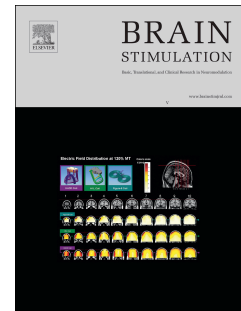


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Effects of bilateral dorsolateral prefrontal cortex high-definition transcranial direct-current stimulation on time-trial performance in cyclists with type 1 diabetes mellitus

Luca Filipas, Gabriele Gallo, Andrea Meloni, Livio Luzi, Roberto Codella



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Full name of the authors:

Luca Filipas^{1,2}, Gabriele Gallo^{3,4}, Andrea Meloni^{1,2}, Livio Luzi^{1,2}, Roberto Codella^{1,2}

Institutional affiliations:

1 Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy

2 Department of Endocrinology, Nutrition and Metabolic Diseases, IRCCS MultiMedica, Milan, Italy

3 Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy

4 Centro Polifunzionale di Scienze Motorie, University of Genoa, Genoa, Italy

Contacts details for corresponding author:

Luca Filipas

Department of Biomedical Sciences for Health

Università degli Studi di Milano

Via F.lli Cervi 93, 20090 Segrate (Milano) – Italy

Phone: +39 3408834392

E-mail: luca.filipas@unimi.it

23 **Abstract**

24 **Background:** HD-tDCS is capable to increase the focality of neuromodulation and has been recently
25 applied to improve endurance performance in healthy subjects. **Objective/Hypothesis:** Whether
26 these putative advantages could be exploited in active subjects with type 1 diabetes mellitus (T1D)
27 remains questionable. **Methods:** In a double-blind, randomized crossover order, 11 high-level
28 cyclists (27 ± 4.3 years; weight: 65.5 ± 8.6 kg; height: 180 ± 8 cm; $\text{VO}_{2\text{peak}}$: 67.5 ± 2.9
29 $\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) with T1D underwent either HD-tDCS (F3, F4) or control (SHAM) and completed a
30 constant-load trial (CLT) at 75% of the 2nd ventilatory threshold plus a 15-km cycling time-trial (TT).
31 **Results:** After HD-tDCS, the total time to cover the TT was 3.8 % faster ($P < 0.01$), associated with
32 a higher mean power output ($P < 0.01$), and a higher rate of power/perception of effort ($P < 0.01$) and
33 power/heart rate at iso-time ($P < 0.05$) than the SHAM condition. Physiological parameters during
34 CLT and TT did not differ in both conditions. **Conclusions:** These findings suggest that upregulation
35 of the prefrontal cortex could enhance endurance performance in high-level cyclists with T1D,
36 without altering physiological and perceptual responses at moderate intensity. Present data open to
37 future applications of HD-tDCS to a wider population of active T1D-subjects.

38
39 **Keywords:** tDCS, brain stimulation, performance, elite cycling, diabetes

