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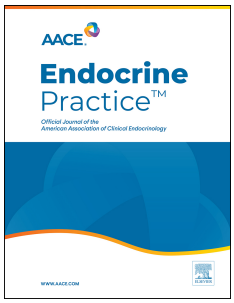

Elite Cyclists with type 1 diabetes show acceptable glycemic excursions during a time-trial performance under high-definition transcranial direct-current stimulation

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Abstract

Background: Patients with type 1 diabetes (T1D) often face glycemic fluctuations during exercise. HD-tDCS, known for enhancing neuromodulation focus, has shown promise in improving endurance. **Objective:** To evaluate the effects of bilateral dorsolateral prefrontal cortex HD-tDCS on glycemic excursions during a time-trial performance in elite cyclists with T1D. **Methods:** In a double-blind, randomized crossover order, nine elite cyclists with T1D (no complications) underwent either HD-tDCS (F3, F4) or control (SHAM) and completed a constant-load trial at 75% of the 2nd ventilatory threshold plus a 15-km cycling time-trial. **Results:** Real-time continuous glucose monitoring revealed similar glycemic variability between the two conditions, showing a significant effect of time but no interaction (stimulation x time) or stimulation effect. **Conclusions:** As glycemic control is crucial for both health and performance, these findings suggest that HD-tDCS could be safely used to enhance performance in athletes with T1D, and potentially in a broader active T1D population.

Keywords: HD-tDCS, endurance exercise, elite cycling, diabetes

Background

Patients with type 1 diabetes mellitus (T1D) are typically challenged by glycemic fluctuations during exercise. There is considerable variability in the glycemic responses to physical activity in real-world scenarios. This variability is influenced by factors such as the type of sport, individual characteristics (participant's fitness level), treatment strategies, and psychosocial factors. Typically, 30-min aerobic exercise of moderate intensity causes drop in blood glucose levels whereas more intensive aerobic exercise/anaerobic exercise may cause hyperglycemia in the fasted state and a rise in lactate [1]. Despite this, there is still limited understanding of how these variables may impact blood glucose responses. Enhancing this knowledge would significantly improve the effectiveness of the diabetes self-management. For instance, post-exercise glucose stabilization is a critical concern for individuals with T1D, emphasizing the need for tight glycemic control for both general health and performance objectives.

We recently applied high-definition transcranial direct current stimulation (HD-tDCS) – a neuromodulation enhancer – both in healthy [2,3] and T1D elite cyclists [4] to improve endurance performance. Transcranial direct current stimulation (tDCS), a noninvasive neuromodulatory method, applies weak direct current to the scalp (usually 1 to 2 mA) through large pads, creating an electric field that modifies cortical excitability by generating excitatory or inhibitory responses [5]. It is widely used in neurological rehabilitation, cognitive enhancement, and psychiatric treatment [6] (Fig. 1). Some research explored the impact of HD-tDCS on motor skill learning showing the enhancement of motor learning processes, which could have implications for sports training. Specific findings related to sports and exercise involved aspects like endurance, strength, or reaction time. tDCS has been claimed to boost several indicators of physical fitness, from sprint and endurance cycling to jumping, pinch force production, and dynamic balance. However, a high individual variability was reported in the effects of tDCS. For instance, anodal tDCS yield inconclusive results on endurance performance [7–10], attributed to electrode type and position. Traditional tDCS, using two large pads, has low focality and associated risks. HD-tDCS, a recent variant, enhances focality with an array of

small circular electrodes (3-5 cm^2), minimizing unintended influences on non-targeted areas [11]. Our recent studies using HD-tDCS over the prefrontal cortex (PFC) have demonstrated improved endurance performance in both long and short time trials (TTs) without altering physiological responses during iso-time TTs (monitored at the same timepoints during a set distance, e.g., 15 km) in elite road cyclists [2,3]. HD-tDCS may also reduce perceived effort during exercise by affecting sensory signals from PFC-connected areas [12]. Improved performance appeared linked to a higher power output to perceptual measures ratio. This suggests that upregulating PFC could enhance endurance performance. Anodal tDCS has shown effects on glucose regulation and metabolic functioning in healthy individuals [13]. Our previous research extended these benefits to a glucose-challenged model, specifically T1D [4], prevalent in high-level cycling [14] and swimming. We previously investigated the effects of HD-tDCS on high-level cyclists with T1D, monitoring both performance and glycemic responses post-stimulation, a novel aspect in empirical verification [4]. Particularly in this study, we sought to evaluate the effects of bilateral dorsolateral PFC HD-tDCS on glycemic excursions during a time-trial performance in elite cyclists with T1D.

