The Effect of tDCS Applied to the Dorsolateral Prefrontal Cortex on Cycling Performance and the Modulation of Exercise Induced Pain

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Abstract

Transcranial direct current stimulation (tDCS) is a neuromodulatory tool purported to enhance endurance performance through reducing fatigue related perceptions, including exercise-induced pain (EIP). We examined whether tDCS of the left DLPFC (1) can reduce EIP during a fixed intensity cycling trial (FI), (2) can improve cycling time trial (TT) performance, and (3) whether this was affected by a bilateral or an extracephalic montage. This investigation was comprised of two parts (study one and two). In both studies, participants completed a 10-minute FI trial and a 15-minute TT after 10 minutes of 2mA anodal left DLPFC tDCS, SHAM or no stimulation. In study one, 11 participants received tDCS via a bilateral montage. In study two, 20 participants received tDCS using an extracephalic montage. Pain was recorded throughout the FI and TT trials, with power output (PO) monitored during the TT. Study one saw no significant changes in pain (tDCS 4.3 ± 2.0; SHAM 4.0 ± 1.8; control 3.8 ± 1.4) during the FI trial and no significant differences in distance covered, pain or PO in the TT. In study two there were no differences in pain reported in the FI trial, or distance covered (P = 0.239), pain or PO in the TT. In summary, tDCS of the DLPFC did not induce analgesia and provided no ergogenic effect for TT performance, moreover these observations were consistent across both the extracephalic and bilateral montage. These findings are in line with an increasing number of studies demonstrating the inconsistent effects of tDCS.

Keywords:

Transcranial Direct Current Stimulation; Exercise Performance; Exercise-induced Pain; Dorsolateral Prefrontal Cortex.

Highlights:

- Anodal tDCS is proposed to reduce naturally occurring pain associated with exercise.
- The effects of DLPFC tDCS on the rating of exercise-induced pain have not been examined.
- Two studies were conducted to assess differences in DLPFC electrode montage.
- Neither DLPFC electrode montage reduced pain or improved time trial performance.

Introduction

Transcranial direct current stimulation (tDCS) is often used in the treatment of various neuropsychiatric disorders[1]. In healthy populations, tDCS is also used to investigate cognitive functions [2] and enhance physical performance [3]. Originally it was presumed that tDCS influences neuronal excitability in a polar dependent fashion [4]. However, the response to tDCS is more complex than this due to the intricate relationship between the non-linearity of the dose response and a multitude of inter-and-intra-individual differences [5-7]. Changes in neuronal excitability are presumed to produce an ergogenic effect through enhancing synergistic muscle coupling and attenuation of decline in motor cortex (M1) excitability [8]. However, due to inconsistencies within research design and reported outcomes, the exact mechanisms remain inconclusive [3].

Tolerance of exercise-induced muscle pain (EIP) influences time trial performance [9], with improvements in performance shown when pain is reduced [10, 11]. As tDCS of the M1 and the dorsolateral prefrontal cortex (DLPFC) in a cephalic montage (anode over left M1 or DLPFC, cathode over right supraorbital area) has been successfully used to treat acute and chronic pain in patient groups [12,13] it is plausible that tDCS induced analgesia could confer an ergogenic effect in exercise with healthy individuals. Applying tDCS to the M1 in an extracephalic montage (Anode: M1, cathode: ipsilateral shoulder) can improve exercise tolerance through a reduction in perceptual stimuli such as the sense of effort [14], but tDCS may be less effective in reducing EIP [15]. Indeed, analgesia during a cold pressor test [15] and enhanced conditioned pain modulation [16] has been observed following conventional [15] and high-definition [16] M1 tDCS, despite no changes in EIP [15,16]. However, experimental pain and EIP are different [17] so M1 tDCS may be more effective in moderating pain of type III afferent origin [18]. Indeed, EIP is commonly described as an aching or burning (akin to type IV afferent stimulation) so M1 tDCS may be less effective in reducing EIP [15]. However, stimulating the dorsolateral prefrontal cortex (DLPFC) can induce analgesia [19,20], and has been used to treat chronic pain disorders [20], increase pain tolerance and empathy to experimental pain [19]. The DLPFC is a fundamental structure for nociceptive control, modulation of emotional valences, attention and working memory [18, 21-23] and houses reciprocal connections to the M1 [18]. tDCS applied to the left DLPFC in a cephalic montage has been shown to reduce effort/pain related perceptions during resistance exercise [24], so anodal tDCS applied to the DLPFC may serve as an effective means to reduce EIP and thus enhance endurance performance.

