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Brain stimulation modulates the autonomic nervous system, rating of perceived exertion and performance during maximal exercise

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ABSTRACT

Background The temporal and insular cortex (TC, IC) have been associated with autonomic nervous system (ANS) control and the awareness of emotional feelings from the body. Evidence shows that the ANS and rating of perceived exertion (RPE) regulate exercise performance. Non-invasive brain stimulation can modulate the cortical area directly beneath the electrode related to ANS and RPE, but it could also affect subcortical areas by connection within the cortico-cortical neural networks. This study evaluated the effects of transcranial direct current stimulation (tDCS) over the TC on the ANS, RPE and performance during a maximal dynamic exercise.

Methods Ten trained cyclists participated in this study (33±9 years; 171.5±5.8 cm; 72.8±9.5 kg; 10–11 training years). After 20-min of receiving either anodal tDCS applied over the left TC (T3) or sham stimulation, subjects completed a maximal incremental cycling exercise test. RPE, heart rate (HR) and R–R intervals (as a measure of ANS function) were recorded continuously throughout the tests. Peak power output (PPO) was recorded at the end of the tests.

Results With anodal tDCS, PPO improved by ~4% (anodal tDCS: 313.2±29.9 vs 301.0±19.8 watts: sham tDCS; p=0.043), parasympathetic vagal withdrawal was delayed (anodal tDCS: 147.5±53.3 vs 125.0±35.4 watts: sham tDCS; p=0.041) and HR was reduced at submaximal workloads. RPE also increased more slowly during exercise following anodal tDCS application, but maximal RPE and HR values were not affected by cortical stimulation.

Conclusions The findings suggest that non-invasive brain stimulation over the TC modulates the ANS activity and the sensory perception of effort and exercise performance, indicating that the brain plays a crucial role in the exercise performance regulation.

INTRODUCTION

'Classical' mechanisms determining exercise tolerance have focused on the cardiovascular, respiratory, metabolic and neuromuscular mechanisms of muscle fatigue[1–3] and produced a brainless model of human exercise performance. 'Contemporary' studies have challenged the current paradigm of exercise physiology by emphasising the crucial role played by the brain in the regulation of exercise performance.[4–9] Studies integrating peripheral and central responses should help to clarify this debate, which is still open.[7 10–13]

Non-invasive brain stimulation has been increasingly used by clinicians and neuroscientists to deliberately alter the status of the human brain. Transcranial direct current stimulation (tDCS) is considered a neuromodulatory intervention that induces excitability changes in the human motor cortex.[14 15] The exposed tissue is polarised, and tDCS modifies spontaneous neuronal excitability and activity by a tonic depolarisation or hyperpolarisation of resting membrane potential.[16] The nature of these modulations depends on stimulation polarity: Anodal stimulation increases excitability, which is decreased by cathodal stimulation.[17] If the stimulation is applied for 9 min or longer, these changes in excitability may persist for an hour or more.[15]

A possible mechanism underlying the tDCS effects might be associated changes in cortical neuronal activity. Pharmacological studies have shown that tDCS-related effects depend on changes of *N*-methyl-D-aspartate (NMDA) receptor-efficacy.[17] Using magnetic resonance spectroscopy, Stagg *et al*[18] demonstrated changes in gamma-aminobutyric acid (GABA) levels after anodal tDCS, suggesting that this stimulation alters both GABAergic inhibition as well as the NMDA receptors. Although tDCS stimulates the cortical area directly beneath the electrode, it could also modulate subcortical structures since there are connections within the cortico-cortical neural networks.[19 20] It has already been shown that tDCS can improve implicit motor learning,[21] motor performance[22 23] and may be valuable in the treatment of depression,[24] of the symptoms of Alzheimer's[25] and Parkinson's disease,[26] chronic pain,[27] stroke[28] and regulation of appetite sensations.[29] Even though tDCS is an attractive, non-invasive neuromodulatory technique for a diverse range of applications, its effect on the dynamic motor performance and tolerance to physical strain has yet to be studied.

