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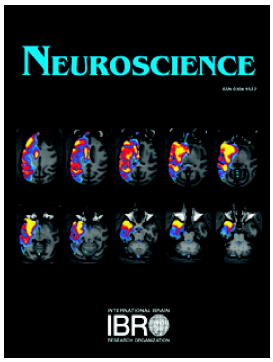

Transcranial Direct Current Stimulation over the Left Dorsolateral Prefrontal Cortex Improves Inhibitory Control and Endurance Performance in Healthy Individuals

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Transcranial direct current stimulation over the left dorsolateral prefrontal cortex improves inhibitory control and endurance performance in healthy individuals

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ABSTRACT

The dorsolateral prefrontal cortex (DLPFC) is a crucial brain region for inhibitory control, an executive function essential for behavioural self-regulation. Recently, inhibitory control has been shown to be important for endurance performance. Improvement in inhibitory control were found following transcranial direct current stimulation (tDCS) applied over the left DLPFC (L-DLPFC). This study examined the effect tDCS on both an inhibitory control and endurance performance in a group of healthy individuals. Twelve participants received either real tDCS (Real-tDCS) or placebo tDCS (Sham-tDCS) in randomized order. The Anodal electrode was placed over the L-DLPFC while the cathodal electrode was placed above Fp2. Stimulation lasted 30 min with current intensity set at 2mA. A Stroop test was administered to assess inhibitory control. Heart rate (HR), ratings of perceived exertion (RPE), and leg muscle pain (PAIN) were monitored during the TTE test, while blood lactate accumulation ($\Delta B[La^-]$) was measured at exhaustion. Stroop task performance was improved after Real-tDCS as demonstrated by a lower number of errors for incongruent stimuli ($p = 0.012$). TTE was significantly longer following Real-tDCS compared to Sham-tDCS ($p = 0.029$, 17 ± 8 vs 15 ± 8 min), with significantly lower HR ($p = 0.002$) and RPE ($p < 0.001$), while no significant difference was found for PAIN ($p > 0.224$). $\Delta B[La^-]$ was significantly higher at exhaustion in Real-tDCS ($p = 0.040$). Our findings provide preliminary evidence that tDCS with the anode over the L-DLPFC can improve both inhibitory control and cycling performance in healthy individuals.

Key words: non-invasive brain stimulation, fatigue, perception of effort, cycling, enhancement, Stroop task.

HIGHLIGHTS

Stroop test performance can be improved by targeting the left DLPFC;

Heart rate during exercise was reduced after targeting the left DLPFC;

Perception of effort during exercise was reduced by targeting the left DLPFC with tDCS;

Endurance cycling performance can be improved by targeting the left DLPFC;

INTRODUCTION

The capacity to sustain high-intensity aerobic exercise is important for endurance performance. Recent experiments suggest that endurance performance might not solely rely on the individual "physical" capacity (Hagger et al., 2010). It has been proposed that cognitive control, and more precisely the inhibitory control, plays an important role for the regulation of strenuous physical tasks (Hagger et al., 2010). Accordingly, the inhibitory control would be important to inhibit unpleasant sensations commonly experienced during exercise such as muscle pain, dyspnoea or thermal discomfort (Hagger et al., 2010). In other words, as exercise progresses, more inhibitory control is necessary to avoid task disengagement.

A common feature of effortful cognitive processes such as inhibitory control, is that when exerted over time, they induce a state of mental fatigue (Muraven and Baumeister, 2000) which has shown to increase perception of effort and have a negative effect on endurance performance (Marcora et al., 2009). Recent experiments demonstrated that professional cyclists have a higher inhibitory control and are more resistant to mental fatigue compared to recreational athletes (Martin et al., 2016), thus providing some evidence on the importance of inhibitory control for endurance performance.

Neuroimaging studies investigating the neural basis of inhibitory control, found a significant activation of cortical networks located on the prefrontal cortex (PFC) (Miller and Cohen, 2001; Diamond, 2013). Increased activity of the PFC has been observed during various cognitive tests involving inhibitory control such as the Stroop task, Go/No-Go task or stop-signal task (Diamond, 2013). Notably, when PFC activity was impaired, a reduction in performance test requiring inhibitory control was observed (Heatherton and Wagner, 2011; Hedgcock et al., 2012). The PFC has been shown to be important for a wide range of other high order cognitive functions such as decision making, working memory and problem solving (Miller and Cohen, 2001; Diamond, 2013). In addition, the PFC has been proposed to play an important role for exercise regulation (Robertson and Marino, 2016). In this regards, neuroimaging studies demonstrated an increase in functional connectivity between PFC, and primary motor cortex (M1) during submaximal fatiguing exercise (Jiang et al., 2012).

Transcranial direct current stimulation (tDCS) has been demonstrated to improve a wide range of cognitive functions in healthy individuals (Kadosh, 2013; Santarnecchi et al., 2015). Improvement in cognitive tests involving inhibitory control were found after tDCS applied over the left dorsolateral prefrontal cortex (L-DLPFC) (Hsu et al., 2011; Loftus et al.,

2015). tDCS has also been recently used to enhance physical capacity in healthy individuals on different exercise paradigms by providing contrasting results about the ergogenic effect of tDCS (Angius et al., 2018b; Machado et al., 2018). To the best of our knowledge, only one study investigated the effect of tDCS on the L-DLPFC on cycling exercise performance by reporting improvement in performance (Lattari et al., 2017). The mechanisms underlying the improvement in performance however are largely unknown as no measurement of physiological and/or cognitive response was performed following tDCS.

In light of this gap in the literature, the primary aims of the present investigation were: 1) verify the hypothesis that tDCS over the L-DLPFC can improve cognitive task performance requiring inhibitory control; 2) verify the hypothesis that tDCS over the L-DLPFC can improve endurance performance; 3) monitor the cognitive and physiological responses following tDCS. We hypothesized that tDCS over the L-DLPFC would improve inhibitory control and reduce perception of effort during cycling exercise to exhaustion.