40 Introduction

41 Transcranial direct-current stimulation (tDCS) is a noninvasive neuromodulatory method that
42 consists of applying weak direct current over the scalp, usually 1 to 2 mA with 2 large pads. It acts
43 by creating an electric field that reversibly modifies the excitability of the cortical areas under the
44 anode and the cathode, eliciting an excitatory or inhibitory response, respectively acting through
45 depolarization or hyperpolarization of resting membrane potential [1]. tDCS is widely used in
46 neurological rehabilitation, cognitive improvement, and psychiatric disease [2]. In the last 10 years,
47 an increasing number of studies have investigated the effects of anodal tDCS on endurance physical
48 performance. The results are inconclusive for all the areas targeted [3,4], with some studies showing
49 positive effects [5–8] while others no variation [9,10]. This discrepancy could be due to the type and
50 position of the applied electrodes. Traditionally, tDCS uses only 2 large pads (25-36 cm²), and it has
51 a low focality therefore with a certain risk of producing excitatory or inhibitory influences in other
52 areas with respect to those targeted [7]. A variant called high-definition transcranial direct current
53 stimulation (HD-tDCS), capable to increase the focality of neuromodulation, has been recently
54 proposed [11]. Instead of using 2 large electrodes, HD-tDCS relies on an array of small circular
55 electrodes (3-5 cm²), with the active electrode (anode or cathode) positioned in the center of the
56 opposite polarity reference electrodes. Recent studies using HD-tDCS over bilateral dorsolateral
57 prefrontal cortex (PFC) showed improvement in endurance performance, both in long and short time
58 trials (TTs) [12,13] without altering physiological responses during the TT at iso-time, that is
59 referring to the variables monitored at the same timepoints during a determined distance (i.e 15 km)
60 to be covered in least time possible. A higher ratio between power output and perceptual measures
61 seems the mechanism behind improved endurance performance. Furthermore, HD-tDCS could
62 reduce perception of effort during exercise apparently because these sensory signals are corollary
63 discharged from areas functionally connected with PFC, such as the presupplementary motor area,
64 the supplementary motor area, the premotor cortex, and the primary motor cortex [14]. Therefore, it
65 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 with T1D. 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.

Materials and methods

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] $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$, 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.

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 (Figure 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 VT₂. 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 Cycclus2 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 VT₂). The experimental visits were completed at the same time of the day (between 8:00 AM and 10:00 AM) and following 7 to 8 hours 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.

Figure 1 about here

Maximal incremental test

After 5 min of warm-up at 100 W, the power increased by 15W 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 (VO₂), while VT₂ was calculated according to the criteria of Binder and colleagues [21].

Constant load trial and time trial

The CLT consisted of performing 10 min at 75 % of the VT₂ 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. 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.

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 VO₂ 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).

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.

HD-tDCS procedures

HD-tDCS was delivered using a battery-driven stimulator device (Neuroelectronics, Barcelona, Spain) using 8 circular electrodes (3.14 cm²) 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 (Figure 2). The montage was chosen based on computational models that generated simulated current maps using the software NIC2 (Neuroelectronics, Barcelona, Spain), to facilitate with high focality the left and right DLPFC. 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/cm². 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.

Figure 2 about here

195

196 **Continuous glucose monitoring**

197 Continuous glucose monitoring (G6, Dexcom, San Diego, CA) data from each 24-h period during the
 198 three days preceding and following the tests were stratified by the percentage time spent within
 199 various glycemic ranges: 3.0-3.9 mmol·L⁻¹ (level 1 hypoglycemia), < 3.0 mmol·L⁻¹ (level 2
 200 hypoglycemia), 3.9-10.0 mmol·L⁻¹ (target range), 10.0-13.9 mmol·L⁻¹ (level 1 hyperglycemia), and
 201 > 13.9 mmol·L⁻¹ (level 2 hyperglycemia), according to recent guidelines [26]. According to
 202 continuous glucose monitoring, no severe hypoglycemia or hyperglycemia were reported during the
 203 tests and the subsequently hours.

204

205 **Statistical analysis**

206 All data are presented as mean (SD). The assumptions of normality and sphericity were checked using
 207 the Shapiro-Wilk test and the Mauchly test, respectively. All the data showed normal distribution,
 208 while the Greenhouse-Geisser correction was used when sphericity was not met. A paired t test was
 209 used to compare the HbA1c at the baseline before HD-tDCS/SHAM treatments, blood lactate
 210 measured at the end of the CLT and TT in the HD-tDCS and SHAM conditions, time and power
 211 during the TT. A two-way repeated-measures analysis of variance (RM-ANOVA) was performed to
 212 analyze HR, RPE, VO₂ and respiratory exchange ratio (RER) during CLT; HR, RPE, power/RPE and
 213 power/HR during the TT; blood glucose concentration and VAS motivation scores. Effect sizes for
 214 RM-ANOVA are reported as partial eta squared (η^2p), using the small (< 0.13), medium (0.13-0.25)
 215 and large (> 0.25) interpretation for effect size [27], while effect sizes for pairwise comparison were
 216 calculated using Cohen's *d* and are considered to be either trivial (< 0.20), small (0.21-0.60), moderate
 217 (0.61-1.20), large (1.21-2.00), or very large (> 2.00) [28]. The data analysis was performed using the
 218 SPSS software (version 26.0; SPSS Inc, Chicago, IL).