It is well known that the autonomic nervous system (ANS) plays a key role in homeostatic control in humans,[30 31] especially when under high metabolic demand as occurs during physical activity.[32 33] There is some evidence that ANS responses are associated with exercise performance in healthy subjects[34] and with the development of fatigue in patients with some specific diseases.[35] Healthy subjects with high aerobic capacity seem to have significantly higher vagal modulation of the heart rate (HR) and, consequently, longer parasympathetic withdrawal as demonstrated by greater heart rate

variability (HRV) when compared to subjects with lower fitness levels.[32] These findings suggest that the ANS may be highly related to the mechanisms underlying physical exercise performance and fatigue.

Assessment of HR and blood pressure (BP) variability[36–38] has implicated the temporal cortex (TC) as one of the cerebral regions involved in the control of cardiac autonomic function. Changes in HR and BP accompany the -ictal discharges in humans with temporal lobe epilepsy.[39] There is also evidence that the TC is involved in motor control perception[40] and is part of a sensory system that detects emotional stimuli.[41 42] In addition, studies suggest that the left cerebral hemisphere is usually associated with pleasant feelings as occurs, for example, when subjects either see or make a smile,[43] or listen to happy voices,[44] or hear pleasant music.[45] On the other hand, negative perceptions, such as heat-related pain sensation,[46 47] subjective cooling[48] and elevated perceived exertion during dynamic cycling exercise,[49] are more usually associated with right hemisphere function.

The insular cortex (IC) has been implicated in the control of cardiac autonomic function in humans and animals.[50–52] In humans, right anterior insular stimulation increased sympathetic cardiovascular responses, whereas left insular stimulation reduced parasympathetic cardiovascular effects.[50] Additionally, there is evidence that the IC is primarily responsible for the awareness of several subjective feelings from the body.[53 54] For example, activation of the right anterior IC is associated with heat-related pain sensation,[46 47 55] subjective cooling[48] and perceived exertion during dynamic cycling exercise.[49] On the other hand, activation of the left AIC was reported in mothers viewing photos of their own child[56]; in subjects who were either seeing or making a smile[43]; listening to happy voices[44] or hearing pleasant music.[45] In summary, the left anterior IC is activated mainly by positive and affiliated emotional feelings, while stimuli that activate the right IC are generally evoked by the body in response to negative and unpleasant sensations.

We have recently shown that anodal tDCS over the TC is able to modulate the ANS in athletes at rest by increasing the parasympathetic activity, as shown by the HRV responses.[57] However, the related effects during a highly demanding cardiovascular exercise, such as a maximal cycling test to exhaustion, have not been described. Since the TC can be associated with both autonomic nervous control[37 58 59] and emotional feelings[41 42] we hypothesise that anodal tDCS over the left TC immediately prior to maximal exercise might enhance parasympathetic activity, increase tolerance to physical strain by decreasing the rating of perceived exertion (RPE) and improve exercise performance. Hence, the purposes of the present study were to verify the effects of a neuromodulation tool (anodal tDCS) on exercise performance, HR, HRV and RPE during an incremental exercise test performed until exhaustion by trained cyclists.

METHODS

Subjects

Ten male national-level road cyclists with 10–11 years of training experience volunteered to participate in this study (33±9 years; 171.5±5.8 cm; 72.8±9.5 kg). Each participant was informed of the procedures and risks before giving written informed consent to participate in the study. In addition, the volunteers were instructed to refrain from vigorous activities and the ingestion of beverages containing caffeine and alcohol or of using tobacco for 24 h prior to each test. This study was approved by the local Institutional Research Ethics Committee.

