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Effects of bilateral dorsolateral prefrontal cortex high-definition transcranial direct-current stimulation on time-trial performance in cyclists with type 1 diabetes mellitus

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ABSTRACT

Background: HD-tDCS is capable to increase the focality of neuromodulation and has been recently applied to improve endurance performance in healthy subjects.
Objective/hypothesis: Whether these putative advantages could be exploited in active subjects with type 1 diabetes mellitus (T1D) remains questionable.
Methods: In a double-blind, randomized crossover order, 11 high-level cyclists (27 ± 4.3 years; weight: 65.5 ± 8.6 kg; height: 180 ± 8 cm; VO_2peak: 67.5 ± 2.9 mL min^{-1} kg^{-1}) with T1D underwent either HD-tDCS (F3, F4) or control (SHAM) and completed a constant-load trial (CLT) at 75% of the 2nd ventilatory threshold plus a 15-km cycling time-trial (TT).
Results: After HD-tDCS, the total time to cover the TT was 3.8% faster ($P < 0.01$), associated with a higher mean power output ($P < 0.01$), and a higher rate of power/perception of effort ($P < 0.01$) and power/heart rate at iso-time ($P < 0.05$) than the SHAM condition. Physiological parameters during CLT and TT did not differ in both conditions.
Conclusions: These findings suggest that upregulation of the prefrontal cortex could enhance endurance performance in high-level cyclists with T1D, without altering physiological and perceptual responses at moderate intensity. Present data open to future applications of HD-tDCS to a wider population of active T1D-subjects.

1. Introduction

Transcranial direct-current stimulation (tDCS) is a noninvasive neuromodulatory method that consists of applying weak direct current over the scalp, usually 1–2 mA with 2 large pads. It acts by creating an electric field that reversibly modifies the excitability of the cortical areas under the anode and the cathode, eliciting an excitatory or inhibitory response, respectively acting through depolarization or hyperpolarization of resting membrane potential [1]. tDCS is widely used in neurological rehabilitation, cognitive improvement, and psychiatric disease [2]. In the last 10 years, an increasing number of studies have investigated the effects of anodal tDCS on endurance physical performance. The results are inconclusive for all the areas targeted [3,4], with some studies showing positive effects [5–8] while others no variation [9,10]. This discrepancy could be due to the type and position of the applied electrodes. Traditionally, tDCS uses only 2 large pads (25–36 cm^2), and it has a low focality, therefore with a certain risk of producing excitatory or inhibitory influences in other areas with respect to those targeted [7]. A variant called high-definition transcranial direct current stimulation (HD-tDCS), capable to increase the focality of neuromodulation, has been recently proposed [11]. Instead of using 2 large electrodes, HD-tDCS relies on an array of small circular electrodes (3–5 cm^2), with the active electrode (anode or cathode) positioned in the center of the opposite polarity reference electrodes. Recent studies using HD-tDCS over bilateral dorsolateral prefrontal cortex (PFC) showed improvement in endurance performance, both in long and short time trials (TTs)

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[12,13] without altering physiological responses during the TT at iso-time, that is referring to the variables monitored at the same timepoints during a determined distance (i.e 15 km) to be covered in least time possible. A higher ratio between power output and perceptual measures seems the mechanism behind improved endurance performance. Furthermore, HD-tDCS could reduce perception of effort during exercise apparently because these sensory signals are corollary discharged from areas functionally connected with PFC, such as the presupplementary motor area, the supplementary motor area, the premotor cortex, and the primary motor cortex [14]. Therefore, it is likely that endurance performance could be increased through the upregulation of the bilateral dorsolateral PFC. In particular, the upregulation of bilateral dorsolateral PFC could potentially reduce pain and perception of effort, increase motivation and improve pacing strategies in endurance events [15].

In addition, anodal tDCS has been shown to affect glucose regulation and metabolic functioning in healthy humans [16]. In particular, tDCS promoted glucose tolerance during a standardized euglycemic-hyperinsulinemic clamp in 15 healthy male volunteers, possibly due to the activation of hypothalamic K_{ATP} channels by transient ATP depletion [17]. In another study, glucose uptake heterogeneity was ameliorated in patients with multiple sclerosis, supposedly through an increased neural drive and a more efficient muscle activation [18].

Since previous improvements in glucose tolerance were obtained independent of insulin, we aimed to transfer greater endurance performance in a model electively glucose-challenged, although without insulin: type 1 diabetes mellitus (T1D). Among those sports played at high level, T1D is particularly prevalent in cycling with an entire professional team [19]. Besides, healthy, and amateur endurance runners/cyclists were already studied with controversial results. For these reasons, we investigated the effect of HD-tDCS on a sample of high-level cyclists withT1D. In this population, the benefits on endurance performance should be monitored together with glycemic responses after the stimulation, since the empiric verification on the glycemic modulation after tDCS has not been provided so far.

The aim of this study was to investigate the effects of bilateral dorsolateral PFC HD-tDCS on time-trial performance in cyclists with T1D. Based on the literature on this topic, we hypothesized an improvement in endurance performance after HD-tDCS, accompanied by an unpredictable effect on blood glucose.