EXPERIMENTAL PROCEDURES

Participants

Twelve recreationally trained participants (3 women and 9 men) whose mean ± standard deviations (SD) of age, height and weight were 23 ± 3 yr, 179 ± 10 cm and 74.9 ± 16.5 kg, respectively, were recruited. All participants signed an informed consent to take part in the study which was performed according to the declaration of Helsinki and approved by the local ethics committee. Participants performed a regular aerobic exercise training (3-5 h/week) and were free of any known cardiorespiratory, psychiatric or neurological disease.

Experimental design

Participants visited the laboratory on three different occasions that included one familiarisation session and two experimental sessions. Participants were advised to avoid strenuous activities, consume alcohol, caffeine and other stimulants or depressant for 48 h prior each visit. All visits were performed at the same time of the day in a temperature-controlled room (20°C, relative humidity between 40-50%) and were interspaced by a minimum of 72 h and completed within 14 days. All experimental procedures are illustrated in Fig 1C.

Visit 1. This visit served as familiarisation session. Participants also performed a maximal incremental test on a stationary cycle ergometer (Lode, Corival, Groningen, Netherlands) to establish their maximal peak power output (W_{peak}). The test consisted on a 5 min warm up at 100 W with a following increase of 30 W/min until volitional exhaustion (defined as a cadence below 60 rpm for more than 5 s).

Visits 2-3. Participants were randomly assigned in a double-blind and counterbalanced manner to a placebo tDCS (Sham-tDCS) and to real tDCS (Real-tDCS) using an online randomizer (http://www.randomization.com).

Stroop Task.

The Stroop task involved a mixed block of 144 trials were the stimulus was either a string of asterisks (72 neutral trials), an incongruent colour word (60 trials) and a congruent colour word (12 trials). Each stimulus was presented in one of the six colours chosen (blue, green, orange, red, purple, or yellow), in the centre of the computer screen with a black

background colour, in a Courier New font bold style and font size 18. During the task, participants were required to press the button of the keyboard corresponding to the presented colour as quickly and accurately as possible. On each trial, the stimulus remained on the computer screen until the volunteer responded, this was then followed by a response to stimulus interval of 1000 ms minus the response time. Ten practice trials were given before commencing. The test was administered before tDCS (Baseline), after tDCS (Post-tDCS) and after the TTE test (Post-TTE). The same version of this Stroop task has been used in previous study (Lowe et al., 2014). The Stroop task was prepared and administered by using E-Prime software 2.0.10 (Psychology Software Tools, Inc).

Psychological assessment

Mood was assessed by using the Brunel mood scale (BRUMS) (Terry et al., 2003). Motivation related to TTE test was measured using the success motivation and intrinsic motivation scales (Matthews et al., 2001). The National Aeronautics and Space Administration Task Load Index (NASA-TLX), (Hart and Staveland, 1988) was used to assess subjective workload related to the TTE test.

Transcranial direct current stimulation procedure

Offline tDCS was delivered by a direct current stimulator (TCT Research Limited, Hong Kong) with the anodal electrode (7×5 cm) placed in correspondence of F3 location according to the 10-20 EEG system, while the cathodal electrode (5x5 cm) was placed on Fp2 location (see Fig 1A and 1B). This montage has been previously used to target and increase the excitability of the L-DLPFC in both healthy and clinical population (Gluck et al., 2015; Heinitz et al., 2017; Silva et al., 2017). In the Real-tDCS condition, stimulation lasted 30 min at an intensity of 2.0 mA (current density (mA/cm^2 of 0.057). These intensity and duration have been shown to induce beneficial effects on cognitive function in both healthy and clinical population (Martin et al., 2013; McIntire et al., 2014). The electrode placement in the Sham-tDCS was identical to Real-tDCS but the stimulation lasted only 30 s. For both conditions, the current was ramped up and down in 30 s. In order to ensure good conductance, electrodes sponges were soaked with a saline solution (NaCl 9%) and elastic straps were used to maintained electrode on the scalp. The electrical resistance was constantly kept within a range between 4 to 5 kΩ. tDCS was not administered during cognitive or physical task (see

Fig. 1C). During the stimulation participants were asked to seat in a comfortable chair and to relax as much as possible.

Time to exhaustion test

Participants performed a cycling TTE test at 70% of W_{peak} to assess endurance performance. After 5 min warm up at 100W, the TTE test started and was interrupted at volitional exhaustion (defined as a cadence below 60 rpm for more than 5 s).

Perceptual and physiological parameters during exercise

Participants reported their leg muscle pain (PAIN) with a 10 points numerical scale (O'Connor and Cook, 1999) and their perception of effort with a 15-point rating of perceived exertion (RPE) scale following the instructions of (Borg, 1998). Participants were familiarized with the RPE procedure during the preliminary incremental exercise test. Each parameter was taken after 30 s, at the end of each min and immediately after exhaustion. Heart rate (HR) was monitored by a HR monitor (Polar RS400; Polar Electro Oy, Kempele, Finland). A 10 ml sample of capillary blood was collected from the thumb to determine blood lactate concentration ($B[La^-]$). Samples were analysed immediately at the end of each session by a lactate analyser (Biosen; EFK Diagnostics, London, UK). Electromyography activity of the right vastus lateralis muscle (VL-EMG) was continuously recorded during the TTE test. The VL-EMG signal was recorded by surface electrodes (Swaromed, Nessler Medizintechnik, Innsbruck, Austria) placed over the muscle belly with the reference electrode placed over the patella. Each electrode was positioned according to the SENIAM guidelines (Hermens et al., 2000). Electrodes position was marked on the skin with a permanent marker to ensure reproducibility for electrodes position in the following visit. The EMG signal was acquired at sample rate of 2 kHz (gain = 1000) by a commercially available software (Acqknowledge 4.2, Biopac Systems Inc., Goleta, USA).