Experimental design

After arriving at the laboratory, subjects first rested for 15 min before receiving either of the experimental conditions—anodal tDCS or sham (see tDCS procedures)—for 20 min. They then performed the maximal incremental exercise test. HR and HRV were recorded continuously throughout the experiment. Both test conditions were completed at the same time of the day and in a counterbalanced randomised order with a minimal 48 h interval between trials. From the data collected during the incremental test, SD1 using Poincaré plots were calculated every minute and HRV 3 ms threshold (HRV_{TH}) was determined.[60] The evaluators and cyclists were blinded to the test conditions. The cyclists received strong verbal encouragement from the same researcher during all tests in order to achieve the highest possible performance.

tDCS procedures

The direct electric current was applied through a pair of sponges humidified with saline solution (150 mMols of NaCl diluted in water Milli-Q) on the electrodes (35 cm2).[14] The electrodes (anode and cathode) were connected to a continuous electric stimulator, with three energy batteries (9 V) connected in parallel. The maximum energy output was 10 mA and was controlled by a professional digital multimeter (DT832, WeiHua Electronic Co., Ltd, China) with a standard error of ±1.5%.

For anodal polarity stimulation over the left TC, the anodal electrode was placed over the scalp on the T3 area located at 40% of the distance on the left from the Cz point, according to the international standards for EEG 10–20 system. The cathode electrode was placed over the contralateral supraorbital area (Fp2). Thereafter, a constant electric current of 2 mA was applied for 20 min. For the sham condition, the electrodes were placed at the same positions as for the anodal tDCS. However, the stimulator was turned off after 30 s of stimulation, according to the methods of Gandiga *et al*.[61] As a result, the cyclists reported the same sensory feelings from the beginning of the real tDCS conditions, specifically itching and tingling feelings on the scalp for the first few seconds of tDCS, but not thereafter, whether or not the stimulation was continued or stopped. This procedure ensured that subjects remained 'blinded' to the condition they had received, since no sensory feelings were reported from any subjects after the initial 30 s period during either condition. Additionally, we asked the cyclists if they could discern any difference between conditions, but none could.

High-resolution computational model

Using a previously developed finite element (FE) model,[62 63] we analysed the effect of our electrode montage on the current flow in the brain, taking into consideration the electrical properties of the cortical and subcortical structures. The human head model was derived from a high spatial resolution (1 mm^3) 3 T MRI of a healthy male adult subject, and segmented into compartments representing the scalp, skull, cerebrospinal fluid, eye region, muscle, grey matter, white matter and air. Sub-cortical and brain stem structures including the insula, cingulate, thalamus, midbrain, pons and medulla oblongata were also segmented (Custom Segmentation, Soterix Medical, New York, New York, USA). Sponge-based electrode stimulation pads as used experimentally were imported as computer-aided design models and placed onto the segmented head to mimic the experimental montage: from the segmented data, volumetric mesh was generated and exported to an FE solver (COMSOL Multiphysics 3.5a, COMSOL Inc., Massachusetts, USA). The

following isotropic electrical conductivities (in S/m) were assigned: scalp: 0.465; skull: 0.01; cerebrospinal fluid: 1.65; eye region: 0.4; muscle: 0.334; grey matter: 0.276; white matter: 0.126; air: 1e-15; synthetic region: 0.17; sponge: 1.4; electrode: 5.8e7. The cingulate cortex, insula and the thalamus were assigned the grey matter conductivity while the midbrain, pons and the medulla oblongata were assigned the white matter conductivity. The Laplace equation was solved, and current density corresponding to 2 mA total current was applied. Induced cortical surface electric field magnitude was determined and plotted across the cortex and insula.

Maximal incremental exercise test

The maximal incremental exercise test began at an initial workload of 15 W with increments of 25 W/min until the subjects voluntarily terminated the test or were unable to sustain the cadence (80 rpm) for longer than 5 s. All tests were performed on an electronic braked cycle ergometer (ERGO-FIT model 167 cycle, Pirmansens, Germany) with similar riding position (saddle and handlebar height and position), and the cadence was kept at 80 rpm. The peak power output (PPO) was defined as the highest intensity sustained by the cyclist on the cycle ergometer for longer than 1 min.