The direction of current flow is determined by the montage of the tDCS electrodes. Finite Element Method modelling studies have demonstrated that traditional M1 cephalic montages (anode: placed over left M1, cathode: placed over the right supraorbital area) induces greater current densities within the prefrontal cortex [25]. Therefore, the cephalic montage used by Angius et al [15] could have induced unintended reductions in excitability of the right DLPFC, and produced changes in performance unrelated to EIP. Alternatively, using an extracephalic (one electrode placed over the brain region of interest with the other placed on a non-brain area such as the deltoid) and/or bilateral (placement of the electrodes symmetrically across both hemispheres) montage could maintain a localised current flow in the targeted area [25,26]. Indeed, when an extracephalic montage was used, tDCS improved isometric [8, 14] and dynamic [27] exercise time to exhaustion.

This study tested whether anodal left DLPFC tDCS would enhance performance of a 15 minute cycling time trial. An additional 10 min fixed intensity trial was used to examine whether tDCS would improve EIP tolerance, as time trials do not usually identify perceptual changes arising from ergogenic interventions [11]. Finally, this study explored whether a bilateral or extracephalic montage changed the response to these tests.

Experimental Procedures

Participants

This investigation comprised two studies (study 1 and study 2). Study one involved 11 recreationally active volunteers (7 males, 4 females, age: 26 ± 6 yr, height: 177 ± 9 cm, body mass: 72 ± 13 kg), study two included 20 recreationally active volunteers (14 males, 6 females, age: 25 ± 5 yr, height: 175 ± 8 cm, body mass: 70 ± 12 kg). Nine participants completed both studies. Inclusion criteria were aged 18 - 44 yr and habitually performing a minimum of 180 min/week of aerobic exercise. Exclusion criteria were any mental health (e.g. schizophrenia) or brain disorders (e.g. epilepsy), intracranial implants, or taking any medication at the time of the study. Prior to providing written informed consent, participants read an overview of experimental procedures, but not the aims or hypothesis. Ethical approval was obtained from the local Ethics Committee (approval number: Prop_92_2015_2016).

Protocol

In both studies, participants visited the laboratory on four occasions, one preliminary and three experimental visits, separated by a minimum of 48 h. Visits were conducted at a similar time of day in a temperature-controlled room (20 ^{o}C, relative humidity between 40 and 50%). Participants abstained from consuming caffeine and analgesic substances for a minimum of 6 h preceding each visit, and completing strenuous physical activity and consuming alcohol for 24 hours before each visit. On visit one, participants completed a maximal incremental test (2 minutes at 100 W with 30 W increases every 2 minutes) to exhaustion on an electromagnetically braked cycle ergometer (SRM ergometer, Julich, Germany). After 30 minutes rest participants were familiarised to tDCS, the experimental pain measures (see evaluations of pain threshold and tolerance), the fixed-intensity cycling trial (FI) and the cycling time trial (TT). On visits 2 to 4, participants completed the experimental procedures (shown in figure 1) after receiving tDCS, SHAM or quiet rest (control) in a randomised, counter-balanced, single-blind design. Changes in mood were assessed using the Brunel Mood Scale questionnaire prior to tDCS administration as well at the end of each visit. To assess blinding, participants were asked to verbally report the trial order which they believed they had completed the investigation in.

Transcranial Direct Current Stimulation Procedures

Under-activation of the left DLPFC has previously been implicated as a source of depression and chronic pain in clinical populations [28]. Therefore, this brain region has been targeted to investigate the effects of non-invasive brain stimulation techniques on acute pain [19]. Brighina et al [29] identified that rTMS of the left DLPFC ameliorated pain, whilst rTMS of the right DLPFC induced no change. In consistency with previous research, the current study targeted the left DLPFC. tDCS was administered using a battery-driven stimulator (Study 1: TCT research limited, Hong Kong. Study 2: Neuroconn Eldith DC stimulator, Magstim, Camathenshire, and the TCT stimulator. The TCT stimulator was used for the final 11 participants whilst the

Neuroconn stimulator was being repaired) through a pair of rubber electrodes (size: 5cm x 7cm, 35cm^2) encased in a saline soaked sponge (9 % NaCl). Electrodes were secured in place by elastic straps. Following previous endurance performance tDCS studies [14,27], the stimulation intensity was set at 2 mA (current density 0.057 mA/cm^2) for 10 minutes in the experimental condition. In the SHAM condition, stimulation lasted for 30 s and was subsequently ramped down. In both conditions, the current intensity was ramped up and down over 10 s. Electrical resistance was maintained between 4-6 kΩ. In the control condition participants rested quietly for 10 minutes.