Materials and methods

Experimental design

In a double-blind, randomized crossover order, international-level road male cyclists (Table 1) with T1D and no complications underwent either HD-tDCS (F3, F4) or control (SHAM) and completed a cycling constant-load trial (CLT) at 75% of the 2nd ventilatory threshold plus a 15-km cycling time-trial (TT).

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 $mA \cdot cm^{-2}$. At the beginning and end of stimulation, there was a gradual 20-second increase and decrease in current intensity. In the SHAM condition, the electrode placement remained identical, but stimulation was active only during the 30-second onset and offset durations.

The experimental procedures concerning either the cycling performance (including the preparation) or the HD-tDCS (Neuroelectrics, Barcelona, Spain) followed those of a previous study [4]. Throughout the cycling performance, blood glucose concentrations were read out by continuous glucose monitoring (CGM) (G6, Dexcom, San Diego, CA) every three minutes. Every athlete received detailed information about the procedures and associated risks before providing written informed consent to partake in the study. The study design and procedures received approval from the local research ethics committee of the Università degli Studi di Milano (n° 121/19, attachment 5) and adhered to the ethical principles outlined in the World Medical Association Declaration of Helsinki concerning medical research involving human participants. Participants were not engaged in the study's design, implementation, reporting, or dissemination plans.

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 two-way (time; stimulation) repeated-measures analysis of variance was performed to analyze blood glucose concentrations by CGM during CLT and TT. The data analysis was performed using the SPSS software (version 26.0; SPSS Inc, Chicago, IL).

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

Comparing the two conditions by real-time CGM readouts (Figure 1), cyclists showed similar glycemic variability in any part of the experimental session, with a significant effect of time ($F=26.32$; $P<0.0001$), but no interaction stimulation x time ($F=0.08$; $P>0.99$) nor effect of stimulation ($F=0.077$; $P=0.79$) (Fig. 2). Further, CGM data were stable for the 3 days preceding and following the tests.

As elsewhere reported, no differences were registered in both conditions during CLT and TT regarding the physiological parameters (lactate, glycemia, heart rate, and cadence) [4]. Instead, after HD-tDCS, the total time to cover the TT was ~ 4% 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.

Discussion

Managing glucose during exercise becomes challenging due to the unpredictable glycemic responses in type 1 diabetes. Elite athletes with this condition may face even more pronounced difficulties, potentially impacting sports performance. Previously, the main strategies factors affecting the magnitude in glucose drop during exercise were: a) the non-competitiveness of the activity, b) low blood glucose level prior to exercise, and c) baseline glucose level elevated [1]. Before the presented experimental setting, the use of a neuromodulator performance enhancer remained unexplored as to the real-time glycemic responses. Overall, these study-findings provided no evidence of a difference in the glycemic excursions registered in the cyclists whether they underwent the HD-tDCS intervention or the SHAM. One possible explanation for this result resides in the intensity of the performance: although the TT is maximal, its duration was probably insufficiently prolonged for these high-level athletes to elicit a catecholamine-induced increase in the rate of glucose appearance through hepatic glycogenolysis [15]. Instead, following HD-tDCS, cyclists achieved performance both in the time to cover the TT distance and the associated power output. These gains, approximately 4%, are of critical relevance in competition as they could lead to

overcoming opponents with less than 1% difference. It is also plausible that these cyclists did not perceive the experiment as stressful as they might perceive a competitive event (especially of a longer duration). It is known indeed that individual's self-perception of competition stress could affect glycemic variability [1].

In conclusion, upregulation of PFC procured by HD-tDCS could enhance endurance performance in high-level cyclists with T1D, with acceptable glycemic excursions pre, during, and post effort. Given that glycemic control becomes of a paramount interest not only for health but also for performance goals, these findings suggest that HD-tDCS can be safely used as a performance improvement device in athletes with T1D, and possibly in a wider population of active T1D-subjects. In fact, the capability to better understand blood glucose fluctuations during and after exercise represents a significant advancement not confined to the use of HD-tDCS: it broadens our understanding of physical activity safety as an essential part of a healthy lifestyle for individuals living with T1D, as well as for the general population.