HR and HRV recordings

The HR and HRV were recorded by an HR monitor (S810i, PolarTM, Finland) with an acquisition rate set at 1000 Hz. The R–R interval data were downloaded by Polar Precision Performance Software (Polar, Finland). The SD1 was calculated using Poincaré plots for every minute by Kubios HRV software (Kuopio, Finland). The HRV_{TH} was considered as the first workload during the maximal incremental exercise test, in which SD1 was less than 3 ms.[60]

RPE responses

RPE was defined as the subjective intensity of effort, strain, discomfort or fatigue that was felt during exercise.[64] The Borg 6-20 RPE scale was used to estimate whole-body perceived exertion during exercise. RPE anchoring was: 'number 7 represents unloaded cycling while number 19 indicates an exertion similar to exhaustive cycling'.[65] The RPE scale was displayed in front of the participants during the tests and instructions about reporting their perceived exertion were given before each test in both conditions. Participants were asked to accurately report the RPE at the end of each minute of the tests.

Statistics

All analyses were performed using the SPSS software (V.19.0, Chicago, USA). Data are reported as means and SD. The distribution of the data was analysed by the Shapiro–Wilk test, and the results showed a normal Gaussian distribution. Mauchly's test of sphericity was used to test this assumption, and a Greenshouse–Geisser was used when necessary. A two-way (RPE and HR measured at different moments during incremental test and stimulation procedure) analysis of variance with repeated measures was applied. Bonferroni's multiple comparisons test was used to check where were the differences previously detected by the analysis of variance. A paired Student's *t*-test was used to compare PPO, HRV_{TH} and TE in anodal tDCS and sham conditions.

RESULTS

Table 1 lists the power outputs corresponding to HRV_{TH} and the PPO as well as the TE during the maximal incremental tests for the anodal and sham conditions. HRV_{TH}, PPO and TE were all significantly higher for anodal tDCS compared to the sham condition.

Table 1 Power output (W) at the heart rate variability threshold (HRV_{THR}), peak power output (PPO) and time to exhaustion (TE) during incremental maximal cyclist test with anodal or sham transcranial direct current stimulation (tDCS)

	Anodal tDCS	SHAM	Degrees of freedom	t	p Value
PPO (W)	313.2±29.9	301.0±19.8	9	−2.358	0.043
TE (s)	751.4±71.5	723.7±45.0	9	−2.261	0.050
HRV_{TH} (W)	147.5±53.3	125.0±35.4	9	−2.377	0.041

The calculated SD1 using Poincaré plots for every minute during the maximal incremental test for anodal or sham tDCS, as well as the HRV_{TH}, is presented in figure 1.

The HR during exercise in both tDCS conditions is shown in figure 2. There was an interaction effect between the stimulation condition and time of measurement for HR ($F_{(10,90)}=3.60$; $p=0.00047$). Anodal tDCS produced significantly lower HR during submaximal exercise compared to the sham condition. Differences between experimental conditions occurred at 125 W ($p=0.00053$), 150 W ($p=0.00007$), 175 W ($p=0.00006$), 200 W ($p=0.00007$), 225 W ($p=0.00001$), 250 W ($p=0.00345$) and 275 W ($p=0.04188$).

Figure 3 shows the RPE during maximal incremental exercise in both experimental conditions. The top graph (A) is plotted against power, whereas the bottom figure (B) is against % exercise duration. For RPE plotted against power, there was an interaction effect between stimulation conditions and time of measurement ($F_{(10,90)}=5.43$; $p=0.00000$). RPEs at 50 W ($p=0.01774$), 75 W ($p=0.00000$), 100 W ($p=0.00003$), 125 W ($p=0.00000$), 150 W ($p=0.00000$) and 175 W ($p=0.00003$) of anodal stimulation were lower than during the sham condition. The maximal RPE was not different across the conditions, and nor were the RPE values when plotted against % exercise duration ($F_{(3,27)}=0.45$; $p=0.71686$).