219

220 **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.

Results

Time trial

Time to complete the TT was significantly lower after HD-tDCS than after SHAM ($P = 0.006$; $d = 1.21$; Figure 3A). Mean power output of the TT was significantly higher after HD-tDCS than after SHAM ($P = 0.006$; $d = 1.21$; Figure 3B). For HR (Figure 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 (Figure 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 (Figure 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 (Figure 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: $8.1 [1.4] \text{ mmol}\cdot\text{L}^{-1}$ vs SHAM: $7.9 [1.2] \text{ mmol}\cdot\text{L}^{-1}$; $P = 0.258$; $d = 0.17$).

Figure 3 about here

Figure 4 about here

Constant load trial

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

Figure 5 about here

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 ($F(2, 40) = 267.3$; $P < 0.001$; $\eta^2p = 0.26$), while no main effect of condition ($F(1, 20) = 0.1$; $P = 0.805$; $\eta^2p = 0.02$; pre stimulation, HD-tDCS: $7.7 [0.8] \text{ mmol} \cdot \text{L}^{-1}$ vs SHAM: $7.7 [0.9] \text{ mmol} \cdot \text{L}^{-1}$; post stimulation, HD-tDCS: $7.8 [0.6] \text{ mmol} \cdot \text{L}^{-1}$ vs SHAM: $7.6 [1.0] \text{ mmol} \cdot \text{L}^{-1}$; post TT, HD-tDCS: $4.8 [1.1] \text{ mmol} \cdot \text{L}^{-1}$ vs SHAM: $4.8 [0.8] \text{ mmol} \cdot \text{L}^{-1}$), and no interaction condition x time ($F(2, 40) = 0.1$; $P = 0.902$; $\eta^2p = 0.01$). Continuous glucose monitoring data from each 24-h period during the three days preceding and following the tests are reported in Supplemental Material.

Motivation

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

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 (Figure 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].

299 According to this scenario, the upregulation of the dorsolateral PFC through HD-tDCS might have
300 reduced the cognitive effort required by the participants to exert inhibitory control, letting them to
301 perform a higher power output at the same RPE and HR. This explanation is supported by the study
302 of Pollastri and colleagues [12] in which the performance improvement in the same 15-km TT, after
303 dorsolateral PFC HD-tDCS, was associated with an unchanged RPE at iso-time.

304 To the best of our knowledge, this is the first study showing putatively positive HD-tDCS effects on
305 endurance exercise performance in athletes with T1D. This gain in performance was associated with
306 an unaltered blood glucose response in the two conditions, extending the benefits of this methodology
307 also to a specific population. This ultimate finding was partially unexpected, considering the
308 controversial results of few studies analyzing the effects of tDCS on glycemic response [17,32]. It is
309 plausible that negative result of previous studies could be due to the lower focality of the traditional
310 tDCS. This latter may have, in fact, excited or inhibited areas involved in the glucose control (e.g.
311 right frontal lobe [33]), leading to confounding results. Given no detrimental effects on blood glucose
312 control, present data may open to future applications of HD-tDCS to a wider population of active
313 T1D-subjects. In fact, post-exercise glucose stabilization represents a particular concern for people
314 exercising with T1D, and this may be even more important for high-level athletes willing to minimize
315 any hypoglycemic episode. A tight glycemic control becomes of paramount interest not only for
316 health but also for performance goals.

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

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.

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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Declarations of interest

None.