Data analysis

During the TTE test, data points were processed as "individualised iso-time" to allow the within-subjects comparison of temporal changes (Angius et al., 2018a).

The VL-EMG signal was normalized by the maximal VL-EMG obtained during 10 s cycling sprint performed prior the TTE test. A period of 3 s during the sprint phase was

isolated, averaged and then used for normalisation (Albertus-Kajee et al., 2010). For the VL-EMG analysis, the recorded signal was digitally filtered with a Butterworth band pass filter (10 and 500 Hz). The root mean square (RMS) of the VL-EMG signal was automatically obtained with the software. The last 5 bursts were averaged prior each time point respectively at 0, 25, 50, 75, 100% and at exhaustion. Before calculate Stroop test parameters a data reduction was performed. We excluded RT < 200 and > 1500 ms, since the former is too fast to represent a conscious response and the latter was considered as outlier (Brunoni et al., 2014). The parameters obtained from the Stroop test were: reaction time (RT), number of errors (ERRORS) and Stroop Interference (SI). The ERRORS were entered into the analysis as raw scores while SI was calculated as the difference between the RT in ms of correct incongruent colour words minus the RT in ms of correct asterisk trials (Lowe et al., 2014).

Statistical analysis.

Data are reported as means ± SD. The normal distribution was checked by using the Shapiro-Wilk test. When assumption of sphericity was violated, the Greenhouse-Geisser correction to the degrees of freedom was applied. A fully repeated measures 2x5 ANOVA (condition x time) were performed to test the effects of tDCS on RPE, PAIN, HR and VL-EMG during the TTE test. The effect of condition on TTE time, $\Delta B[La^-]$, HR, PAIN and VL-EMG at exhaustion was analysed by paired t-test. Because violation of the normal distribution of RPE at exhaustion was violated, a Wilcoxon signed-rank test was performed. ERRORS and RT were analyses by using a fully repeated 2x2x3 ANOVA with condition (Real-tDCS - Sham-tDCS), type of stimulus (congruent - incongruent) and time (Baseline, Post-tDCS and Post-TTE). A fully repeated 2x3 ANOVA (condition x time) was performed for the analysis of SI, RT and ERRORS for the asterisks trials and self-reported mood. Motivation and NASA-TLX results were assessed by using a paired t-test. When a significant simple main effect of condition or time was found, a Holm-Bonferroni follow-up test was performed. Pearson correlation was computed to observe the relationships between decreases in ERRORS in incongruent word and increase in TTE. Effect size for each statistical test was also calculated as partial eta squared ($\eta^2 p$). The statistical significance was set at $p < 0.05$. Statistics analysis was conducted by using SPSS version 23.

RESULTS

All participants completed both experimental sessions and none of them reported any side effects during or after tDCS. The average W_{max} measured during the maximal incremental cycling test was 277 ± 62 W.

Effect of tDCS on mood, motivation and subjective workload

No significant condition x time interaction was found for any of self-reported mood subscales (all *ps* > 0.05). No significant differences between conditions and over time were found for Anger ($F_{(1, 11)} = 0.082$, $p = 0.780$, $\eta^2p = 0.007$ and $F_{(2, 22)} = 0.237$, $p = 0.671$, $\eta^2p = 0.021$), Confusion ($F_{(1, 11)} = 3.605$, $p = 0.084$, $\eta^2p = 0.247$ and $F_{(2, 22)} = 2.005$, $p = 0.177$, $\eta^2p = 0.154$), Depression ($F_{(1, 11)} = 0.671$, $p = 0.671$, $\eta^2p = 0.017$ and $F_{(2, 22)} = 1.492$, $p = 0.250$, $\eta^2p = 0.119$) and Tension ($F_{(1, 11)} = 0.244$, $p = 0.631$, $\eta^2p = 0.022$ and $F_{(2, 22)} = 1.748$, $p = 0.212$, $\eta^2p = 0.137$). A significant increase in fatigue after the TTE test has been found ($F_{(2, 22)} = 14.209$, $p = 0.001$, $\eta^2p = 0.590$) without any difference between conditions ($F_{(1, 11)} = 0.463$, $p = 0.510$, $\eta^2p = 0.040$). Vigour significantly decreased after the TTE test ($F_{(2, 22)} = 3.851$, $p = 0.037$, $\eta^2p = 0.289$) without any difference between conditions ($F_{(1,11)} = 0.516$, $p = 0.488$, $\eta^2p = 0.045$). Intrinsic motivation and success in the task related to the TTE tests did not differ between the two conditions ($p = 0.178$ and $p = 0.905$ respectively). Regarding the NASA-TLX questionnaire, statistics did not show any difference between conditions for Effort ($p = 0.641$), Frustration ($p = 0.293$), Mental demand ($p = 0.126$), Performance ($p = 0.406$) and Temporal demand ($p = 0.410$).

Effect of tDCS on Stroop test

Statistical analysis found a significant condition x type of stimulus x time interaction for ERRORS ($F_{(2, 22)} = 3.538$, $p = 0.047$, $\eta^2p = 0.243$). Follow-up tests showed a significantly a higher number of ERRORS for the incongruent words in both conditions ($F_{(1, 11)} = 60.067$, $p = 0.001$, $\eta^2p = 0.845$). A significant decline in the number of ERRORS at Post-tDCS in the Real-tDCS condition was found only for incongruent words ($F_{(1, 11)} = 47.021$, $p = 0.012$, $\eta^2p = 0.810$). The number of ERRORS significantly increased at Post-TTE compared to Baseline and Post-tDCS in both conditions ($F_{(2, 22)} = 47.021$, $p = 0.001$, $\eta^2p = 0.941$). Regarding RT, no significant condition x type of stimulus x time interaction was found ($F_{(2, 22)} = 1.372$, $p = 0.274$, $\eta^2p = 0.111$). There was no significant main effect of condition ($F_{(1, 11)} = 0.016$, $p = 0.902$, $\eta^2p = 0.001$), while a significant main effect of type of words ($F_{(1, 11)} = 45.409$, $p =$