Consistent with previous modelling studies,[66] tDCS produces current flow in the brain under and between electrodes (figure 4). In addition to diffuse clustering in parietal and frontal regions, our montage resulted in current hotspots in the IC of comparable magnitude to cortical peaks. The relatively

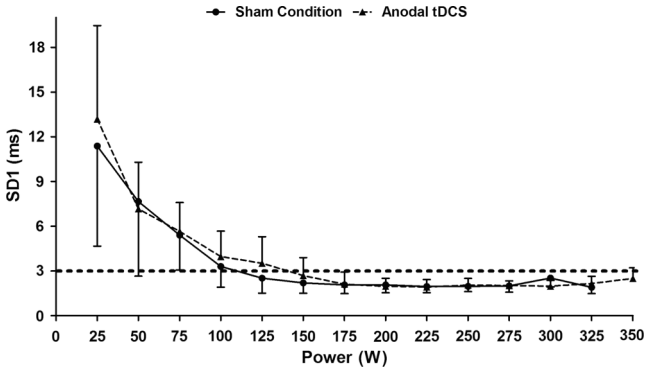

Figure 1 Heart rate variability responses (SD1) and respective heart rate variability threshold during the maximal incremental cycling test for the anodal transcranial direct current stimulation and sham conditions. The dotted line represents the 3 ms of heart rate variability threshold.

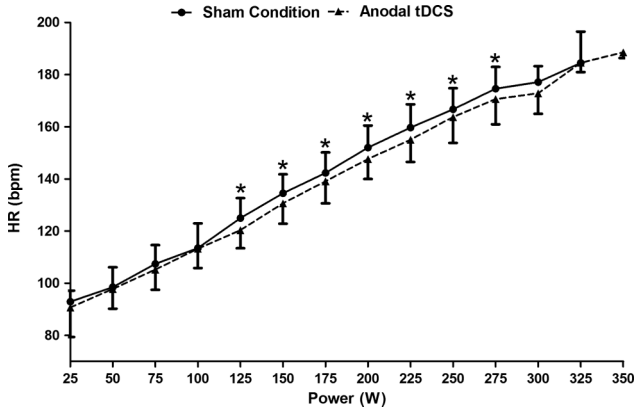

Figure 2 Heart rates at the different power outputs during the maximal incremental cycling test with either anodal or sham transcranial direct current stimulation. *p<0.05.

high current density in this deeper structure represents the combination of the electrode montage and neuroanatomy where highly conductive cerebrospinal fluid can guide current to adjacent deeper brain regions.

