 mA condition) or 0.057 mA/cm^2 (2 mA condition). In the sham conditions, 2 mA of current was delivered for 60 s. To blind participants to stimulation type, the current was ramped on and off for 30 seconds at the start of each stimulation.

Transcranial Magnetic Stimulation

Assessment of corticospinal excitability was performed using mono pulse TMS, delivered using a Magstim200 stimulator, which has a maximum output of 2.5 Tesla (Magstim Company, Whitland, UK) with 110-mm diameter concave double-cone coil. The method was the same across all three experimental trials. Coil placement was determined using the following method: after marking the vertex, the optimal site for stimulation was identified as the area of left motor cortex which, when stimulated using a stimulator intensity of 50% of maximum stimulator output, results in the greatest peak-to-peak MEP amplitude in the right VL. This site was marked with ink on a swim cap, and its distance from the vertex recorded to ensure consistency across trials. All subsequent stimulations were delivered with the coil placed at this site. The stimulator intensity was equal to 120% of the resting motor threshold. Resting motor threshold was determined at the start of each trial using an adaptive estimation method (Awiszus, 2003; Awiszus & Borckardt, 2010). Ten stimulations (stimulation frequency < 0.25 Hz) were performed in each block, and the mean peak-to-peak amplitude of the 10 MEP's was used as the measure of corticospinal excitability.

Electromyography

Surface EMG was recorded from the right VL using electrodes with a 10-mm recording diameter (Meditrace 100, Covidien, Mansfield, MA) and 30-mm inter-electrode distance. EMG and force signals were analog-to-digitally converted at a sampling rate of 2000 Hz by a PowerLab system (16/35, ADInstruments, Bella Vista, Australia) and an octal bio-amplifier (ML138, ADInstruments) and analyzed offline with LabChart V.8. The root mean square of the raw EMG signal at 30-s intervals (time window = 0.5 s) was also processed offline using LabChart V.8. RMS data from the 20%MVC was normalized to the maximal RMS obtained from the baseline maximal isometric contraction performed at the start of each trial.

Perceived Fatigue

The effect of tDCS on perceived fatigue was measured using the rating-of-fatigue (ROF) scale (Micklewright *et al.*, 2017) post-tDCS, every 30 s during exercise and at task failure.

Statistical analysis

All data analysis was performed with the experimenter blinded to the stimulation condition. The change in both MEP amplitude and MVC force was calculated by expressing the post tDCS values relative to the pre tDCS values (post/pre). A value over 1 indicates an increase; a value under 1 indicates a reduction. The effect of tDCS on exercise time, change in the MEP and MVC (post/pre), and the slope for EMG and ROF during exercise was examined using a one-way repeated measures ANOVA with stimulation condition (1 mA $\times$ 2 mA $\times$ sham) as the within-subjects factor. Data were checked for normality using the Shapiro-Wilk's test. Sphericity was checked used Maulchy's test, and where necessary, degrees of freedom were adjusted using the Greenhouse-Geisser correction. The effect of tDCS condition on ROF at task failure was compared using a Friedman ANOVA. Partial Eta squared (*np*, for ANOVA) was used as the estimate of the effect size.

The effects of tDCS were also analyzed using Bayesian repeated measure ANOVA (priors: r scale fixed effects 0.5, r scale random effects = 1, r scale covariates = 0.354) to give a likelihood of the data under both the null and alternative hypotheses. A Bayes factor (BF_{10} or BF_{01}) of > 3 was considered as evidence for the alternative or null hypothesis, respectively. To test our hypothesis that the ergogenic effects of tDCS would be associated with changes in corticospinal excitability following 1 mA, but not 2 mA, tDCS, we performed exploratory analysis (not pre-registered) to examine the Pearson's product-moment correlations between change in corticospinal excitability, exercise time and ROF. We also examined the association between baseline MEP amplitude and exercise time. Multiple comparisons were controlled by adjusting the false discovery rate

(Benjamini *et al.*, 2006). All statistical tests were performed using R (version 3.4.1). References for the packages used in these analyses can be found in the supplementary material.

Results

Table 1 shows the raw values for exercise time, MEP amplitude and MVC force (both pre and post tDCS) and ROF (post tDCS and post-exercise).