2. Materials and methods

2.1. Participants

A total of 12 male national- and international-level road cyclists with type 1 diabetes mellitus volunteered to participate in this study. One participant was excluded from the final analysis due to the absence from post-testing, therefore 11 participants were eligible for the study (age: 27.0 [4.3] years, VO_2peak: 67.5 [2.9] $mL \cdot min^{-1}$ kg^{-1}, weight: 65.5 [8.6] kg, height: 180 [8] cm). Considering each participant's competition level and training history, they can be classified as “highly trained/national level” according to the guidelines of McKay and colleagues [20]. All cyclists were diagnosed with type 1 diabetes for >10 years and were on a stable multiple daily dose regimen consisting of a range of rapid-acting/short-lasting and long-lasting insulin (bolus: n = 4 Fiasp, n = 8 NovoRapid; basal: n = 10 Lantus, n = 2 Levemir). All athletes took basal insulin in the evening. Cyclists' self-reported total insulin doses ranged between 23 ± 7 (minimum) and 25 ± 10 (maximum) IU daily, consisting of a bolus of 10 ± 4 (minimum) to 12 ± 4 (maximum) IU daily, and basal of 14 ± 7 (minimum) to 15 ± 7 (maximum) IU daily. The riders used NovoPen Echo Plus smart insulin pens (Novo Nordisk, Bagsværd, Denmark) to record insulin dosing. Each athlete was informed of the procedures and risks before giving a written informed consent to participate in the study. The study design and procedures were approved by the local research ethics committee of the Università degli Studi di Milano (n° 121/19, attachment 5) and followed the ethical principles for medical research involving human participants set by the World Medical Association Declaration of Helsinki. Participants were not involved in the design, or conduct, or reporting, or dissemination plans of the study.

2.2. Experimental design

The experimental procedures followed those of a previous study in a healthy population [12]. The participants visited the laboratory on four different occasions. During the first session, they performed a maximal incremental cycling test to establish their VO_2peak and power output at the second ventilatory threshold (VT_2). During the second visit, they were familiarized with the constant load and the TT to be performed on sessions 3 and 4. During the third and fourth visits (Fig. 1), in a double-blind and counterbalanced order, the participants underwent either the experimental treatment (HD-tDCS) or SHAM. Immediately before and after the treatment, they were required to fill the psychological questionnaires and underwent a blood withdrawal from the antecubital vein. Other blood samples from earlobe and antecubital vein were taken at the end of the constant load trial (CLT) and TT. Five minutes after the end of the treatment, participants carried out a 10-min CLT at 75% of the power output at VT_2. They rested for 3 min, sitting on the bike, and subsequently, performed a simulated 15 km TT. Athletes carried out all cycling tests on the frame of their own bike, fitted on the Cyclus2 ergometer (RBM Elektronik-automation GmbH, Leipzig, Germany). Each subject completed all sessions within a maximum of 3 weeks. The day before visits 2, 3, and 4, cyclists performed a standardized training session (volume: < 3 h, intensity: < 80% of VT_2). The experimental visits were completed at the same time of the day (between 8:00 a.m. and 10:00 a.m.) and following 7–8 h of night sleep. The participants were asked to maintain the same diet on the day of the tests and were asked not to consume caffeine, in order to minimize external influences on the trials. Participants were also instructed to keep their TT routine for insulin dosage during the hours preceding the testing sessions.

2.3. Maximal incremental test

After 5 min of warm-up at 100 W, the power increased by 15 W every 30 s until voluntary exhaustion. The entire test was conducted at a freely chosen cadence. During the test, the expired gases were recorded through a breath-by-breath method with a metabolic cart (Quark CPET respiratory gas analyzer; COSMED s.r.l., Rome, Italy), calibrated according to the manufacturer's recommendations. VO_2peak was calculated as the mean highest 30-s oxygen consumption (VO_2), while VT_2 was calculated according to the criteria of Binder and colleagues [21].

2.4. Constant load trial and time trial

The CLT consisted of performing 10 min at 75% of the VT_2 power output at a freely chosen cadence. After 3 min of passive rest sitting on the bike, they performed a simulated 15 km TT, with the aim to cover the distance in the shortest possible time. The TT began with the standard virtual gear, and then the participants were free to shift it. The only feedback provided during TT was the time elapsed from the beginning and the remaining distance to be completed.

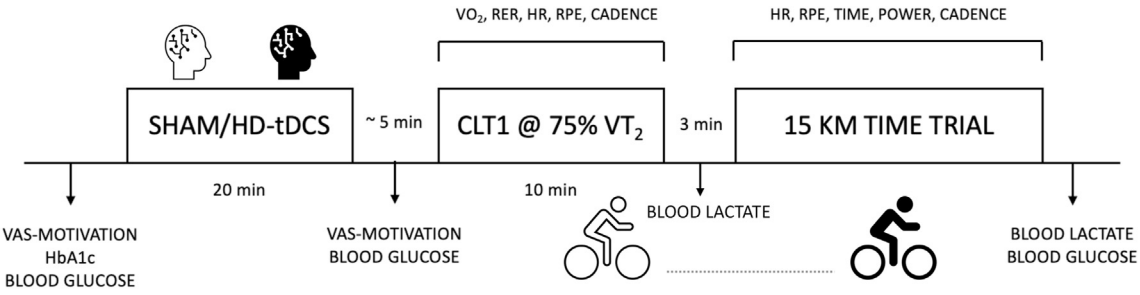

Fig. 1. Flow-chart of the design study and the experimental sessions.

The participants were allowed to drink water ad libitum, while no verbal encouragement was provided. During both the CLT and TT, the ergometer recorded the power, speed, and distance. For data analysis, we averaged these parameters in splits of 3 min (TT) and 5 min (CLT) in length, except the last one (from the 18th minute to the end of TT), which had a different length based on the total time needed to complete the TT. The participants were blinded to their performance and physiological data until the end of the entire protocol.