0.001, η^2p = 0.805) and time ($F_{(2, 22)}$ = 8.369, p = 0.002, η^2p = 0.432) was found. Follow-up tests showed a significantly higher RT for incongruent colour words (p = 0.001, η^2p = 0.805) and at Post-TTE (p = 0.029, η^2p = 0.473) compared to Baseline and Post-tDCS. Regarding SI, no significant condition x time interaction ($F_{(2, 22)}$ = 2.507, p = 0.104, η^2p = 0.186), no significant main effect of condition ($F_{(1, 11)}$ = 0.723, p = 0.413, η^2p = 0.062) and time ($F_{(2, 22)}$ = 0.046, p = 0.955, η^2p = 0.004) were found (See Fig 2).

Statistical analysis did not find a significant condition x time interaction for asterisks trials on ERRORS ($F_{(2, 22)}$ = 0.149, p = 0.862, η^2p = 0.013) and RT ($F_{(2, 22)}$ = 1.287, p = 0.296, η^2p = 0.105). For ERRORS there was no significant main effect of conditions ($F_{(1, 11)}$ = .279, p = 0.608, η^2p = 0.025), while a significant main effect of time was found ($F_{(1, 11)}$ = 22.462, p = 0.001, η^2p = 0.671). Follow-up test showed a higher number of ERRORS at post-TTE in both conditions ($F_{(1, 11)}$ = 14.614, p = 0.001, η^2p = 0.745). Regarding RT, there was no significant main effect of conditions ($F_{(1, 11)}$ = 1.392, p = 0.263, η^2p = 0.112), while a significant main effect of time was found ($F_{(2, 22)}$ = 11.438, p < 0.001, η^2p = 0.510). Follow-up test however showed only an higher RT at post-TTE in both conditions ($F_{(1, 11)}$ = 7.301, p = 0.006, η^2p = 0.594).

Effects of tDCS on TTE and physiological and perceptual responses during TTE test.

TTE test was significantly longer in the Real-tDCS condition compared to Sham-tDCS (17 ± 8 vs 15 ± 8 min, p = 0.029, η^2p = 0.249). A significant condition x time interaction was found for HR ($F_{(4, 44)}$ = 3.761, p < 0.034, η^2p = 0.592) while no significant condition x time interaction was found for RPE, PAIN and VL-EMG (all *ps* > 0.05). A significant main effect of time was found for RPE ($F_{(4, 44)}$ = 162.493, p < 0.001, η^2p = 0.937), PAIN ($F_{(4, 44)}$ =128.642, p < 0.001, η^2p = 0.921), HR ($F_{(4, 44)}$ = 284.824, p < 0.001, η^2p = 0.963) and VL-EMG ($F_{(4, 44)}$ = 4.160, p = 0.037, η^2p = 0.274). Statistical analysis revealed significant reduction of RPE ($F_{(1, 11)}$ = 20.758, p = 0.001, η^2p = 0.654) and HR ($F_{(1, 11)}$ = 15.974, p < 0.002, η^2p = 0.592) in the Real-TDCS compared to Sham-tDCS while no significant differences between conditions were found for PAIN ($F_{(1, 11)}$ = 1.662, p = 0.224, η^2p = 0.131) and VL-EMG ($F_{(1, 11)}$ = 0.199, p = 0.664, η^2p = 0.18). $\Delta B[La^{-1}]$ at exhaustion was significantly higher in the Real-tDCS condition compared to Sham-tDCS (12.03 ± 1.60 vs 11.04 ± 1.90 mmol·l-1, p = 0.040, η^2p = 0.565) while no significant differences were found for RPE (p = 0.564, η^2p = 0.092), PAIN (p =0.887, η^2p = 0.060), HR (p = 0.085, η^2p = 0.181)

and VL-EMG (p =0.638, $\eta^2 p$ = 0.285) (Fig 2). There was no correlation between decrease in ERRORS in incongruent words and increase in TTE duration (p = 0.519, r -0.159).

DISCUSSION

This study demonstrates that tDCS with the anodal electrode over the L-DLPFC, improves Stroop task performance, significantly improves TTE and reduces HR and RPE during cycling exercise. As initially hypothesised, this improvement on endurance performance occurred in association with a lower perception of effort during exercise.

Effects of tDCS on cycling performance

Previous studies have investigated the ergogenic effect of tDCS on cycling performance by reporting contrasting results (Angius et al., 2018b). Okano and colleagues (2015) reported a 4% improvement in the peak power output of a maximal cycling incremental test together with a reduction in RPE, HR and change in heart rate variability (HRV) following anodal stimulation over the T3. The effect of anodal stimulation over T3 however are uncertain, as in a following study by Okano and colleagues (2017), no changes in HR, RPE and HRV during constant load cycling exercise were found. A lack of effect on tDCS over T3 has also been reported during a 20 km cycling time trial in the heat (Barwood et al., 2016).

The study of Vitor-Costa and colleagues (2015) reported improvement in cycling TTE test following tDCS with anodal electrodes over both M1 without significant changes in physiological (i.e. HR and VL-EMG) with a trend for a reduction in RPE which might explain the improvement in performance. Angius and colleagues (Angius et al., 2018a) confirmed the improvement in TTE performance with bilateral extracephalic montage with anodal electrodes over both M1, with a significant reduction in RPE and an increase in corticospinal excitability. Another study however failed to find improvement in TTE duration (Angius et al., 2015) is likely be caused by the cephalic montage used (Angius et al., 2016).