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456 **Figure legends**

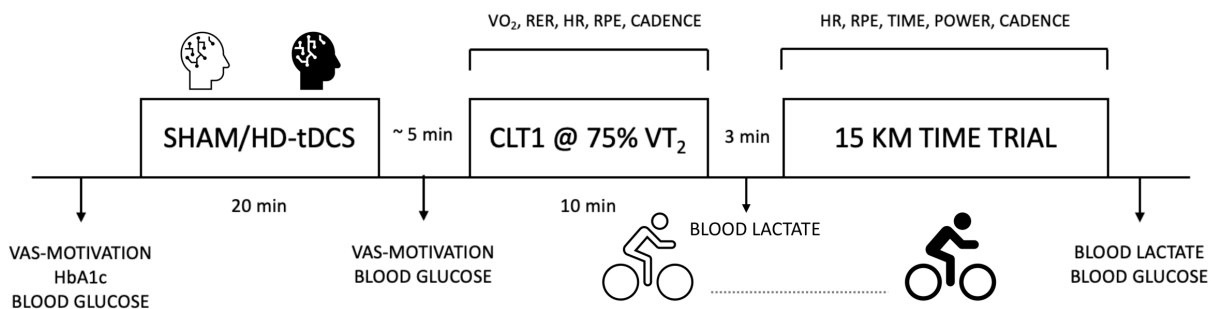
457 **Figure 1.** Flow-chart of the design study and the experimental sessions.

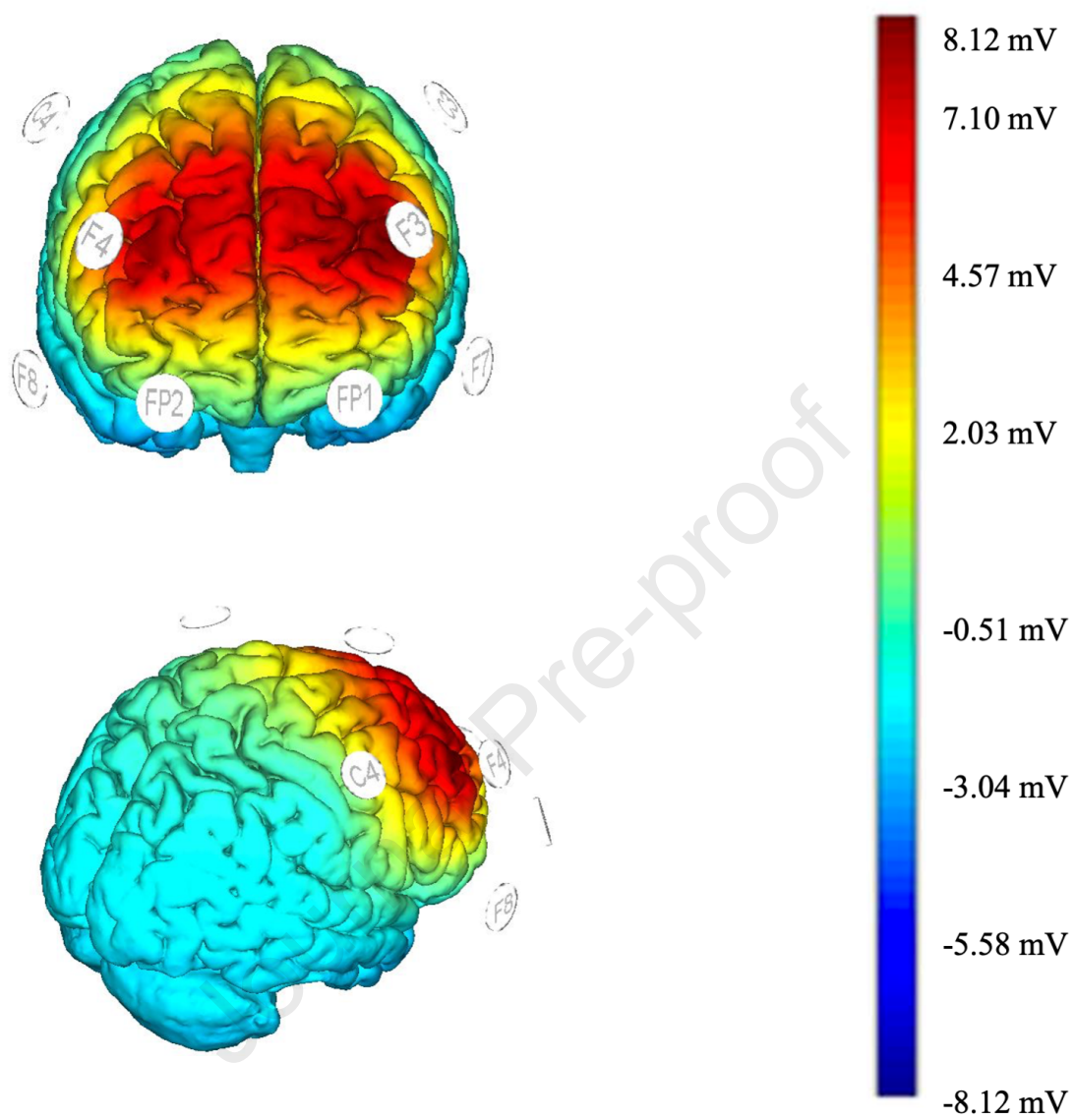
458 **Figure 2.** Computational models and influence maps that generated simulated current maps using
459 NIC2 software provided by Neuroelectronics. For readers viewing the figure in grayscale/black and
460 white, please note that the darker areas illustrated on the brains correspond to the top of the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