2.5. Physiological and perceptual measures

During visits 3 and 4, the heart rate (HR) and rating of perceived exertion (RPE) were measured every 3 min during both the CLT and TT, and at the end of the TT. The HR was recorded as the average of 30 s before each time point, using an HR monitor fitted with a chest strap (Garmin Edge 530 Plus, Olathe, KS). The RPE was recorded using Borg 6 to 20 scale [22] to measure whole-body perceived exertion. The standardization procedures have been followed both during the instructions and the scale administration. During the CLT, the expired gases were also recorded, using the same methods as in the incremental test. For the analysis, the gases expired at the third, sixth, and ninth minutes were considered, calculated as the average of the last 30 s preceding the relative time point. The parameters considered were: the VO_2 and respiratory exchange ratio. Immediately after the CLT and TT, a blood sample was taken from the earlobe for the determination of blood lactate (Lactate Pro 2; Arkray Inc, Tokyo, Japan). Before and after HD-tDCS/SHAM, and after the TT, blood glucose concentration was monitored via blood sampling by the conventional glucose oxidase method routinely used in clinical laboratories, while glycosylated hemoglobin (HbA_{1c}) at baseline pre-HD-tDCS/SHAM treatments was assessed using a highly sensitive method of ion-exchange liquid chromatography with a D-10™ System analyzer and BIO-RAD D-10™ reagents (Bio-Rad; Hercules, California, USA).

2.6. Psychological questionnaire

The visual analog scale (VAS), related to participants' motivation toward the TT [23], were submitted to the participants immediately before (pre-) and after (post-) HD-tDCS/SHAM.

2.7. HD-tDCS procedures

HD-tDCS was delivered using a battery-driven stimulator device (Neuroelectrics, Barcelona, Spain) using 8 circular electrodes (3.14 cm^2) soaked in a saline solution. The electrodes were placed in two 3 × 1 arrays according to the EEG 10–20 international system [24], with the 2 anodes over the DLPFC (F3 and F4) and the return electrodes placed in Fp1/F7/C3 and Fp2/F8/C4, respectively (Fig. 2). The montage was chosen based on computational models that generated simulated current maps using the software NIC2 (Neuroelectrics, Barcelona, Spain), to facilitate with high focality the left and right DLPCF. In the HD-tDCS condition, the anodes were set to deliver a total current of 1.5 mA, and the return electrodes shared the same current intensity (0.5 mA each) for a duration of 20 min at a current density of 0.059 mA/cm^2. A recent review on the effects of tDCS on exercise performance [4] reported that a large number of studies (half of those presented) have used a 1.5-mA stimulation, which is also in line with the safety guidelines provided by Bikson and colleagues [25]. At the onset and offset of stimulation, there were 20 s of gradual increase and decrease of current intensity. In the SHAM condition, the placement of the electrodes was the same, but stimulation was only active for the 30-s duration of onset and offset. All participants tolerated the HD-tDCS well, and no side effects were reported during or after the sessions.

2.8. Continuous glucose monitoring

Continuous glucose monitoring (G6, Dexcom, San Diego, CA) data from each 24-h period during the three days preceding and following the tests were stratified by the percentage time spent within various glycemic ranges: 3.0–3.9 mmol L^{-1} (level 1 hypoglycemia), <3.0 mmol L^{-1} (level 2 hypoglycemia), 3.9–10.0 mmol L^{-1} (target range), 10.0–13.9 mmol L^{-1} (level 1 hyperglycemia), and >13.9 mmol L^{-1} (level 2 hyperglycemia), according to recent guidelines [26]. According to continuous glucose monitoring, no severe hypoglycemia or hyperglycemia were reported during the tests and the subsequently hours.

2.9. Statistical analysis

All data are presented as mean (SD). The assumptions of normality and sphericity were checked using the Shapiro-Wilk test and the Mauchly test, respectively. All the data showed normal distribution, while the Greenhouse-Geisser correction was used when sphericity was not met. A paired *t*-test was used to compare the HbA1c at the baseline before HD-tDCS/SHAM treatments, blood lactate measured at the end of the CLT and TT in the HD-tDCS and SHAM conditions, time and power during the TT. A two-way repeated-measures analysis of variance (RM-ANOVA) was performed to analyze HR, RPE, VO_2 and respiratory exchange ratio (RER) during CLT; HR, RPE, power/RPE and power/HR during the TT; blood glucose concentration and VAS motivation scores. Effect sizes for RM-ANOVA are reported as partial eta squared (η^2p), using the small (<0.13), medium (0.13–0.25) and large (>0.25) interpretation for effect size [27], while effect sizes for pairwise comparison were calculated using Cohen's *d* and are considered to be either trivial (<0.20), small (0.21–0.60), moderate (0.61–1.20), large (1.21–2.00), or very large (>2.00) [28]. The data analysis was performed using the SPSS software (version 26.0; SPSS Inc, Chicago, IL).