Lattari and colleagues (2017) investigated the effect of tDCS over the L-DLPFC on TTE performance at maximal cycling intensity (100% W_{max}) by reporting improvement in performance. Contrarily to our findings, no changes in RPE between conditions were found which is most likely caused by the ceiling effect during high intensity exercise. The exact mechanisms for this ergogenic effect are unknown, as no physiological or cognitive responses were measured.

Effects of tDCS on Stroop test, mood, motivation and subjective workload

The Stroop task is acknowledged as a well-established test to assess inhibitory control. In our study, a significant reduction of number of ERRORS following Real-tDCS was found only for the incongruent colour words which is indicative of an improvement in inhibitory control and in agreement with previous studies (Jeon and Han, 2012; Loftus et al., 2015). Although we cannot provide the exact neurophysiological mechanism, such improvement was probably achieved by an increased neuronal excitability of the targeted brain area (Hsu et al., 2011; Keeser et al., 2011). As expected, the RT was significantly higher for incongruent colour words compared to neutral stimuli. In our study, Real-tDCS did not induce improvement in RT, a findings which has been previously reported (Loftus et al., 2015). The lack of effect on RT might also explain the unchanged SI. Stroop task performance decreased after the TTE as demonstrated by the increased RT and number of ERRORS in both conditions. This is in agreement with previous findings (Labelle et al., 2013). However, opposite effects on Stroop performance were also found (Alves et al., 2012; Tsukamoto et al., 2016). This is not surprising as cognitive performance may be either enhanced or impaired depending on exercise modality and intensity (Brisswalter et al., 2002; Tomporowski, 2003). Additionally, a U-shaped relationship between exercise intensity and cognitive function was proposed (Brisswalter et al., 2002; Tomporowski, 2003), where low and moderate-intensity exercise would improve cognitive function, whereas high-intensity would be detrimental. These results suggest a complex relationship between exercise and cognition and therefore further experimental studies should be performed.

In line to what has been reported (Morgan et al., 2014) no changes in self-reported motivation were observed following tDCS. However, opposite findings were found by Soutschek and colleagues (2018) were tDCS increased willingness to exert physical effort and countered the devaluation of reward at different effort levels. It should be acknowledged that the changes in TTE and RPE were possibly not exclusively caused by modulation of the L-DLPFC. Previous investigations proposed that the decision to exert effortful tasks or behavioural inhibition are associated with frontal asymmetry (Coan and Allen, 2003). More precisely, higher activity of the left frontal area is related to approach motivation, whereas higher activity of the right frontal are is related to withdrawal motivation (Coan and Allen, 2003). Previous studies inducing frontal asymmetry by tDCS were able to support this hypothesis (Hortensius et al., 2012; Ohmann et al., 2018; Riva et al., 2015). In light of these findings involving a montage similar to the one employed in this study (see Fig.1), it is possible that changes in TTE and RPE caused changes in participants' motivation to exert

physical effort (Soutschek et al., 2018). As also proposed by the psychobiological model of endurance performance based on the Brehm's motivational intensity theory (Brehm and Self, 1989; Marcora and Staiano, 2010), both an increase in motivation and a decrease in perception of effort can improve endurance performance. It should be acknowledged that also previous studies failed to find changes in self-reported motivation or mood following tDCS (Koenigs et al., 2009; Tadini et al., 2011; Vitor-Costa et al., 2015). A similar conclusion has been given in a review by Remue et al., (2016) in healthy individuals. It should be considered that all studies differed in terms of tDCS montage, stimulation, targeted area and questionnaire, and therefore our results cannot be equally compared with other experiments. Further experiments should be performed to elucidate the effect of tDCS on mood, effort and motivation related to physical effort.

Effects of tDCS on perceptual and physiological responses during exercise

$\Delta B[La^-]$ at exhaustion was significantly higher in the Real-tDCS compared to Sham-tDCS which is most probably caused by the longer exercise duration. Interestingly, HR was significantly lower in the Real-tDCS compared to Sham-tDCS. To our knowledge, no studies reported decrease in HR during constant cycling exercise following tDCS. The PFC is known to modulate brain areas involved in the regulation of the cardiovascular autonomic control (Thayer et al., 2012). Increase in PFC activity are associated with an augmented parasympathetic tone, while, in contrast, a decrease in PFC activity leads to an augmented sympathetic tone (Thayer et al., 2012) by therefore inducing variations in HR. Similar conclusion were provided in studies involving tDCS were variations in heart rate variability were found (Brunoni et al., 2013; Montenegro et al., 2014; Morgan et al., 2014). In addition, a recent meta-analysis (Makovac et al., 2017), proposed the PFC as ideal cortical area to induce changes in cardiovascular system by means of non-invasive brain stimulation. In light of these evidences, the reduction in HR during exercise, can be the result of an augmented parasympathetic activity induced by tDCS. It should be considered that we didn't monitor HRV and therefore further research should be performed to explore mechanisms leading to a lower HR during exercise following tDCS.

VL-EMG following tDCS was unchanged. Similarly, previous experiments involving cycling TTE (Vitor-Costa et al., 2015) or isometric contractions of upper (Abdelmoula et al., 2016) and lower limbs (Angius et al., 2016b) did not find any effect of tDCS on EMG activity despite improvement in exercise duration.

PAIN during exercise was not affected by tDCS. A lack of effect of tDCS on exercise induced muscle pain has been previously shown during cycling exercise (Angius et al., 2017) and sustained isometric contraction (Angius et al., 2016b). The DLPFC has been proposed to play an important role in the affective, cognitive, and attentional aspects of pain (Mylius et al., 2012). tDCS studies involving stimulation of the L-DLPFC found a significant reduction in cold pain perception (Mariano et al., 2016), increase in thermal pain threshold (Mylius et al., 2009) or a decrease of self-unpleasantness when viewing emotionally aversive pictures (Boggio et al., 2009). Probably, different methodological aspects as well as the different kinds of pain investigated may explain these discrepancies.