Table 1. Here, please.

The effect of tDCS on exercise time and perceived fatigue

There was no effect of tDCS on exercise time ($F_{(1.5,27.6)}$=0.38, p=0.686, np=0.02, Figure 1A), and the data were six times more likely under the null hypothesis compared to the alternative hypothesis (BF_{01}=6). There was also no effect of tDCS on the slope of the rating of fatigue during exercise ($F_{(2,38)}$=0.11, p=0.899, np<0.01, Figure 1B) and data were seven times more likely under the null hypothesis compared to the alternate hypothesis (BF_{01}=7). Examination of the individual data for ROF over time indicated that the relationship was not always linear, with correlation coefficients ranging from 0.98 to 0.1. There was no difference in rating of fatigue post-stimulation ($X^2_{(2)}$=2.1, p=0.344) or at the end of exercise ($X^2_{(2)}$=1.8, p=0.407).

Figure 1. Here, please.

The effect of tDCS on MEP amplitude

Because two participants were unable to tolerate TMS at 120% resting motor threshold, the data for 18 participants was used for the analysis of MEP amplitude. In over half of the participants,

MEP amplitude was decreased in all conditions after tDCS (see Figure 2). There was no effect of tDCS on the change (post/pre) in MEP amplitude ($F_{(2,34)}$=0.77, p=0.471, np=0.04) and data were six times more likely under the null hypothesis than the alternate (BF_{01}=6). We performed exploratory one-sample t-tests for each stimulation condition to see if the average change in MEP was different to 1 (i.e. no change pre-to-post tDCS). The reduction in MEP amplitude was below 1 (i.e. reduced post tDCS) in all three conditions (1 mA; p=0.002, d=-0.85, BF_{10}=18, 2 mA; p<0.001, d=-1.18, BF_{10}=258, Sham; p<0.001, d=-1.21, BF_{10}=323).

Figure 2. Here, please.

The effect of tDCS on MVC force and EMG

There was also no effect of tDCS on MVC force ($X^2_{(2)}$=0.7, p=0.711) or the slope of EMG during exercise ($X^2_{(2)}$=4.3, p=0.115).

Exploratory correlation analysis

There was evidence that change in MEP amplitude due to tDCS was positively associated with exercise time (Figure 3) in the 1 mA (r=0.50, p=0.043) and sham conditions (r=0.53, p=0.036), with a similar-sized effect in the 2 mA condition (r=0.46, p=0.064). Confidence intervals for these correlations are displayed in Figure 3.

Figure 3. Here, please

There was also a negative correlation between change in MEP amplitude due to tDCS and the slope of the rating of fatigue during exercise in the 1 mA (r=-0.48, p=0.043) and 2 mA (r=-0.60, p=0.023) conditions, with a smaller effect in the Sham condition (r=-0.41, p=0.093). The correlations and their associated confidence intervals are displayed in Figure 4. Baseline MEP

amplitude was not significantly associated with exercise time in any condition (all r<0.31, all p>0.3).

Figure 4. Here, please

Discussion

The primary aim of this study was to examine whether 1 and 2 mA anodal tDCS of the primary motor cortex improved isometric knee extensor exercise performance and reduced perceived fatigue. In contrast to our hypothesis, 10 minutes of 1 and 2 mA tDCS did not affect exercise performance or perceived fatigue. In fact, there was moderate to strong evidence for a null effect. This study has failed to replicate previously reported effects of tDCS of the primary motor cortex on isometric exercise performance and adds to the growing body of literature indicating that the effects of tDCS on exercise performance and perceptions of fatigue is highly variable between individuals, and tDCS cannot presently be considered an effective ergogenic aid.