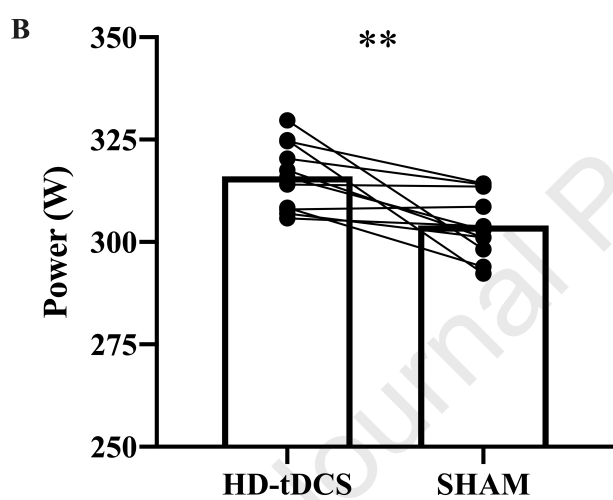
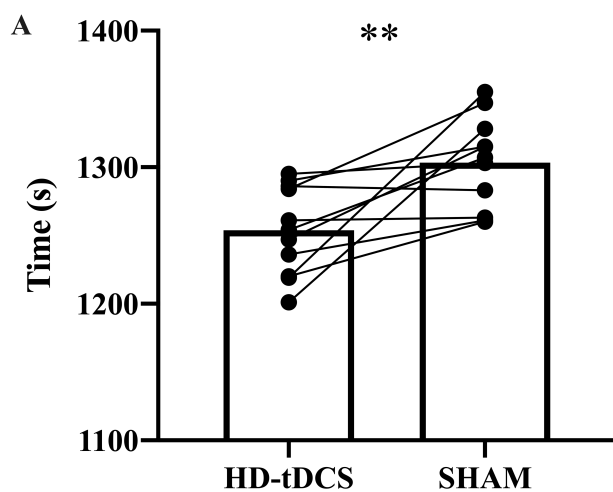
462 **Figure 3.** Effects of HD-tDCS on time trial (A) and power (B) under stimulation or SHAM
463 conditions.