We found a significant lower RPE in the Real-tDCS without any differences at exhaustion between conditions. This demonstrates that participants reached the point of exhaustion later compared to Sham-tDCS. This finding is in agreement with the psychobiological model of endurance performance proposed by Marcora (2009), where in highly motivated individuals, task disengagement coincides with the attainment of maximal perception of effort.

High-intensity physical tasks requires inhibitory control to prevent task disengagement. This cognitive process is associated with subjective feeling of effort (Shenhav et al., 2017) that might contribute to the overall perception of effort during exercise. Therefore, we suggest that the reduction of RPE is the results of the improved inhibitory control following Real-tDCS. In our scenario, this implies that less cognitive effort was required by participants to exert the inhibitory control and consequently avoid task disengagement. Our findings are also in accordance with the strength model of self-control (Muraven and Baumeister, 2000) where effortful actions of self-control have a limited resources. The more inhibitory control is required, more effort is expended and therefore less resources would be further available leading to a temporary reduction of the self-control capacity and willingness to engage or further continue volitional actions (Muraven and Baumeister, 2000).

Additionally, previous research (Jiang et al., 2012) showed that stronger inputs from the PFC to SMA and M1 are necessary to reinforce the descending command to compensate for muscle fatigue. In this scenario, tDCS could have facilitated the input of the L-DLPFC into these motor areas during exercise, by therefore permitting a longer TTE. Given the multiple anatomical connections of the PFC to other cortical and/or subcortical areas (Miller

and Cohen, 2001), we cannot exclude that effect of tDCS was limited only to the L-DLPFC. For instance, the supplementary motor area (SMA) and the anterior cingular cortex (ACC) have been shown to have connections with the PFC (Miller and Cohen, 2001; Zénon et al., 2015)and have been also addressed as important brain areas for the generation of the perception of effort (de Morree et al., 2012; McCloskey, 2011; Williamson et al., 2002). Therefore, it is possible that the beneficial effects of tDCS could have been extended to SMA and ACC.

Technical considerations and study limitations

Our experiment differs with previous studies for some methodological aspects such as tDCS montage, stimulation protocol and the task used for cognitive assessment, which can in part explain the different outcomes across each study. For instance, opposite effects compared to what initially hypothesised have been observed when anodal stimulation lasted more than 10 min (Monte-Silva et al., 2013) or when the intensity of cathodal stimulation was doubled from 1 to 2 mA (Batsikadze et al., 2013). In addition, given the size of the electrode adjacent brain areas could have also been affected. Therefore, other cognitive functions also loading on the same region were affected (Tremblay et al., 2014). This in turn makes it difficult to attribute our findings on a specific mechanism. In addition the PFC has been proposed to shown to integrate and supersede multiple input sources of information regarding the task performed in order to provide the appropriate response (Robertson and Marino, 2016) as well as to play an important role in human volition (Haggard, 2008). The literature investigating the role of the PFC and its relationship with other brain areas for exercise regulation is very limited. As such, a precise and conclusive explanation for the improvement in performance following tDCS cannot be provided.

Conventional bipolar tDCS montages are well known to induce diffuse current flow between electrodes and so potentially affecting other brain areas than the targeted one. In regards to our montage, we cannot exclude that the cathodal electrode (over Fp2) could have affected the right inferior frontal cortex which is known to implement inhibitory control via a wider prefrontal network and therefore potentially inducing frontal asymmetry (Aron et al., 2014; Ohmann et al., 2018). At present, optimal tDCS montage and stimulation parameters involving bipolar electrodes to specifically and reliably target the PFC are yet to be defined (Dedoncker et al., 2016; Seibt et al., 2015; Tremblay et al., 2014). A better standardisation of these parameters together with more robust protocols to test the effect of tDCS as well as a

larger sample size are required to improve study quality before any solid conclusions can be drawn. In our opinion, the inclusion of neurophysiological measurements such as Electroencephalography (EEG), TMS-EEG or functional magnetic resonance imaging (fMRI) is necessary to appropriately interpret our findings.

Conclusion and future perspectives

Our study provides experimental evidence that anodal tDCS over the L-DLPFC improves endurance performance, together with an improved inhibitory control and reduction of perception of effort. Our findings confirm the potential ergogenic effect of tDCS on physical capacity in healthy individuals and further confirm the important role of the brain, and the prefrontal lobe in particular on exercise regulation. Our results however, add further contrasting evidences regarding the ergogenic effect of an acute session of tDCS. Further empirical studies are required to confirm the beneficial effects of an acute session of tDCS on physical performance.

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CONFLICT OF INTEREST

Dr. Santarnecchi serves as a consultant for EBNeuro Ltd, a manufacturer of TMS and tDCS devices. None of the devices used in the present experiments were provided by EBNeuro. Dr. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync; and is listed as an inventor on several issued and pending patents on the Real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging.