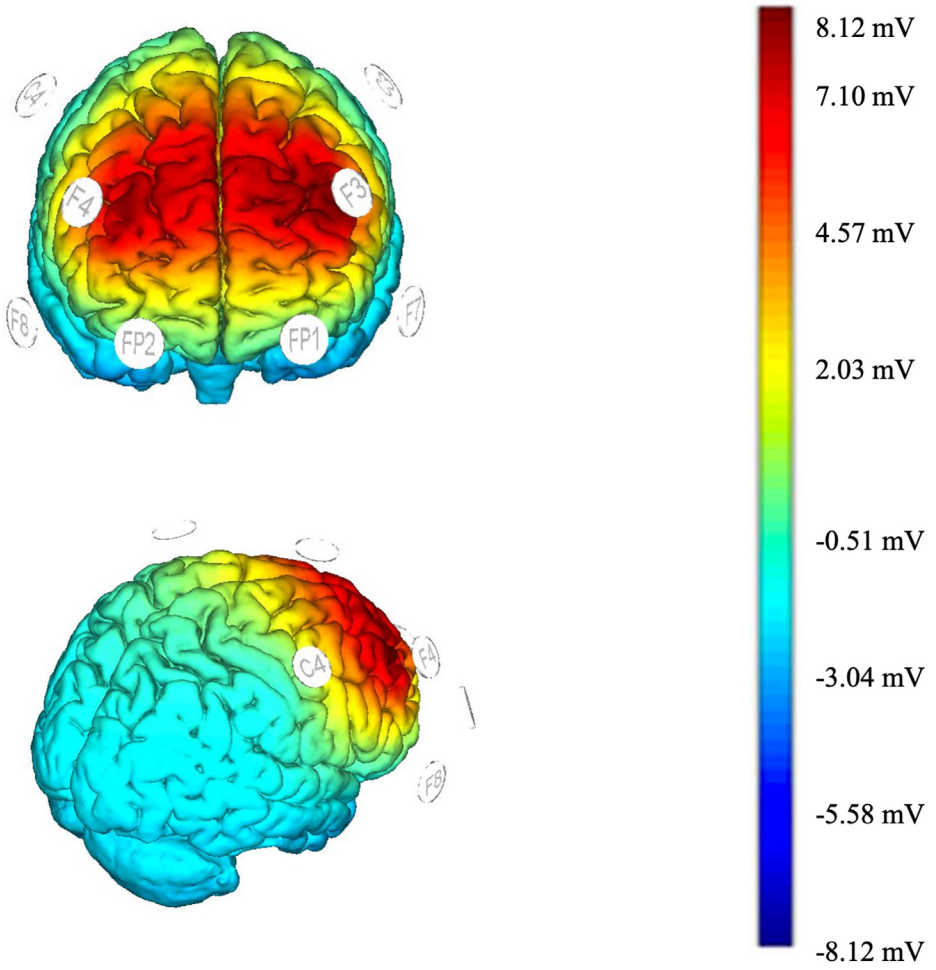

Fig. 2. Computational models and influence maps that generated simulated current maps using NIC2 software provided by Neuroelectrics. For readers viewing the figure in grayscale/black and white, please note that the darker areas illustrated on the brains correspond to the top of the scale at right, not the bottom.

2.10. Data and resource availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request. No applicable resources were generated or analyzed during the current study.

3. Results

3.1. Time trial

Time to complete the TT was significantly lower after HD-tDCS than after SHAM ($P = 0.006$; $d = 1.21$; Fig. 3A). Mean power output of the TT was significantly higher after HD-tDCS than after SHAM ($P = 0.006$; $d = 1.21$; Fig. 3B). For HR (Fig. 4A), there was a significant main effect of time (F (6, 120) = 5717.0; $P < 0.001$; $\eta^2p = 0.29$), while no main effect of condition (F (1, 20) = 0.2; $P = 0.700$; $\eta^2p = 0.04$), and no interaction condition x time (F (6, 120) = 1.0; $P = 0.411$; $\eta^2p = 0.05$). For RPE (Fig. 4B), there was a significant main effect of time (F (6, 120) = 196.3; $P < 0.001$; $\eta^2p = 0.27$), while no main effect of condition (F (1, 20) = 1.8; $P = 0.196$; $\eta^2p = 0.09$), and no interaction condition x time (F (6, 120) = 0.8; $P = 0.548$; $\eta^2p = 0.05$). For power/HR ratio (Fig. 4C), there was a significant main effect of condition (F (1, 20) = 5.5; $P = 0.029$; $\eta^2p = 0.17$) and time (F (6, 120) = 2653.0; $P < 0.001$; $\eta^2p = 0.26$), and interaction condition x time (F (6, 120) = 2.4; $P = 0.032$; $\eta^2p = 0.16$). For power/RPE ratio (Fig. 4D), there was a significant main effect of condition (F (1, 20) = 8.5; $P = 0.009$; $\eta^2p = 0.18$) and time (F (6, 120) = 159.8; $P < 0.001$; $\eta^2p = 0.24$), while no interaction condition x time (F (6, 120) = 0.4; $P = 0.864$; $\eta^2p = 0.03$). Blood lactate measured immediately at the end of the TT was not different between the conditions (HD-tDCS: 8.1 [1.4] mmol·L^{-1} vs SHAM: 7.9 [1.2] mmol·L^{-1}; $P = 0.258$; $d = 0.17$).

3.2. Constant load trial

For HR (Fig. 5A), there was a significant main effect of time (F (1, 20) = 4.6; $P = 0.043$; $\eta^2p = 0.13$), while no main effect of condition (F (1, 20) = 0.6; $P = 0.467$; $\eta^2p = 0.05$), and no interaction condition x time (F (1, 20) = 0.1; $P = 0.787$; $\eta^2p = 0.02$). For RPE (Fig. 5B), there was a significant main effect of time (F (1, 20) = 138.8; $P < 0.001$; $\eta^2p = 0.25$), while no main effect of condition (F (1, 20) = 0.5; $P = 0.499$; $\eta^2p = 0.05$), and no interaction condition x time (F (1, 20) = 0.2; $P = 0.629$; $\eta^2p = 0.03$). For VO_2 (Fig. 5C), there was a significant main effect of time (F (1, 20) = 17.6; $P = 0.001$; $\eta^2p = 0.21$), while no main effect of condition (F (1, 20) = 0.3; $P = 0.591$; $\eta^2p = 0.05$), and no interaction condition x time (F (1, 20) = 0.4; $P = 0.540$; $\eta^2p = 0.04$). For RER (Fig. 5D), there was no main effect of condition (F (1, 20) = 1.0; $P = 0.326$; $\eta^2p = 0.06$) and time (F (1, 20) = 0.3; $P = 0.621$; $\eta^2p = 0.03$), and no interaction