tDCS has been reported to improve isometric exercise performance in the upper and lower limb (Cogiamanian *et al.*, 2007; Williams *et al.*, 2013; Abdelmoula *et al.*, 2016; Angius *et al.*, 2016). It has been proposed that increasing the excitability of the primary motor cortex reduces the perceptions of fatigue during exercise (Angius *et al.*, 2017). In contrast to these reports, we found no group-wide effect -of tDCS on isometric exercise performance or perceptions of fatigue. To our knowledge, this is the second pre-registered study to find no effect of tDCS on isometric exercise performance. Radel *et al.*, (2017) also reported no effect of 2 mA high definition-tDCS of the primary motor cortex on upper limb isometric exercise performance. The small effects we report here are also similar to the standardized effects reported by Radel *et al.*, (2017). The results of these two pre-registered studies, plus other exploratory studies (Kan *et al.*, 2013; Flood *et al.*, 2017) and recent systematic reviews (Holgado *et al.*, 2019; Machado *et al.*, 2019), suggest that,

contrary to recent proposals (Angius *et al.*, 2017; Edward *et al.*, 2017), tDCS does not enhance exercise performance, at least not for a sustained isometric contraction. However, it should be noted that in 13 of the 20 participants, at least one condition (1 or 2 mA) improved exercise time compared to sham (data available: https://osf.io/rh82g/files). There was no concomitant difference in MEP amplitude. Although we have no a priori hypotheses for the cause, it is possible that a 'preferred' stimulation intensity may exist, which exerts ergogenic effects on performance, and this is a possible avenue for future research.

Although Angius *et al.*, (2016, 2018) reported that an extra-cephalic reference electrode was required to elicit improvement in both exercise performance and corticospinal excitability, we found no effect of this electrode montage. However, it is possible that other methodological choices caused this replication failure. In the present study, we used 10 minutes of stimulation, whilst in previous studies, stimulation was applied for 20 minutes (Angius *et al.*, 2017). It is possible, therefore, that longer stimulation times are required to increase exercise tolerance. Ten minutes of stimulation time was chosen because, in the original and widely-cited seminal tDCS papers (Nitsche & Paulus, 2000, 2001), 10-13 minutes of anodal stimulation caused distinct increases in corticospinal excitability. Longer stimulation times, such as 20 minutes, may instead reverse stimulation effects (Monte-Silva *et al.*, 2010), and so perhaps it is the reversal of the canonical stimulation polarity to excitability changes which underpins previously reported effects. We consider this unlikely, however, because others have also reported no effects in exercise performance following 20 minutes of stimulation (Flood *et al.*, 2017; Radel *et al.*, 2017) . Instead, it is far more likely that the present and previous failures to replicate the ergogenic effect of tDCS simply represent the substantial inter-individual variability that exists in response to stimulation. While this variability has been well recorded for other behavioural paradigms (see Horvath *et al.*, 2014 and Parkin *et al.*, 2015 for reviews), it is less acknowledged in studies of fatigue. However,

our results, in addition to others (Kan *et al.*, 2013; Flood *et al.*, 2017; Radel *et al.*, 2017), indicate that such variability is also present when tDCS is applied as an ergogenic aid.

In the present study, neither 1 nor 2 mA tDCS elicited group-wide effects on MEP amplitude. Although in contrast to numerous studies in the upper limb (for a review, see Horvath *et al.*, 2014), and a data in the lower limb (Jeffery *et al.*, 2007), this finding is in accordance with a number of studies reporting no effect on the MEP evoked in the knee extensors with a similar extra-cephalic electrode montage (Angius *et al.*, 2016). Indeed, even in the upper limb, the effects of tDCS on corticospinal excitability appear to be variable (Tremblay *et al.*, 2016). We examined both 1 mA and 2 mA tDCS in the present study, because 2 mA stimulation may exert nonlinear homoplastic effects on corticospinal excitability (Batsikadze *et al.*, 2013) confounding reports of ergogenic effects of tDCS without changes to corticospinal excitability (Angius *et al.*, 2016). However, neither stimulation intensity elicited a measurable change in MEP amplitude, compared to sham.

In all conditions, there was an (average) decrease in MEP amplitude following tDCS, with a reduction in MEP amplitude occurring in over half of all participants. There are two possible causes of this MEP depression: (i) fatigue induced by the three MVCs performed prior to stimulation being delivered (Brasil-Neto *et al.*, 1993) or (ii) a more general transient depression of the MEP following muscle activity (McDonnell & Ridding, 2006; Teo *et al.*, 2012). Although there appeared to be a slight reduction in peak MVC force following stimulation, this was within the error of this measure (Todd *et al.*, 2004) and may represent the lack of warm-up post tDCS (i.e. after 10 minutes of rest). Thus, it is unlikely that this depression is a result of fatigue. Instead, sustained suppression of the MEP appears to be a typical response of the central nervous system to both fatiguing and non-fatiguing motor tasks, including passive movement and is likely cortical in origin (Brasil-Neto *et al.*, 1993; McDonnell & Ridding, 2006; Teo *et al.*, 2012; Otsuka *et al.*, 2017). To our knowledge, this is the first study to show that this depression in MEP is associated with both subsequent exercise time and ratings of fatigue. Although the mechanisms underpinning this