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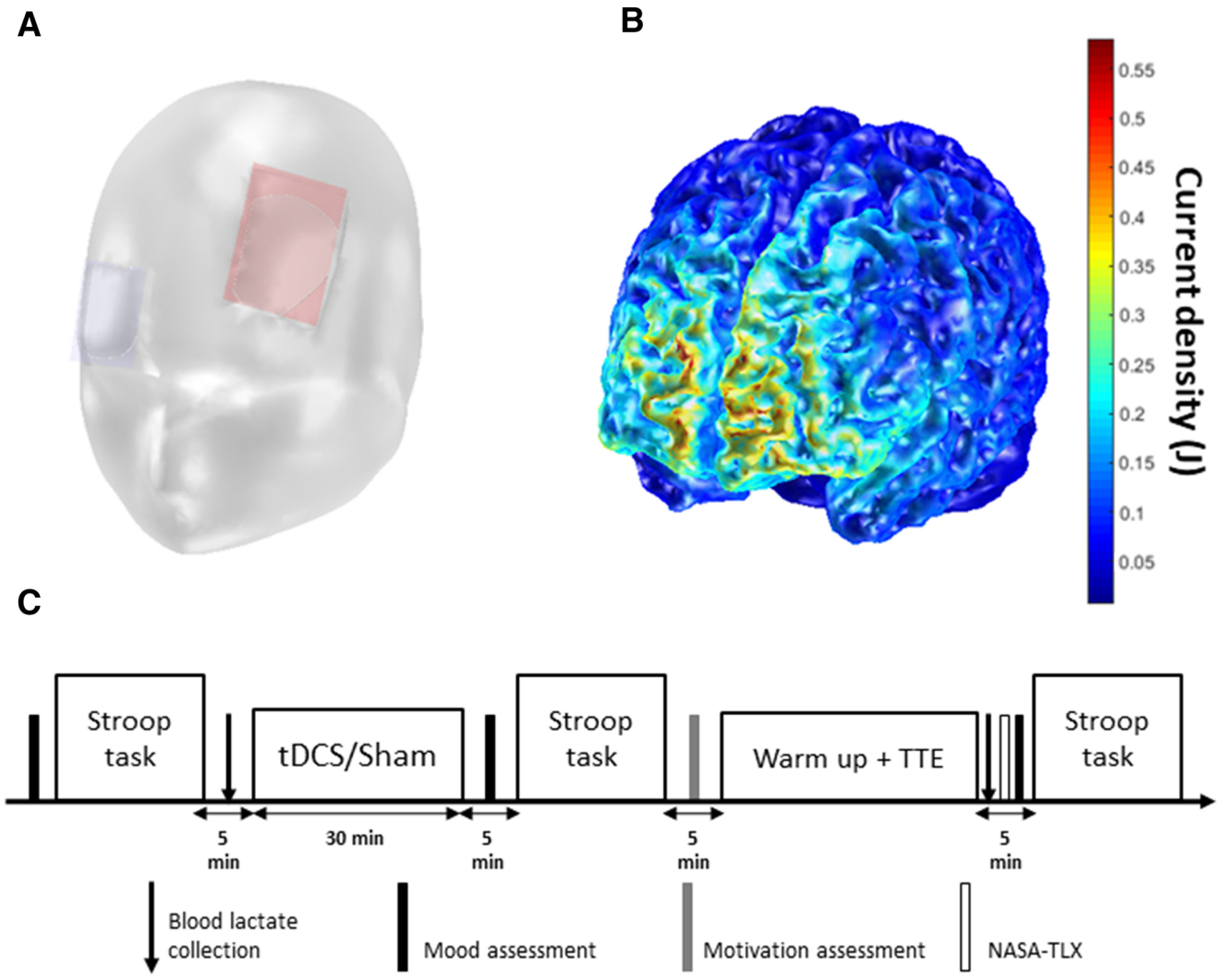
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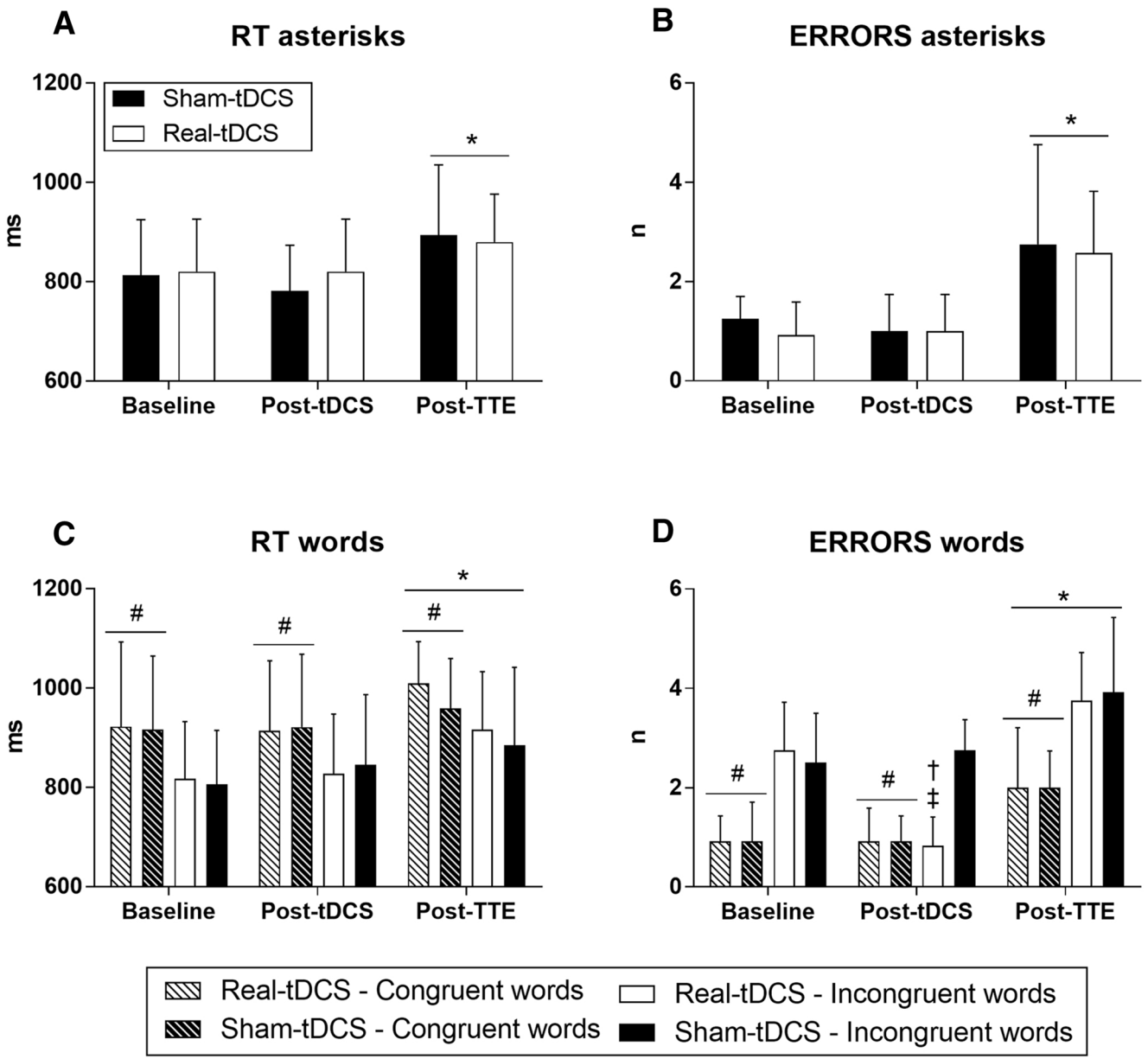
Current density (J)
C
Stroop task
tDCS/Sham
Stroop task
Warm up + TTE
Stroop task
5 min
30 min
5 min
5 min
5 min
Blood lactate collection
Mood assessment
Motivation assessment
NASA-TLX