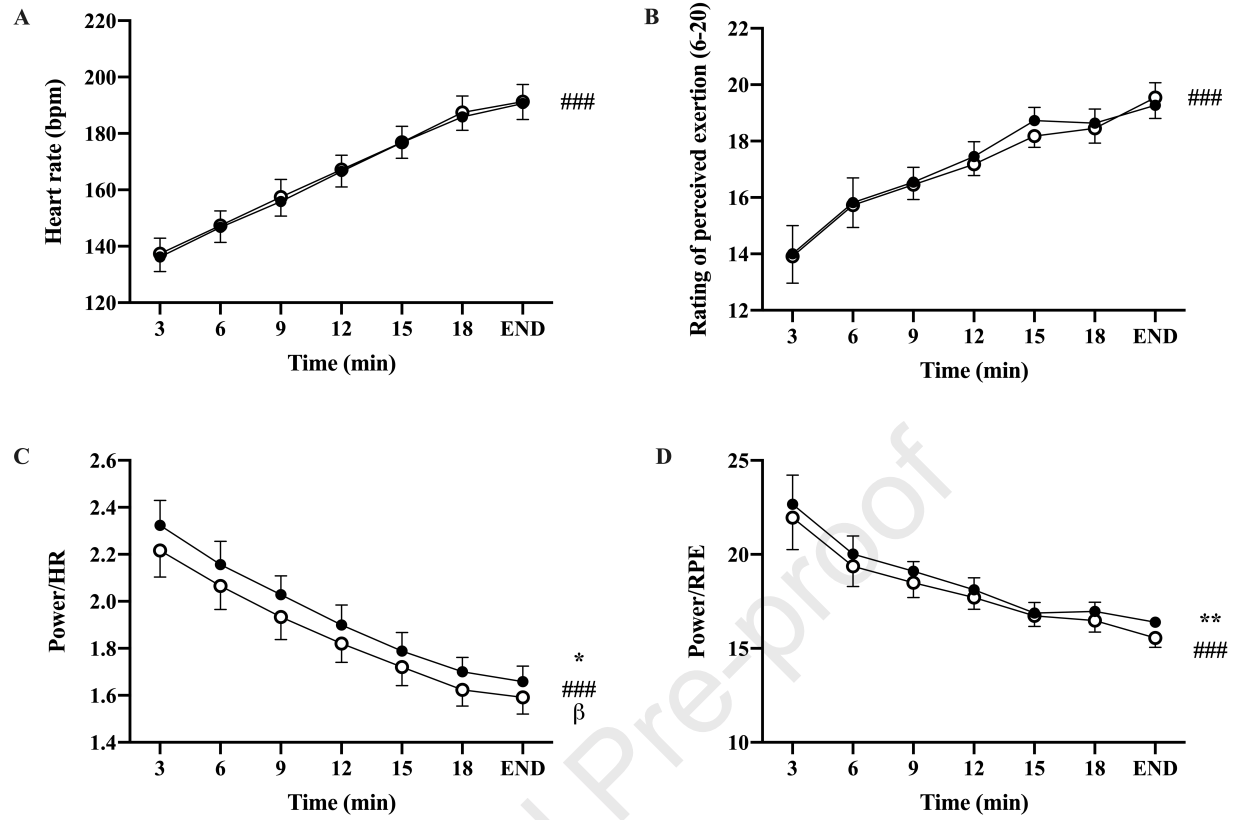
464 **Figure 4.** Effects of HD-tDCS on heart rate (A), rate of perceived exertion (B), power/HR (C),
465 power/RPE (D) under HD-tDCS (black circles) or SHAM (white circles) conditions.