effect are unclear, movement-related suppression of cortical excitability may limit subsequent descending motor drive during exercise. However, this proposal is speculative, and the analyses used here were exploratory. Replication and examination of the causes of these effects should be a topic for further study. It could be argued that the failure of tDCS to improve exercise tolerance in the current study is because of the suppression of corticospinal excitability caused by our paradigm. However, we do not consider this a limitation of the study. Other studies have reported ergogenic effects with similar paradigms (Angius *et al.*, 2016), and an ergogenic effect which is abolished by a very brief muscular warm-up procedure, common in most exercise performances, is unlikely to be effective.

Some limitations of this study should be acknowledged. Recent studies have used a bilateral electrode montage (e.g. Angius *et al.*, 2018), while in the present study used a unilateral montage. A bilateral montage may be more effective at altering corticospinal excitability and reducing fatigue. However, we consider this unlikely because the effects of bilateral montages appear to be extremely variable and unlikely to induce reliable changes to corticospinal excitability (Parkin *et al.*, 2019). We have not included a computational model for the current flow for the electrode montage used here, nor to our knowledge has this been done previously (e.g. (Angius *et al.*, 2016, 2018). The use of computational models to infer current flow is a necessary step when evaluating new electrode montages, and the absence of such a model is a limitation of this study (Bikson & Datta, 2012; De Berker *et al.*, 2013). The inclusion of computational models of the predicted current flow is recommended for future studies employing this montage. We used the slope of the rating of fatigue over the trial to control for different exercise durations. However, in some participants, the relationship between the two was only weakly linear. Nonetheless, the final ROF was not different between conditions, and so we do not believe this analysis masks possible differences in perceived fatigue. tDCS may have a greater effect on affective valence during isometric exercise, which increases linearly with exercise performance (Greenhouse-Tucknott *et*

al., 2019). The sham stimulation used here is frequently assumed to provide sufficient blinding, although this has recently been challenged (Turi *et al.*, 2019), and we did not explicitly ask participants which trials they believed were sham or real. While there no statistically significant differences in the magnitude of side effects reported (see supplementary material, Table 2), there did appear to be a tendency for more severe side effects during the 2 mA stimulation, and this may have interfered with blinding efficacy. Indeed, one participant withdrew from the study after experiencing 60 s of 2 mA tDCS.

Conclusion

Neither 1 mA nor 2 mA tDCS improved exercise performance or reduced perceived fatigue. There also appeared to extremely variable responses to stimulation. Our failure to replicate previous reports of an ergogenic effect of tDCS represents the well documented inter-individual variability that occurs in both physiological and behavioural responses to stimulation. This study adds to the growing evidence base indicating that the ergogenic effects of tDCS at best are highly variable. Despite increasing evidence of null or trivial effects, manufacturers of commercially available stimulators still propose ergogenic benefits for their devices. We argue that, in collaboration with researchers, the onus for providing well-powered and pre-registered evidence for these devices now lies with these manufacturers.

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Conflict of interest statement

The authors report no conflicts of interest.

Data accessibility

Data and code is accessible online at the Open science framework: https://osf.io/rh82g/files/

Abbreviations

EMG: Electromyography

MVC: maximum voluntary contraction

MEP: Motor evoked potential

ROF: Rating of fatigue

tDCS: Transcranial direct current stimulation

TMS: Transcranial magnetic stimulation

VL: Vastus lateralis

Author contributions

JW, RT and GM designed the study. JW, SY and RT collected data. JW and SY analyzed data. JW, RT, SY and GM were involved in creating and editing the manuscript.