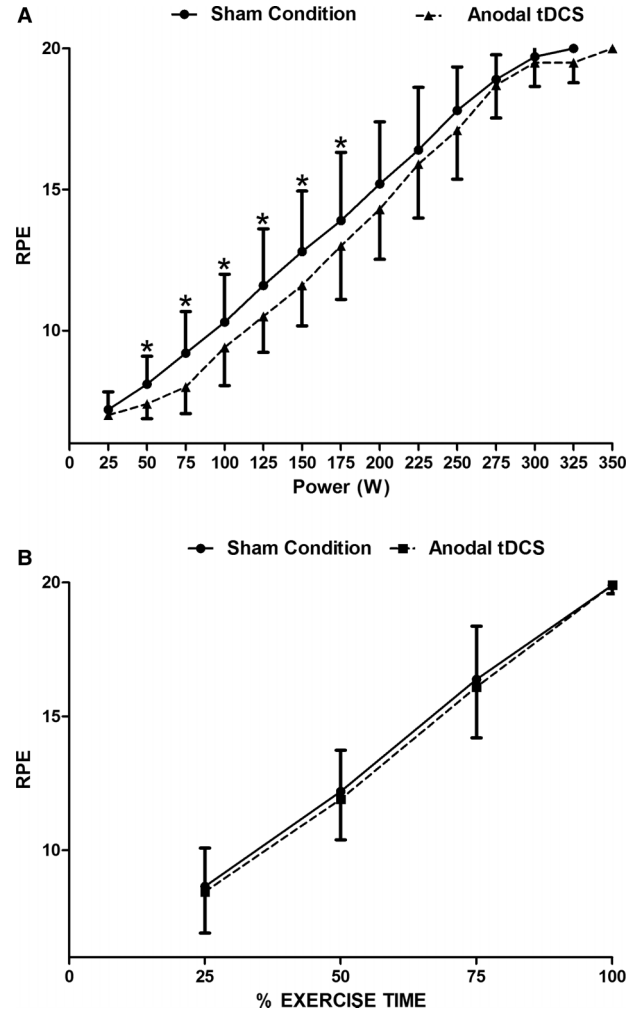

Figure 3 Rating of perceived exertion (RPE) during the maximal incremental cycling test in the anodal and sham transcranial direct current stimulation conditions. (A) RPE versus workload. (B) RPE versus %exercise duration. *p<0.05.

DISCUSSION

To the best of our knowledge, this is the first study to show the influence of tDCS on ANS, RPE and performance during a maximal dynamic exercise test. Our main findings indicated that anodal tDCS applied over the left TC of cyclists for 20 min before exercise modulated ANS by delaying vagal withdrawal and improved performance by ~4% during a maximal incremental exercise test. In addition, HR was reduced during the initial submaximal portion of the maximal exercise test. The RPE increased more slowly during exercise that followed anodal tDCS application. However, maximal RPE and HR values were not influenced by cortical stimulation.

Autonomic nervous system

We have recently shown that tDCS applied over T3 targeting the left IC increases the parasympathetic modulation in athletes at rest.[57] The present study extends this finding by showing that the anodal tDCS effect remains during light and moderate exercise, as shown by the delayed vagal withdrawal. Previous research has shown that the TC and IC are associated with autonomic cardiovascular control.[37 38 67–69] Besides the direct effects of anodal tDCS on TC, this stimulation might also have reached subcortical areas, such as the IC located just below the TC as demonstrated in figure 1. Thus, anodal tDCS over the left TC may have increased the parasympathetic modulation and increased the HRV_{TH}. The HRV_{TH} HRV_{TH} is strongly associated with indices of human aerobic capacity.[32] Indeed, the SD1 changes during the incremental exercise measured in the present study were associated with a greater capacity to continue to a higher work rate during maximal exercise.

Additionally, our data found that HR was decreased at submaximal exercise intensities. Since cardiovascular control has a strong feedforward component,[33 70] it can be speculated that the anodal tDCS might have increased the parasympathetic modulation or reduced the sympathetic modulation and, consequently, decreased the HR. Hence, it seems quite likely that anodal tDCS may induce improvements in cardiac autonomic control and cardiac efficiency during aerobic exercise.[71] This possibility certainly invites further study.

Rating of perceived exertion

The present study showed that anodal tDCS reduced the RPE during the initial and submaximal phases of the maximal exercise test. It has been proposed that the RPE is a psychophysiological construct based on peripheral/central and cognitive cues.[64 65 72] tDCS has been shown to provide an analgesic effect when applied over the motor cortex.[27] fMRI studies of the neural mechanisms of pain showed an increased signal in the temporal gyrus.[73] Furthermore, verum acupuncture significantly altered the brain response to pain stimuli by decreasing the activation of the temporal gyrus.[74] In addition, the pain modulation system is influenced by factors such as cognition and emotion,[75 76] which also modulate the ANS activity[77] and can alter the perception of pain. Moreover, there is evidence that the left hemisphere is related more to positive emotional feelings[43–45] and that vagal nerve stimulation induces high levels of pleasant sensations.[67] Thus, since the RPE is also under the influence of cognitive factors,[69] and since tDCS might induce similar effect as vagal nerve stimulation, it follows that tDCS may improve exercise tolerance by lessening the discomfort levels and consequently decreasing the RPE.