Electrode Montage

Study 1

tDCS was applied in a bilateral montage, with the anodal and cathodal electrodes placed over F3 and F4 (according to the 10-20 EEG system) to stimulate the left and right DLPFC respectively. This montage was selected based on previous findings of increased current density within the brain region of interest [26].

Study 2

Study 2 adopted an extracephalic montage, with the anodal electrode placed over the left DLPFC (F3) and the cathodal electrode placed on the ipsilateral shoulder. This montage was selected to minimise undesired effects of the cathodal electrode on other cortical areas.

Evaluations of Pain Threshold and Pain Tolerance

Peripheral electrical stimulation was used to assess pain threshold. A cathodal Ag/Cl electrode coated in conductive gel (2 x2 cm; Nessler, Medizintechnik, Innsbruck, Austria) was applied to the right index finger. The anode, a carbon rubber electrode (100 mm x 50 mm; Phoenix Healthcare Products ltd, Nottingham, UK) was applied to the back of the hand proximal to the knuckles. Current intensity of the electrical stimulator (Pulse duration 100 μs; Digitimer DS7AH, Welwyn Garden City, UK) started at 0.0 mA and increased by 0.1 mA until the participant reported sensation (perception threshold) and then pain (pain threshold). The ischemic pain test assessed pain tolerance. Participants flexed their right elbow to 90^o, with the hand elevated and elbow supported by a table. A manual sphygmomanometer (Accoson, Dekamet, UK) was inflated on the upper arm and held at a pressure corresponding to 100 mmHg above resting systolic pressure, measured using a digital sphygmomanometer (Carescape- V100, Dinamap, GE technology, USA). Participants rhythmically contracted their hand to a metronome beat at a rate of one contraction per second to induce ischemia. Pain intensity was verbally reported every 15 seconds on a 10-point scale [30]. Pain tolerance was defined as the number of hand contractions. If the participants had not already disengaged from the trial, the experimenter ended the trial at 3 min to avoid potential complications such as tourniquet pain, although participants were blinded to this cut-off point. The cut-off point was reached by 6 participants in study 1, and 8 participants in study 2.

Fixed Intensity Cycling Trial

Participants cycled at 75% of their peak power output (PPO) for 10 minutes on a cycle ergometer (Lode Excalibur sport, Lode, Groningen, Netherlands, or Cyclus 2, RBM elekronik-automotion GmbH, Leipzig, Germany - workloads have shown to be transferrable across these two ergometers [31]). During each visit, participants maintained a constant cadence, established from the familiarisation trial. Pain intensity (1-10 scale),

RPE (6-20 scale, [32]), and heart rate (Polar FT1, Polar Electro Oy, Kempele, Finland) was recorded at the end of every minute.

Time Trial

On a cycle ergometer (SRM ergometer, Julich, Germany) participants cycled as far as they could in 15 min by changing their RPM whilst keeping the same gear selected from the familiarisation trial. Participants were provided with feedback on time elapsed but were blinded to power output (PO), and distance. Participants provided their rating of pain and RPE at the end of every minute, whilst HR and PO were recorded continuously.

Statistical Analysis

Statistical analyses was performed using SPSS (Version 24). One-way analysis of variance (ANOVA) with repeated measures (RM) was conducted to analyse pain thresholds and TT distance covered. Friedman's test was conducted to analyse pain tolerance due to a violation in normality. To accommodate for the delay in achieving adequate feedback, the first two minutes of the FI and TT were excluded from the RM ANOVA [33]. Therefore, a 3 x 8 and 3 x 13 RM ANOVA assessed tDCS induced physiological and perceptual changes in the FI and TT respectively. A 3 x 6 RM ANOVA compared reported pain within the ischemic pain test. A 3 x 2 ANOVA with RM compared mood subsets reported in the BRUMS questionnaires.

To account for difference in pain tolerance, a combination of intra-individual iso-times and percentage of time to task disengagement (TD) was used. For this, the shortest time to TD was assigned as 100 % iso-time and compared to the equivalent time in the two other conditions. This 100 % iso-time was further divided by 5 and rounded up to acquire values corresponding to 20-80% isotime. This provided 5 data points for statistical comparison for each subject (20-100%), for each condition.