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Table

Table 1. Mean+SD values for exercise time, MEP amplitude, MVC force and rating of fatigue (median) pre and post tDCS, in each stimulation condition

	1 mA		2 mA		Sham	
	Pre	Post	Pre	Post	Pre	Post
Exercise Time (s)	*	253+103	*	260+101	*	250+99
MEP amplitude (mV)	0.24+0.17	0.16+0.13	0.22+0.13	0.17+0.11	0.29+0.21	0.14+0.07
MVC force (N)	590+163	534+175	603+179	539+148	595+172	534+164
Rating of Fatigue (Median [range])	2 [1-3]	10 [7-10]	2 [1-3]	9 [8-10]	2 [1-3]	10 [7-10]

MEP; Motor Evoked Potential, MVC; Maximum Voluntary Contraction

Figures

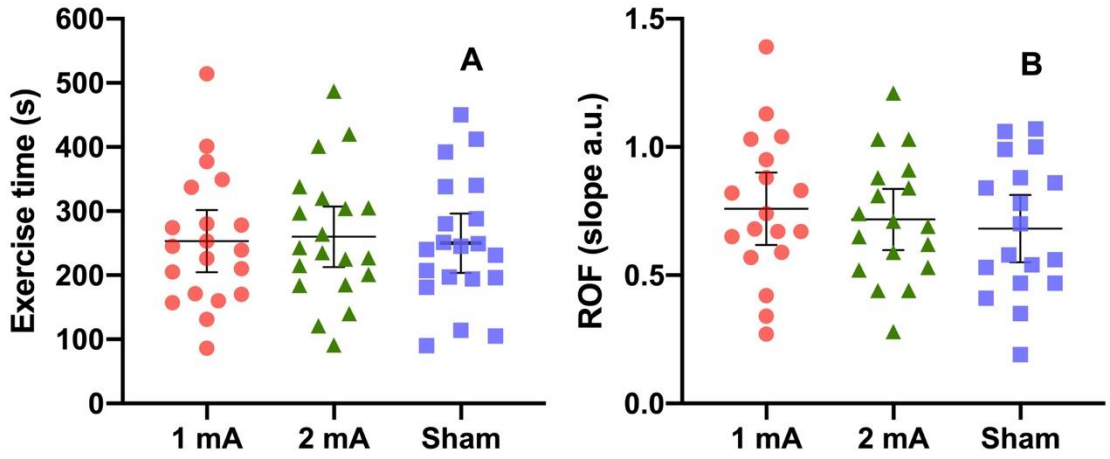

Figure 1. Effect of tDCS on exercise time (A) and the slope of perceived fatigue (B). Error bars are mean and 95% CI

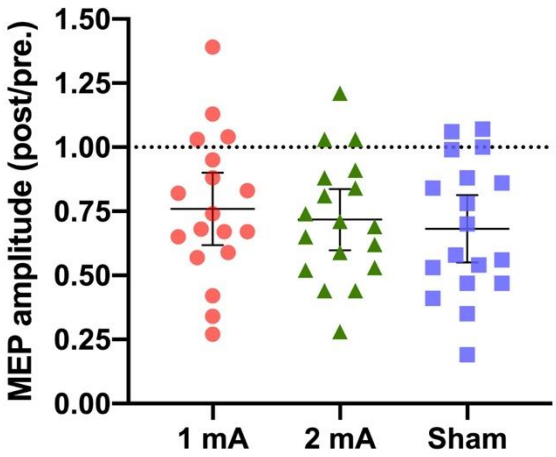

Figure 2. Effect of tDCS on change in MEP amplitude. Error bars are mean and 95% CI. Data points below the horizontal line represent decreases pre to post stimulation in MEP amplitude, points above represent increases. In all conditions, mean change in MEP amplitude was below 1 ($p<0.002$, $BF_{10}>10$) indicating a reduction in MEP amplitude following tDCS.