Limitations

The primary limitation of this study is the relatively small sample size. This stems from the challenge of recruiting high-level athletes with T1D for multi-day standardized laboratory research projects, given their demanding racing calendars and training schedules. Another limitation is the absence of monitoring brain responses during exercise and post-stimulation using techniques like electroencephalography or near-infrared spectroscopy. This limitation only allows for speculation regarding the physiological mechanisms through which HD-tDCS may have enhanced performance.

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CRediT authorship contribution statement

R.C.: Conceptualization, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Supervision. G.G.: Methodology, Software, Investigation, Data curation. A.M.: Software, Investigation, Data curation, Visualization. L.L: Resources, Writing – review & editing, Supervision. L.F.: Conceptualization, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration.

Declarations 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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256 **Captions**

257

258 **Figure 1.** Depiction summarizing the applications of HD-tDCS.

259 **Figure 2.** Glycemic excursions in the T1D elite cyclists during the experimental session under SHAM

260 (top) or HD-tDCS (bottom) conditions. Bold line = mean value; dotted lines = min & max values.

261 CGM readings were sampled every 3 min.

262

263 **Table 1**. Subjects' characteristics of the nine international-level cyclists with type 1 diabetes mellitus

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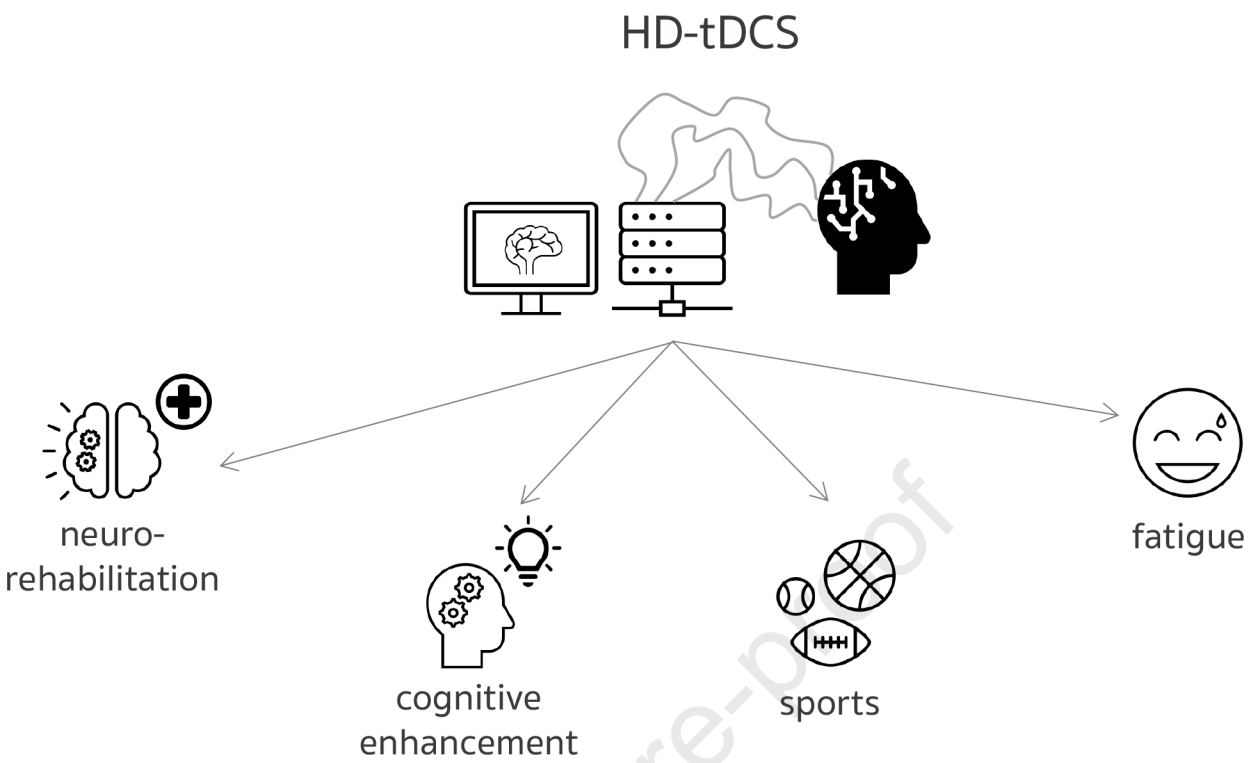
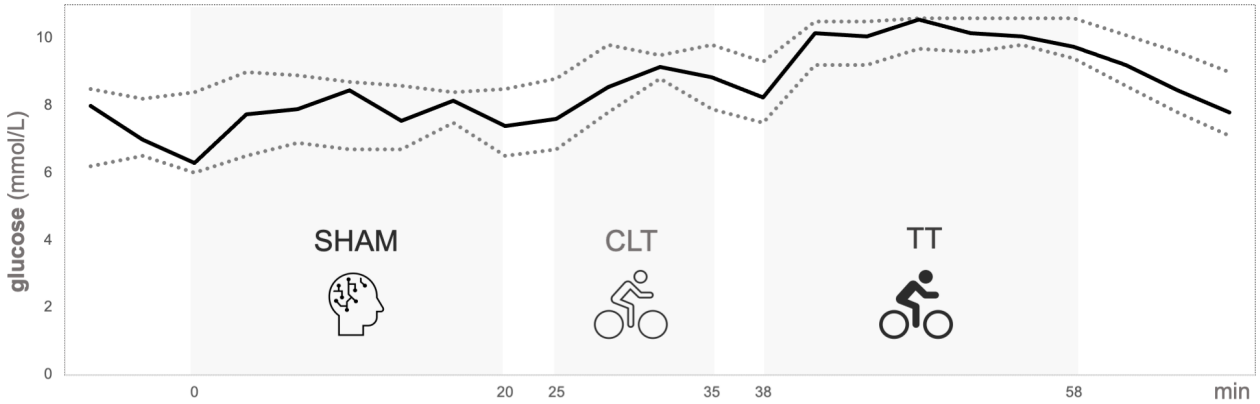
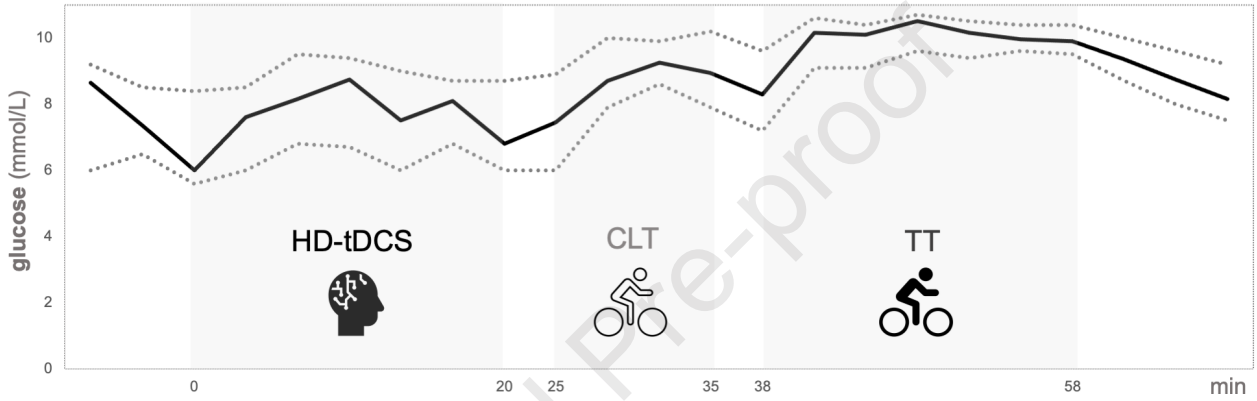
Table 1. Subjects' characteristics of the nine international-level cyclists with type 1 diabetes mellitus

Age (years)	28 ± 3.5
BMI ($kg \cdot m^{-2}$)	20.8 ± 1.3
Diabetes duration (years)	> 10
Insulin doses (minimum to maximum, $IU \cdot day^{-1}$)	23 ± 7 to 25 ± 10
VO_2peak ($mL \cdot min^{-1} \cdot kg^{-1}$)	65.3 ± 1.7
Training frequency ($day \cdot week^{-1}$)	> 5







Declaration of interests

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