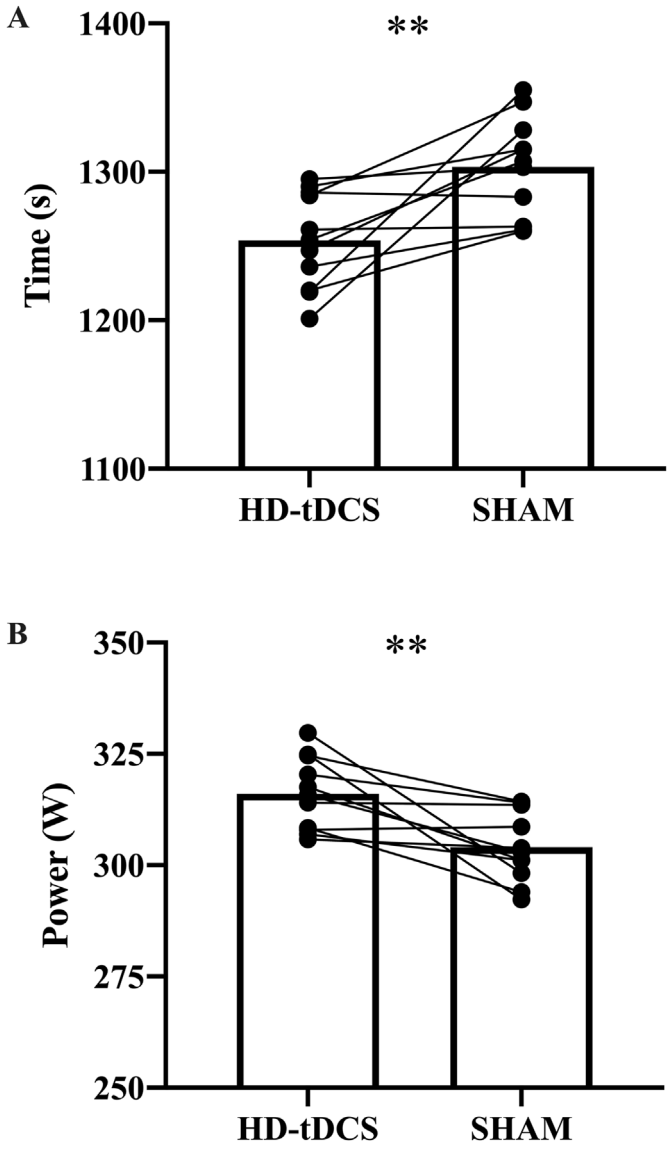

Fig. 3. Effects of HD-tDCS on time trial (A) and power (B) under stimulation or SHAM conditions.

condition x time (F (1, 20) = 0.1; P = 0.817; η^2p = 0.01). Blood lactate measured immediately at the end of the CLT was not different between the conditions (HD-tDCS: 2.6 [1.4] mmol·L^{-1} vs SHAM: 2.4 [1.2] mmol·L^{-1}; P = 0.419; d = 0.13).

3.3. Glucose profile

HbA_{1c} at baseline did not differ before HD-tDCS or SHAM conditions (HD-tDCS: 5.9 [0.4] % vs SHAM: 6.0 [0.4] %; P = 0.278; d = 0.17). For blood glucose, there was a significant main effect of time (F (2, 40) = 267.3; P < 0.001; η^2p = 0.26), while no main effect of condition (F (1, 20) = 0.1; P = 0.805; η^2p = 0.02; pre stimulation, HD-tDCS: 7.7 [0.8] mmol·L^{-1} vs SHAM: 7.7 [0.9] mmol·L^{-1}; post stimulation, HD-tDCS: 7.8 [0.6] mmol·L^{-1} vs SHAM: 7.6 [1.0] mmol·L^{-1}; post TT, HD-tDCS: 4.8 [1.1] mmol·L^{-1} vs SHAM: 4.8 [0.8] mmol·L^{-1}), and no interaction condition x time (F (2, 40) = 0.1; P = 0.902; η^2p = 0.01). Continuous glucose monitoring data from each 24-h period during the three days preceding and following the tests are reported in Supplemental Material.

3.4. Motivation

For participants' motivation toward the TT, there was no main effect of condition (F (1, 20) = 0.0; P = 0.954; η^2p = 0.01) and time (F (1, 20) = 0.3; P = 0.607; η^2p = 0.03), and no interaction condition x time (F (1, 20) = 1.5; P = 0.237; η^2p = 0.04).

4. Discussion

The main finding of this study is that bilateral HD-tDCS of the dorsolateral PFC improved performance in 15 km cycling TT in high-level cyclists with T1D. Cyclists covered TT distance faster (+3.8%) under HD-tDCS than SHAM condition. That improvement was accompanied by an equal increase (+3.8%) in power output. This gain in performance is considered significant in the high-level endurance sport context [29]. This study confirms the results of a previous study observing an increase in self-paced whole-body endurance performance following anodal HD-tDCS techniques [12] and confirms our hypothesis on the positive effect of dorsolateral PFC HD-tDCS on cycling performance, even in a specific population. This improvement in performance in the HD-tDCS condition was found to be associated at a significantly higher power output than the SHAM condition. This was totally expected, since mean power output is strictly linked to cycling performance. In addition, the effect size in the performance improvement was large, with all the individual changes among the two conditions going in the same direction (Fig. 3).

Regarding the physiological mechanisms through which HD-tDCS would have positively modulated the performance outcome, speculations only can be made, given the lack of a manipulation check in this study. According to the psychobiological model of endurance performance, self-paced endurance performance determining factors are motivation and perception of effort [30]. In the present study motivation was similar between conditions; thus, a treatment effect on RPE could be the cause of the superior performance in the HD-tDCS condition. Specifically, the higher power output with unchanged RPE and HR in the HD-tDCS condition could be a consequence of improved inhibitory control during exercise following HD-tDCS treatment, as inhibitory control is a cognitive process involving PFC that might contribute to the overall perception of effort during exercise [12,13,31]. According to this scenario, the upregulation of the dorsolateral PFC through HD-tDCS might have reduced the cognitive effort required by the participants to exert inhibitory control, letting them to perform a higher power output at the same RPE and HR. This explanation is supported by the study of Pollastri and colleagues [12] in which the performance improvement in the same 15-km TT, after dorsolateral PFC HD-tDCS, was associated with an unchanged RPE at iso-time.