Where appropriate, post-hoc tests using the Bonferroni correction were applied. Effect sizes were estimated to establish the size of the difference between the three conditions and are reported as partial eta-squared (η_p^2).

Results

Participants reported a mild itching sensation underneath the electrodes during all tDCS conditions. No other side-effects were reported during or after tDCS administration.

Study 1

Pain thresholds & tolerance

All results of the ANOVA are displayed in supplementary material A. No significant differences between the three experimental conditions were found for pain threshold (figure 2) or pain tolerance (χ^2 (2) =3.6, P = 0.163). No significant interaction effects or main effect of condition were observed in the iso-time data of pain rating throughout the ischemic pain tests. As pain increased throughout the trial, a significant main effect of time was detected.

Fixed Intensity Cycling Trial

Outcomes of the RM ANOVA are detailed in supplementary material B. A significant interaction effect of the rating of pain was observed, however post-hoc analysis failed to demonstrate between group differences (*P*'s ≥ 0.098, figure 3). No significant interactions or main effect of condition were observed for RPE or HR. A significant main effect of time was detected for all three variables.

Time trial

Supplementary material B displays the results of the ANOVA. No significant differences were observed in distance covered between the tDCS (8.00 ± 0.56 km), SHAM (7.98 ± 0.57 km) and the control (7.93 ± 0.59 km) conditions. No significant interaction or condition effects were observed for pain, RPE, HR and PO (Figure 4). A significant main effect of time was observed for pain, RPE, HR and PO.

Mood Scales

Results of the RM ANOVA are shown in supplementary material C. A significant interaction effect of fatigue was observed, although post-hoc analysis revealed no significant between group differences ($P = 1.000$). No significant interactions were found for the remaining subsets. A significant main effect of condition was observed for both confusion and tension subsets, however post-hoc analysis revealed no significant differences for both subsets (Confusion (*P*'s ≥ 0.128) Tension (*P*'s ≥ 0.088)). A significant main effect of time was observed for the fatigue subset with fatigue higher at the end compared to the start of the visit.

Study 2

Pain threshold & tolerance

Full ANOVA results are shown in supplementary material A. Pain thresholds were significantly different, however post-hoc analysis failed to show a significant between group difference (*P*'s ≥ 0.087, figure 2). No significant differences were observed for pain tolerance (χ^2 (2) = 0.3, $P = 0.876$). Analysis of iso-time data of the pain reported during the ischemic pain test revealed no significant interaction effects or main effect of condition, however a significant main effect of time was observed.

Fixed Intensity Cycling Trial

Supplementary material B presents full results of RM ANOVA. No significant interaction effects were observed for pain intensity, RPE or HR during the FI trial, nor was there a significant main effect of condition (figure 3). A significant main effect of time was found where pain, RPE and HR increased throughout the trial.

Time trial

ANOVA's are reported in supplementary material B. There was no significant difference in the distance completed between the tDCS (8.02 ± 0.592 km), SHAM (7.85 ± 1.08 km) and the control condition (7.95 ± 1.03 km). No significant interaction effects or main effects of condition existed for pain intensity, RPE, HR or PO during the TT (Figure 4). A significant main effect of time was detected for all of these variables.

Mood Scales

Results of the RM ANOVA are shown in supplementary material C. No significant interaction effects were detected for any of the BRUMS subsets. A significant main effect of condition was detected for the tension subset, however post-hoc analysis revealed no significant between group differences (all P's ≥ 0.58). No significant main effects of condition were detected for the remaining 5 subsets. A significant main effect of time was detected for the depression, tension, anger and fatigue subsets, where the first 3 subsets reduced at the end of the trial, whilst fatigue increased. No significant main effects were detected for the vigour and confusion subsets.

Discussion

The present investigation explored whether anodal tDCS of the left DLPFC could reduce EIP during a FI and TT cycling bout, and whether this could enhance TT performance. This is the first study to investigate efficacy of tDCS of the DLPFC on these parameters using both an extracephalic and a bilateral electrode montage. The principal finding was that DLPFC tDCS was unable to induce analgesia. Consequently, no changes in cycling performance occurred. These findings were consistent across both electrode montages.