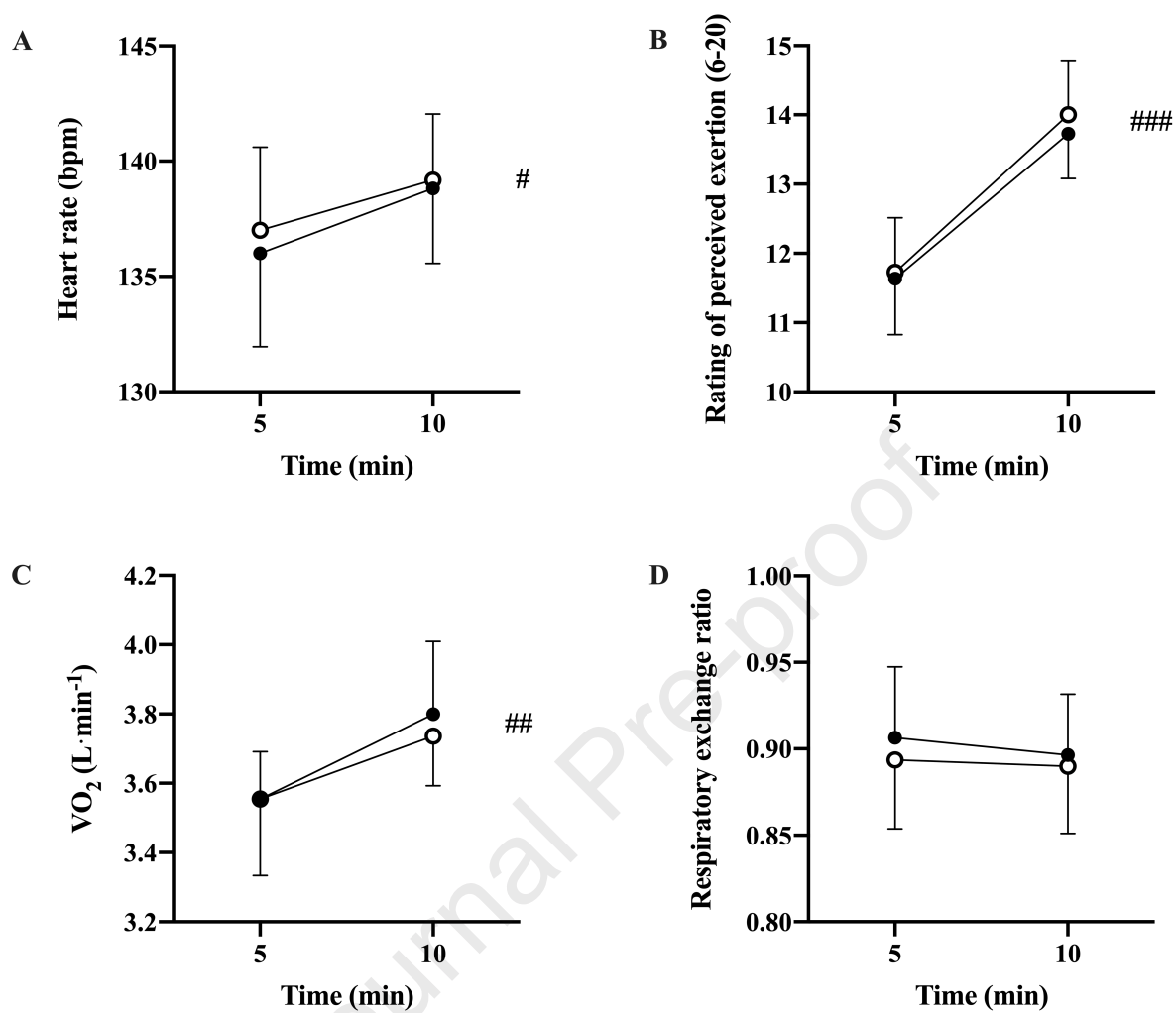
466 **Figure 5.** HR (A), RPE (B), VO_2 (C), RER (D), during the constant load trial under HD-tDCS (black
467 circles) and SHAM (white circles) conditions.











Highlights

- Upregulation of the prefrontal cortex enhanced time trial performance in high-level cyclists with type 1 diabetes.
- Physiological parameters during constant load trial and time trial did not change after HD-tDCS.
- The gain in performance was associated with an unaltered blood glucose response.

Declaration of interests

☒ 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.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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