To the best of our knowledge, this is the first study showing putatively positive HD-tDCS effects on endurance exercise performance in athletes with T1D. This gain in performance was associated with an unaltered blood glucose response in the two conditions, extending the benefits of this methodology also to a specific population. This ultimate finding was partially unexpected, considering the controversial results of few studies analyzing the effects of tDCS on glycemic response [17,32]. It is plausible that negative result of previous studies could be due to the lower focality of the traditional tDCS. This latter may have, in fact, excited or inhibited areas involved in the glucose control (e.g. right frontal lobe [33]), leading to confounding results. Given no detrimental effects on blood glucose control, present data may open to future applications of HD-tDCS to a wider population of active T1D-subjects. In fact, post-exercise glucose stabilization represents a particular concern for people exercising with T1D, and this may be even more important for high-level athletes willing to minimize

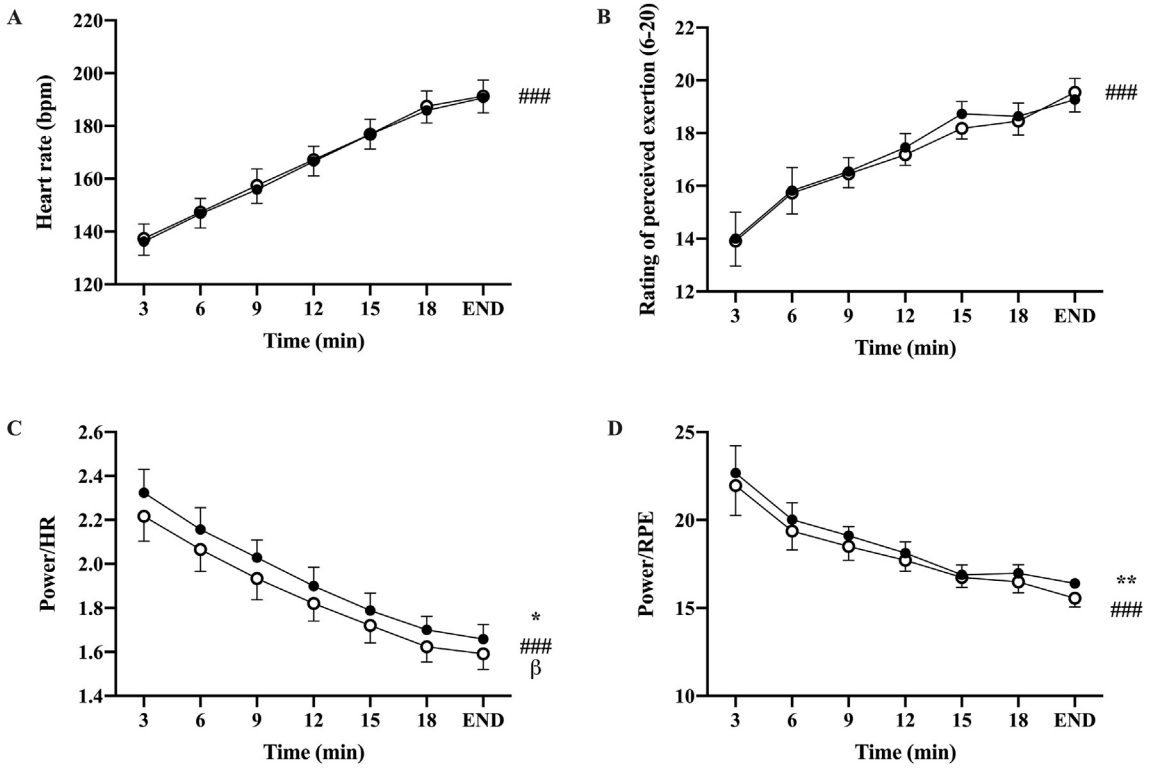

Fig. 4. Effects of HD-tDCS on heart rate (A), rate of perceived exertion (B), power/HR (C), power/RPE (D) under HD-tDCS (black circles) or SHAM (white circles) conditions.