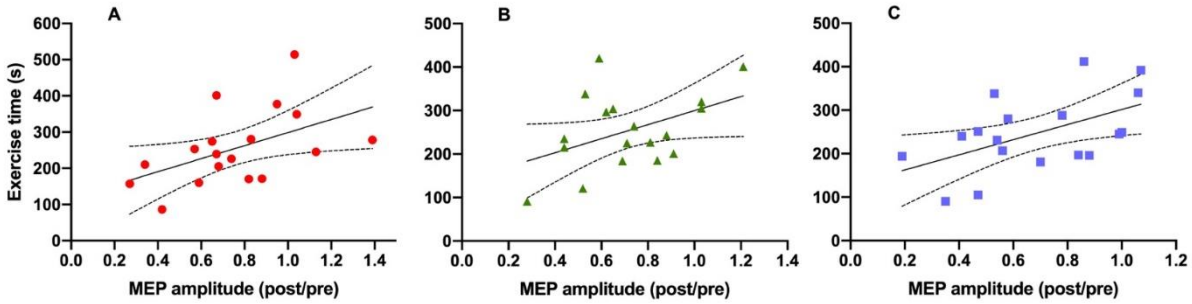

Figure 3. Correlations between change (post/pre) in MEP amplitude and exercise time (s) in the 1 mA (A), 2 mA (B) and Sham (C) conditions. Curved lines represent the 95% CI of the correlation coefficient.

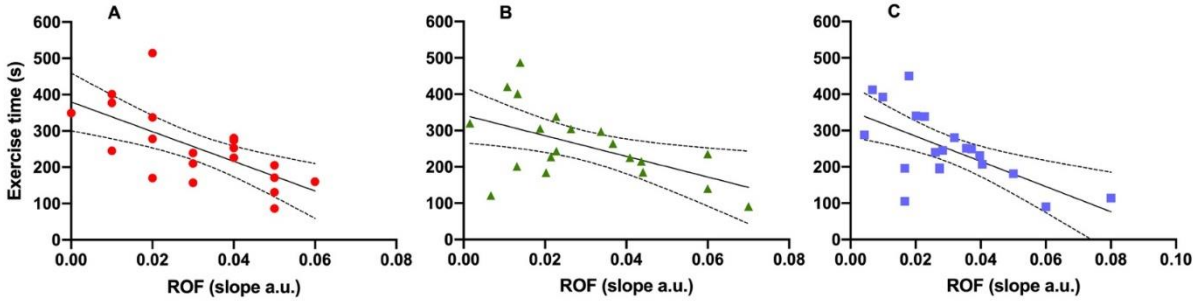

Figure 4. Correlations between change (post/pre) in MEP amplitude and rating of Fatigue (ROF; slope) in the 1 mA (A), 2 mA (B) and Sham (C) conditions. Curved lines represent the 95% CI of the correlation coefficient.

Supplementary material

Table 2. Median (range) side effects reported after each trial.

	Headache	Neck pain	Scalp pain	Tingling	Itching	Burning sensation	Skin redness	Sleepiness	Trouble Concentrating	Mood change
1 mA	1 (1-2)	2(1-3)	1(1-2)	1(1-2)	1(1-3)	1(1-2)	1(1-3)	1(1-3)	1(1-3)	1(1-1)
2 mA	1(1-3)	1(1-2)	1(1-3)	2(1-4)	2(1-3)	1(1-3)	1(1-3)	1(1-4)	1(1-3)	1(1-1)
Sham	1(1-3)	1(1-2)	1(1-3)	2(1-4)	1(1-3)	1(1-3)	1(1-3)	1(1-4)	1(1-4)	1(1-2)

Scores range between 1-4, 1= side effect s absent, 2 = mild, 3 is moderate, 4 = severe

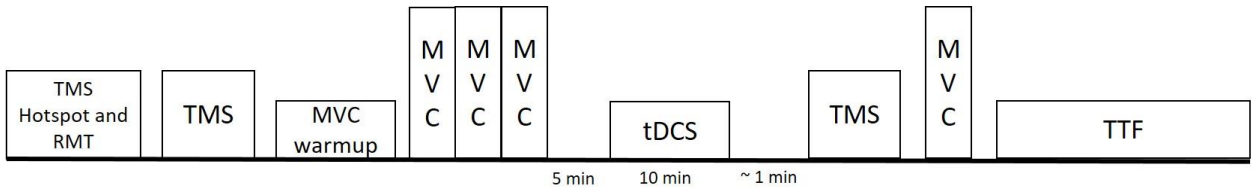

Figure 5. A schematic of the testing protocol. TMS; transcranial magnetic stimulation, MEPs; motor evoked potentials, MVC; maximum voluntary contraction; TTF; time to task failure (exercise)

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