The IC acts as the main brain site responsible for the awareness of subjective feelings from the body[53 54] and is related to

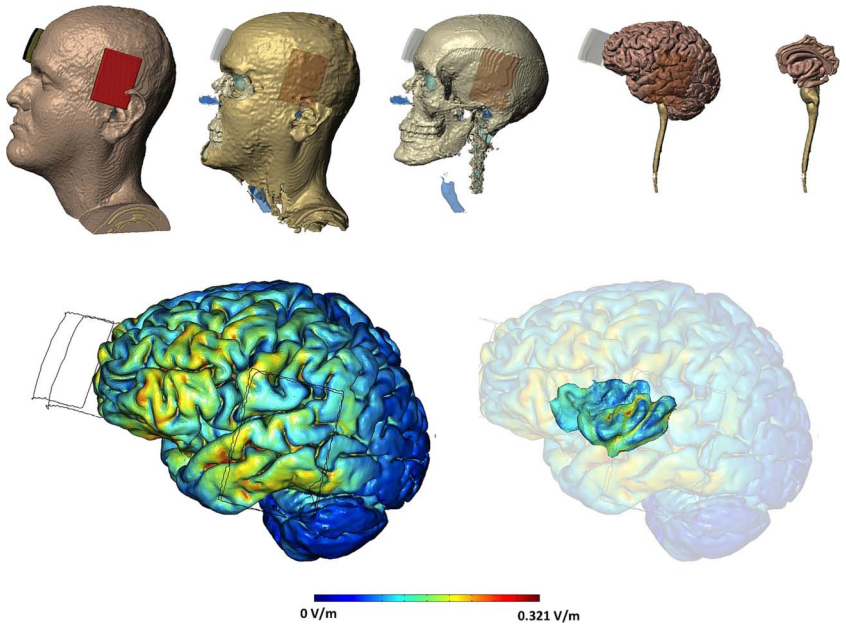

Figure 4 Computational model of brain current flow during transcranial direct current stimulation (tDCS). The model development workflow preserved the high resolution of the MRI scans (1 mm^3). tDCS produces a diffused clustering of electric fields across the parietal and frontal brain regions. Importantly, using this montage, the electric field peak in the insula cortex was comparable to the maximum electric fields produced on the superficial cortex. The false colour map indicates the electric field magnitude.

the RPE during dynamic exercise.[49] The IC has pathways from the premotor and parietal cortex[78] but also receives homeostatic afferent signals, which provide the basis for the insular stream of integration towards the 'sentient self'.[79] Then the ongoing decision process during the exercise exertion ('How do I feel now?'; 'Do I go on?'; 'Do I try harder?'; 'Am I near the end?'), based on 'willpower', must provide the subjective sense of engagement that underlies the feeling of 'effort'.[49 53] Thus, anodal tDCS might also have modulated IC (figure 4) and probably affected the subjective feelings of effort, decreasing the RPE during the submaximal part of the maximal exercise test (figure 3A).

Also, experiments that have induced muscle pain produce an increase in neural activity within widespread regions of both the insular and cingulate cortices.[80] Furthermore, the IC is involved not only in pain processing but also in the evaluation of other homeostatic processes.[81] Under adverse conditions, the rate at which the RPE increases during exercise can be elevated by previous strenuous exercise,[82] by hot environment[83] and by reduced muscle glycogen stores.[84] However, in these studies when the RPE slopes were plotted as a function of the percentage of exercise duration, the differences disappeared, as also shown in our data between anodal tDCS and sham conditions (figure 3B). Noakes and colleagues[13 85] suggest that the teleoanticipation phenomenon would explain this response. This idea was first suggested by Ulmer[86] who associated this concept to the existence of an extracellular controller of the sustainable metabolic rate during exercise. Therefore, our findings might indicate the roles of the TC and the IC in integrating the homeostatic and emotional tolerance control for more demanding maximal exercise performance.