In this investigation the experimental pain measures provided a manipulation check to ascertain whether changes in performance were due to an analgesic effect. With no significant differences observed for both pain threshold and tolerance, our results demonstrate that tDCS was insufficient to induce an analgesic effect. In contrast, Boggio et al [19] and Mylius et al [34] reported increased pain tolerance following stimulation of the left and right DLPFC. However, these studies [19,34] assessed pain tolerance during the tDCS period. Previous studies have suggested that the effectiveness of tDCS is enhanced through task-specific modulation [35]. This assumes that tDCS preferentially stimulates active neuronal networks, whilst inactive networks remain unchanged [35]. Therefore, the analgesic effect previously observed [19,34] could be attributed to task-specific mechanisms, which may have been inactive in the current study. However, no analgesic effects of tDCS were observed in the FI trial where EIP was present, which also supports studies showing that tDCS does not moderate EIP [14-16,27]. It is therefore not surprising perhaps, that no differences in power output or total distance completed was shown in the TTs. As exercise activates an endogenous analgesic system which mitigates the intensity of EIP through the release of catecholamines, growth factors and endogenous opioids [36], tDCS may not be able to exert an additive effect [15]. Some previous trials have been able to demonstrate a behavioural change through the manipulation of experimental pain tolerance [15,16] or a reduction in RPE during the physical trials [14,27], but the current study does not corroborate these findings. .

Recently, the reliability and reproducibility of conventional tDCS has come into question. Wiethoff et al [6] concluded that the polar dependent effects of tDCS are not always present due to variability found following 2 mA stimulation of the M1. Of the participants they tested, 50% demonstrated poor or no responses to tDCS. Of those who did respond, 21% showed an 'inverted classical response' where anodal tDCS inhibited and cathodal stimulation increased corticospinal excitability. It is likely that variability in the response to tDCS is due to a variety of inter-individual differences including; anatomy, neurochemistry, baseline neurophysiological states and psychological states, gender and genetics [37]. Due to this inter-individual variability and the growth in the number of studies reporting a null effect of tDCS, the conventional 'plug in and play' vision of tDCS is unlikely

to be a viable method of enhancing athletic performance for the majority [38,39]. Further research is needed to examine whether there are optimal stimulation and timing parameters which produce reliable and repeatable ergogenic responses to tDCS. *If* this is achievable it is likely that individualisation of stimulation parameters would be required.

The present investigation is not without limitations. Firstly, the relatively small sample size may limit the statistical power of the collected data, increasing the likelihood of a type II error [40]. Although the sample size used within this investigation exceeds that of many previous studies employing similar protocols, a post-hoc power analysis on the TT distance covered revealed that both studies had a low statistical power (Study 1 η_p^2 = 0.07, 1-β = 0.44, α = 0.05; Study 2 1 η_p^2 = 0.07, 1-β = 0.74, α = 0.05). This implies that the effect size of conventional tDCS may have been previously overestimated and is unlikely to elicit a significant benefit to endurance performance [39]. Secondly, an a-priori power analysis was not conducted for this study. However, given the reported publication and reporting bias associated with this field, a similar sample size to the one used within this investigation would have been predicted. Lastly, this investigation did not include measurements to account for neurophysiological effects of tDCS. Future investigations should employ a measurement of cortical activity such as functional magnetic resonance imaging [41] or single-photon-emission tomography [42].

Conclusions

This is the first study to examine the effects of tDCS of the left DLPFC on EIP and endurance performance using two different electrode montages. Our results demonstrate that tDCS could not induce analgesia and consequently no improvements in exercise performance were observed.

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Figure Captions

Figure 1. Schematic of the experimental protocol. After 10 minutes of either tDCS, SHAM or quiet rest (control), participants completed measures of experimental pain threshold and tolerance. After 5-minute warm-up participants completed the 10-minute fixed intensity cycling trial followed by a 15-minute self-paced time trial.

Figure 2. The effects of tDCS on experimental pain thresholds and tolerance in study one (panels A-C) and study two (Panels D-F). TD, task disengagement. Data presented as mean ± SD, bold line on panels A- E signifies the group mean. * denotes a significant main effect of time ($P > 0.05$).

Figure 3. The effects of tDCS on perceptual and physiological responses during the 10-minute fixed intensity cycling trial in study one (Panels A-C) and study two (Panels D-F). Data presented as mean ± SD. * denotes a significant main effect of time ($P > 0.05$).

Figure 4. The performance and perceptual responses during the 15-minute time trial performed in study one (panels A-D) and study two (Panels E-H). Data presented as mean ± SD, * denotes a significant main effect of time ($P > 0.05$).