Figure 1


A
RT asterisks
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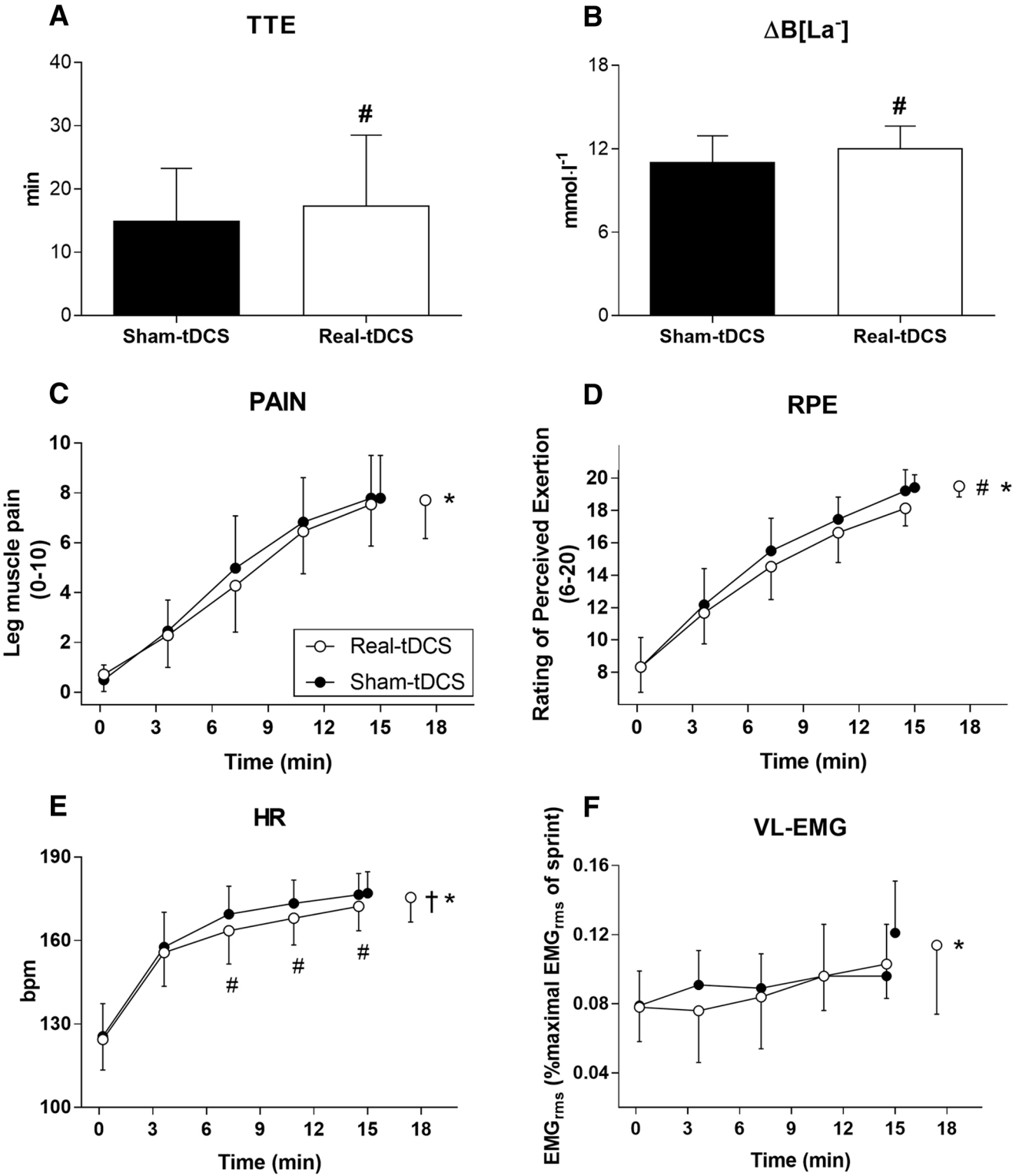
Post-TTE
Real-tDCS - Congruent words
Sham-tDCS - Congruent words
Real-tDCS - Incongruent words
Sham-tDCS - Incongruent words

Figure 2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Sham-tDCS
Real-tDCS
B
ΔB[La-]
mmol·l-1
18
12
6
0
#
Sham-tDCS
Real-tDCS
C
PAIN
Leg muscle pain (0-10)
10
8
6
4
2
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*
Real-tDCS
Sham-tDCS
0 3 6 9 12 15 18
Time (min)
D
RPE
Rating of Perceived Exertion (6-20)
20
18
16
14
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190
160
130
100
# # #
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0 3 6 9 12 15 18
Time (min)
F
VL-EMG
EMGrms (%maximal EMGrms of sprint)
0.16
0.12
0.08
0.04
*
0 3 6 9 12 15 18
Time (min)

Figure 3