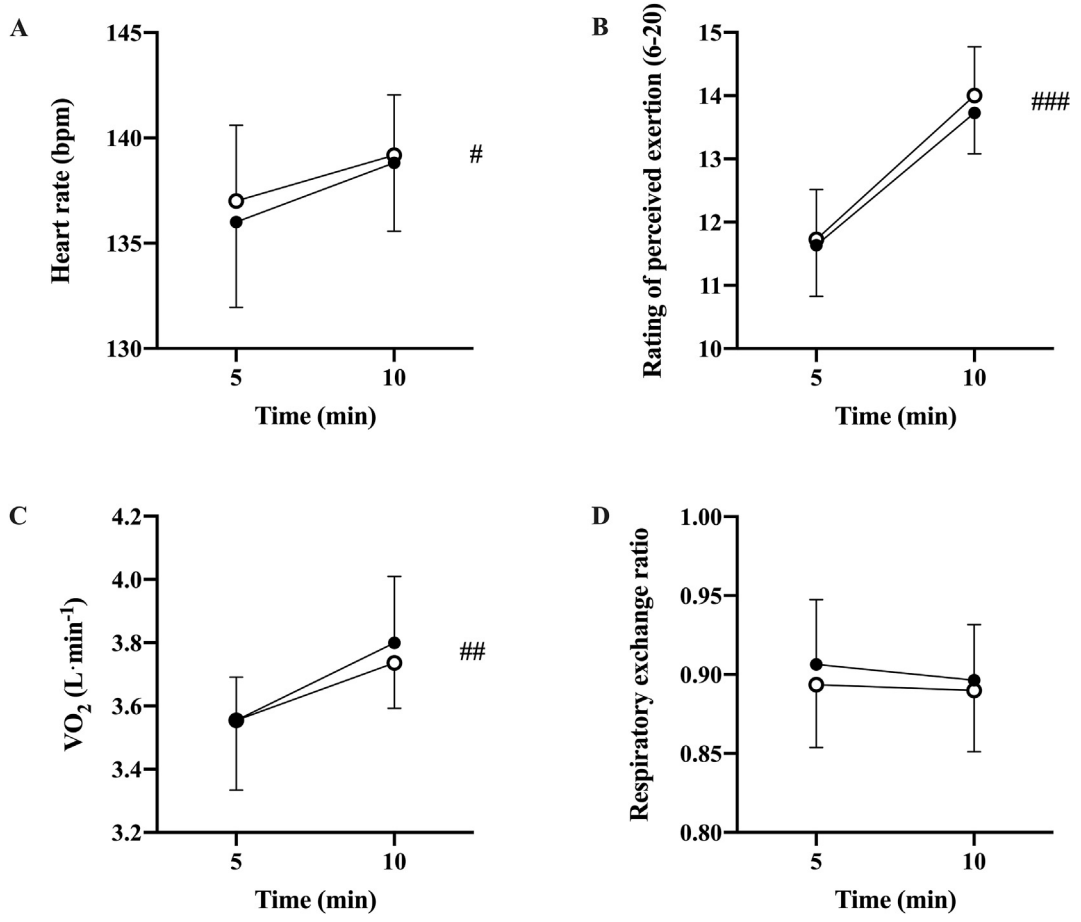

Fig. 5. HR (A), RPE (B), VO_2 (C), RER (D), during the constant load trial under HD-tDCS (black circles) and SHAM (white circles) conditions.

any hypoglycemic episode. A tight glycemic control becomes of paramount interest not only for health but also for performance goals.

Finally, none of the measured variables during constant load were different in the two conditions. The difference in the results obtained between the CLT and TT (i.e. improved TT performance but unchanged physiological and perceptual response during CLT) could be due to the different exercise intensity: the CLT was carried out at a lower intensity than VT_2, while the TT was performed in order to complete the distance in the minimum time possible. As a decrease in the oxygenation response and fatigue of PFC takes place only at very high intensity [34,35], the effects of HD-tDCS could have emerged only during the TT and not the CLT.

4.1. Clinical implication

Altogether these data suggest that upregulation of the PFC could enhance endurance performance in high-level cyclists with T1D, without altering physiological and perceptual responses at moderate intensity regime. This method could be used in clinical and field settings to induce changes in performance without any acute side effects on glycemia of athletes with T1D.

4.2. Limitations

The main limitation of this study is the relative low sample size. This is a consequence of the difficulty in recruiting high-level level athletes with T1D in multiday standardized laboratory research projects due to athletes' busy racing calendar and training schedule. Another limitation is that brain response was not monitored during exercise and post-stimulation through electroencephalography or near infrared spectroscopy, permitting only to speculate about the physiological mechanism through which HD-tDCS had increased performance.

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CRediT authorship contribution statement

Luca Filipas: Conceptualization, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Gabriele Gallo:** Methodology, Software, Investigation, Data curation. **Andrea Meloni:** Software, Investigation, Data curation, Visualization. **Livio Luzi:** Resources, Writing – review & editing, Supervision. **Roberto Codella:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.09.005.