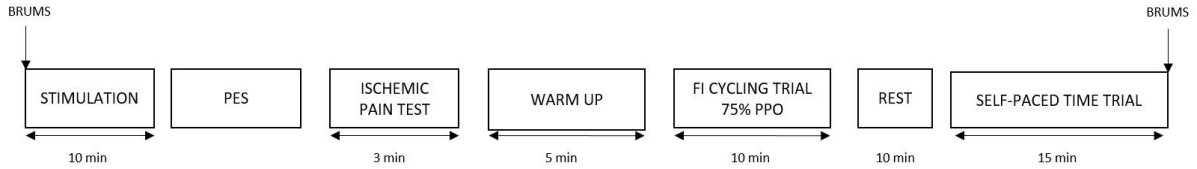

Figure 1

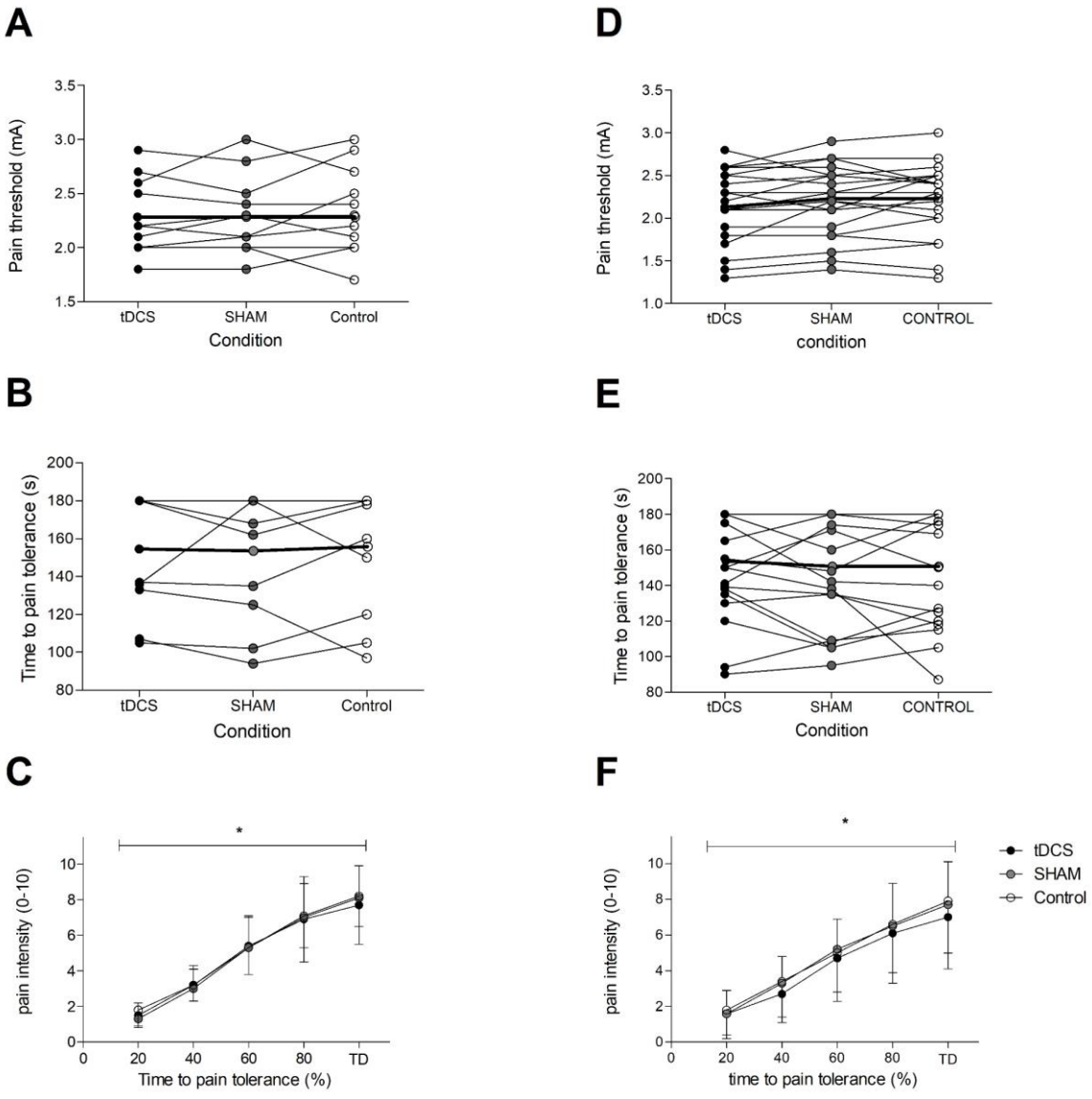

Figure 2

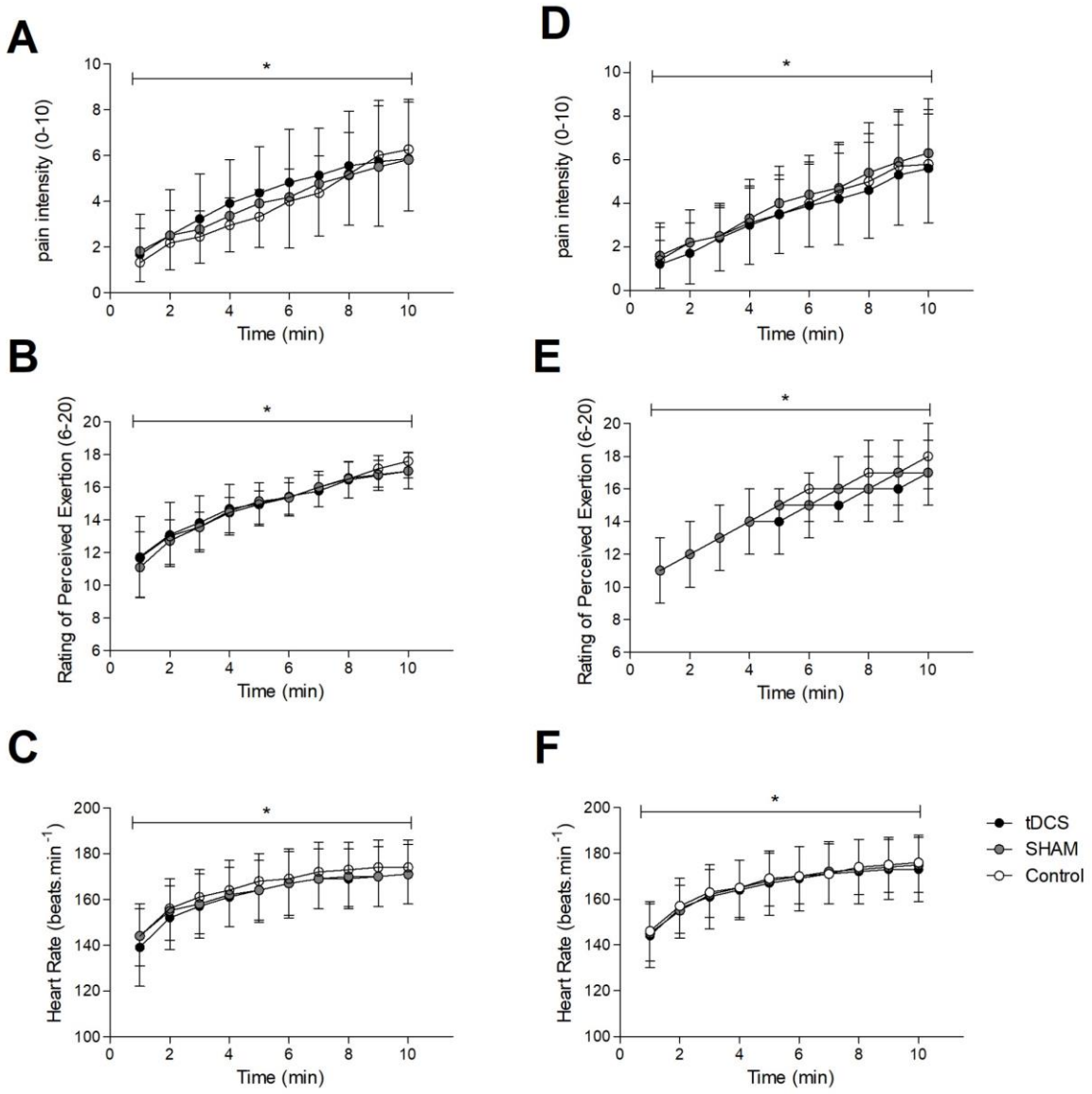
A
pain intensity (0-10)
Time (min)
D
pain intensity (0-10)
Time (min)
B
Rating of Perceived Exertion (6-20)
Time (min)
E
Rating of Perceived Exertion (6-20)
Time (min)
C
Heart Rate (beats.min-1)
Time (min)
F
Heart Rate (beats.min-1)
Time (min)
tDCS
SHAM
Control