Exercise performance

Our findings indicated that anodal tDCS applied over the left TC before exercise modulated improved performance by ~4% during a maximal dynamic exercise (incremental exercise test). We speculated that anodal tDCS have modulated TC and probably the IC. Thus, affected by the subjective feelings of effort, decreasing the RPE during the submaximal intensities improved the performance in maximal exercise test. Studies investigating the neural activity during a maximal 2 min handgrip contraction reported that the activity of brain structures such as the IC and cingulate cortex can be associated with the integration of inhibitory influences arising from group III and IV muscle afferents.[87] Hilty and colleagues[88] have shown that, during an isometric muscle fatiguing handgrip contraction until exhaustion, the IC mediated the task failure, probably alerting the organism of impending homeostatic imbalance.

Cogiamanian and colleagues[22] applied anodal tDCS over the motor cortex and improved the performance of a submaximal isometric motor task at 35% of the maximum voluntary contraction. It has been suggested that these results could be due to an increase in cortical excitability. Since the present study evaluated tDCS during a more demanding activity, we propose that the enhancement in the performance could be related to a different mechanism, in which the delayed vagal withdrawal or sympathetic activity attenuation shown by the reduced HR could play an important role in the homeostatic regulation. Even though a different brain region than the motor cortex was targeted in the present study (ie, T3 and IC), the tDCS was effective in modulating dynamic exercise performance.

In summary, together with the evidences provided by Cogiamaniam, our data indicate the role of the brain in the regulation of exercise. Although there is still a debate about 'peripheral' and 'central' mechanisms determining exercise tolerance,[7 10–13] the brainless model of human exercise physiology, solely, may not explain exercise performance.

Electrode montage

The selection of electrode montage (tDCS dose) in tDCS governs the underlying brain current flow; computational models of current flow are a standard tool in the analysis and optimisation of resultant brain current flow.[66] Although the focality of tDCS is limited by the electrode dimensions and current flow physics (anatomy and tissue resistivity), the tDCS montage used in the present study was selected to optimise current flow to the IC. While influence from current flow in collateral brain regions cannot be ruled out, the outcomes of the present study are consistent with our hypothesis and predictions of current flow in IC.

With regard to the electrodes montage used in this study (bi-cephalic), the 'active/stimulating' electrode was placed over T3 and the 'reference' electrode over the contralateral orbita,[14] both of which receive similar currents. This is a functional definition that does not imply that the 'reference' electrode is physiologically inert. It is possible that the cephalic reference electrode might also have modulated the brain regions involved in the cortical cardiovascular regulation and decision making,[89] such as the prefrontal cortex,[90] to tolerate high levels of effort. Additionally, frontal lobe afferents to TC come from the orbital cortex,[78] which may also have been influenced the 'reference' electrode, accounting for additional cardiac autonomic and RPE modulation.

Limitations

The present results are the first to present the potential effects of tDCS as a non-invasive and ergogenic method to enhance dynamic exercise performance. However, some limitations of the present study must be acknowledged. The use of bipolar electrodes and the assessment of physiological responses (such as muscle activity, cerebral oxygenation, and pulmonary oxygen consumption) could have helped to better describe the mechanisms of action of tDCS on exercise performance.

CONCLUSIONS

In conclusion, non-invasive brain stimulation applied over the TC induces electrical fields to IC and modulates the ANS activity and RPE during submaximal exercise. It also improves the maximal exercise performance. This study indicates how the brain plays a crucial role in the exercise performance regulation by integrating physiological and psychological cues.

What this study adds

- Novel way to improve maximal exercise performance using a non-invasive brain stimulation technique.
- Brain stimulation modulates the autonomic nervous system and the sensory perception of effort.
- Brainless model of human exercise physiology, solely, cannot explain the exercise performance.

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Contributors AHO and EBF contributed to the conception and study design, analysis and interpretation of data, as well as the writing and review of this manuscript. RAM contributed to the acquisition and analysis of data, and writing. TD, LLM, MB, ESC and PTVF contributed to the interpretation of data and revised it critically for important intellectual content.

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Competing interests None.

Patient consent Obtained.

Ethics approval The National Commission of Research Ethics approved this study.

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