References

[1] Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist 2011. https://doi.org/10.1177/1073858410386614.
[2] Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol 2017. https://doi.org/10.1016/j.clinph.2016.10.087.
[3] Machado DGdS, Unal G, Andrade SM, Moreira A, Altimari LR, Brunoni AR, et al. Effect of transcranial direct current stimulation on exercise performance: a systematic review and meta-analysis. Brain Stimul 2019. https://doi.org/10.1016/j.brs.2018.12.227.
[4] Angius L, Hopker J, Mauger AR. The ergogenic effects of transcranial direct current stimulation on exercise performance. Front Physiol 2017. https://doi.org/10.3389/fphys.2017.00090.
[5] Okano AH, Fontes EB, Montenegro RA, De Tarso Veras Farinatti P, Cyrino ES, Li LM, et al. Brain stimulation modulates the autonomic nervous system, rating of perceived exertion and performance during maximal exercise. Br J Sports Med 2015. https://doi.org/10.1136/bjsports-2012-091658.
[6] Vitor-Costa M, Okuno NM, Bortolotti H, Bertollo M, Boggio PS, Fregni F, et al. Improving cycling performance: transcranial direct current stimulation increases time to exhaustion in cycling. PLoS One 2015. https://doi.org/10.1371/journal.pone.0144916.
[7] Angius L, Mauger AR, Hopker J, Pascual-Leone A, Santarnecchi E, Marcora SM. Bilateral extracephalic transcranial direct current stimulation improves endurance performance in healthy individuals. Brain Stimul 2018. https://doi.org/10.1016/j.brs.2017.09.017.
[8] Angius L, Santarnecchi E, Pascual-Leone A, Marcora SM. Transcranial direct current stimulation over the left dorsolateral prefrontal cortex improves inhibitory control and endurance performance in healthy individuals. Neuroscience 2019. https://doi.org/10.1016/j.neuroscience.2019.08.052.
[9] Holgado D, Zandonai T, Ciria LF, Zabala M, Hopker J, Sanabria D. Transcranial direct current stimulation (tDCS) over the left prefrontal cortex does not affect time-trial self-paced cycling performance: evidence from oscillatory brain activity and power output. PLoS One 2019. https://doi.org/10.1371/journal.pone.0210873.
[10] Valenzuela PL, Amo C, Sánchez-Martínez G, Torrontegi E, Vázquez-Carrión J, Montalvo Z, et al. Enhancement of mood but not performance in elite athletes with transcranial direct-current stimulation. Int J Sports Physiol Perform 2019. https://doi.org/10.1123/ijspp.2018-0473.
[11] Alam M, Truong DQ, Khadka N, Bikson M. Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS). Phys Med Biol 2016. https://doi.org/10.1088/0031-9155/61/12/4506.
[12] Pollastri L, Gallo G, Zucca M, Filipas L, la Torre A, Riba U, et al. Bilateral dorsolateral prefrontal cortex high-definition transcranial direct-current stimulation improves time-trial performance in elite cyclists. Int J Sports Physiol Perform 2021. https://doi.org/10.1123/IJSPP.2019-0910.
[13] Gallo G, Geda E, Codella R, Faelli E, Panascì M, Ranieri LE, et al. Effects of bilateral dorsolateral prefrontal cortex high-definition transcranial direct-current stimulation on physiological and performance responses at severe-intensity exercise domain in elite road cyclists. Int J Sports Physiol Perform 2022;1–9. https://doi.org/10.1123/ijspp.2022-0019.
[14] de Morree HM, Klein C, Marcora SM. Perception of effort reflects central motor command during movement execution. Psychophysiology 2012. https://doi.org/10.1111/j.1469-8986.2012.01399.x.
[15] Jaberzadeh S, Zoghi M. Transcranial direct current stimulation enhances exercise performance: a mini review of the underlying mechanisms. Front Neuroergonomics 2022. https://doi.org/10.3389/fnrgo.2022.841911.
[16] Binkofski F, Loebig M, Jauch-Chara K, Bergmann S, Melchert UH, Scholand-Engler HG, et al. Brain energy consumption induced by electrical stimulation promotes systemic glucose uptake. Biol Psychiatr 2011. https://doi.org/10.1016/j.biopsych.2011.05.009.
[17] Kistenmacher A, Manneck S, Wardzinski EK, Martens JC, Gohla G, Melchert UH, et al. Persistent blood glucose reduction upon repeated transcranial electric stimulation in men. Brain Stimul 2017. https://doi.org/10.1016/j.brs.2017.03.011.
[18] Fietsam AC, Deters JR, Workman CD, Ponto LLB, Rudroff T. Alterations in leg muscle glucose uptake and inter-limb asymmetry after a single session of tdcs in four people with multiple sclerosis. Brain Sci 2021. https://doi.org/10.3390/brainsci11101363.
[19] Scott SN, Hayes C, Castol R, Fontana FY. Type 1 diabetes and pro cycling: 10 years of learning from the professionals. Practical Diabetes 2022;39:7. https://doi.org/10.1002/pdi.2382.
[20] McKay AKA, Stellingwerff T, Smith ES, Martin DT, Mujika I, Goosey-Tolfrey VL, et al. Defining training and performance caliber: a participant classification framework. Int J Sports Physiol Perform 2022;17:317–31. https://doi.org/10.1123/ijspp.2021-0451.
[21] Binder RK, Wonisch M, Corra U, Cohen-Solal A, Vanhees L, Saner H, et al. Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing. Eur J Prev Cardiol 2008. https://doi.org/10.1097/HJR.0b013e328304fed4.
[22] Borg G. Borg's rating of perceived exertion and pain scales. 1998.

[23] Filipas L. The effect of mental fatigue on sport-specific endurance and technical performances (PhD Academy Award). Br J Sports Med 2021;55:67–8. https://doi.org/10.1136/bjsports-2020-102397.
[24] Herwig U, Satrapi P, Schönfeldt-Lecuona C. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 2003. https://doi.org/10.1023/B:BRAT.0000006333.93597.9d.
[25] Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul 2016. https://doi.org/10.1016/j.brs.2016.06.004.
[26] Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017. https://doi.org/10.2337/dc17-1600.
[27] Bakeman R. Recommended effect size statistics for repeated measures designs. Behav Res Methods 2005. https://doi.org/10.3758/BF03192707.
[28] Hopkins WG, Marshall SW, Batterham AM, Hanin J. Progressive statistics for studies in sports medicine and exercise science. Med Sci Sports Exerc 2009. https://doi.org/10.1249/MSS.0b013e31818cb278.
[29] Filipas L, Bonato M, Gallo G, Codella R. Effects of 16 weeks of pyramidal and polarized training intensity distributions in well-trained endurance runners. Scand J Med Sci Sports 2022;32:498–511. https://doi.org/10.1111/sms.14101.
[30] Pageaux B. The psychobiological model of endurance performance: an effort-based decision-making theory to explain self-paced endurance performance. Sports Med 2014. https://doi.org/10.1007/s40279-014-0198-2.
[31] Shenhav A, Musslick S, Lieder F, Kool W, Griffiths TL, Cohen JD, et al. Toward a rational and mechanistic account of mental effort. Annu Rev Neurosci 2017. https://doi.org/10.1146/annurev-neuro-072116-031526.
[32] Mares T, Ceresnakova S, Albrecht J, Buday J, Klasova J, Horackova K, et al. The onset of diabetes during transcranial direct current stimulation treatment of anorexia nervosa — a case report. Front Psychiatr 2020. https://doi.org/10.3389/fpsyt.2020.00040.
[33] DeVore BB, Harrison DW. Brain mechanisms in blood glucose mobilization and absorption: the role of the left and the right frontal regions in the regulatory control of blood glucose levels. Diabetes Res – Open J 2017. https://doi.org/10.17140/droj-3-131.
[34] Thomas R, Stephane P. Prefrontal cortex oxygenation and neuromuscular responses to exhaustive exercise. Eur J Appl Physiol 2008. https://doi.org/10.1007/s00421-007-0568-7.
[35] Bhambhani Y, Malik R, Mookerjee S. Cerebral oxygenation declines at exercise intensities above the respiratory compensation threshold. Respir Physiol Neurobiol 2007. https://doi.org/10.1016/j.resp.2006.08.009.