Figure 3

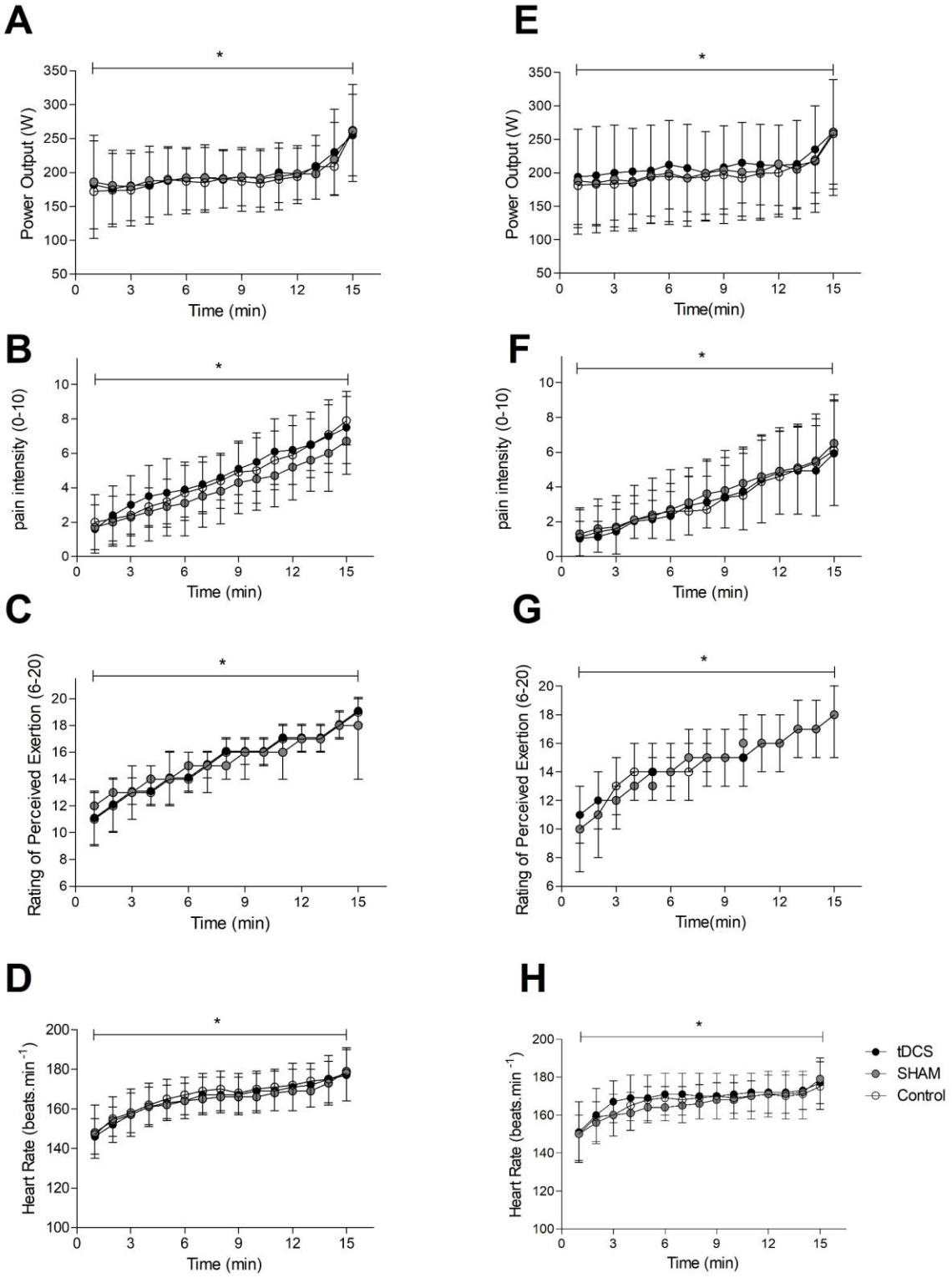
A
E
B
F
C
G
D
H
Power Output (W)
pain intensity (0-10)
Rating of Perceived Exertion (6-20)
Heart Rate (beats.min -1)
Time (min)
Time(min)
*
tDCS
SHAM
Control

Figure 4