Original Article

Effects of transcranial continuous current stimulation (tDCS) associated with aerobic exercise in the treatment of food compulsion: A randomized clinical trial

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ABSTRACT

Introduction: Binge eating disorder (BED) is closely associated with obesity, characterized by the repeated consumption of large amounts of food accompanied by a feeling of loss of control during the episode of binge eating. Existing treatments are moderately effective with high rates of recurrence; thus, physical exercise and neuromodulation techniques have emerged with positive potential associated with self-control in reward brain regions. Objective: To investigate whether 20 sessions of transcranial direct current (tDCS) stimulation alone or combined with aerobic exercise (AE) could reduce food consumption and the perception of hunger and satiety in adult individuals with BED. Methods: Adult individuals with BED were included in a randomized, double-blind study. Participants received 20 sessions according to random randomization (1) active tDCS, (2) placebo and AE tDCS or (3) active tDCS and AE, simultaneously with videos of foods that cause fissures, such as sweets and fast foods. tDCS was applied at 2mA / 20 min, with the anode over the right dorsolateral prefrontal cortex and the cathode over the contralateral supraorbital region (Soterix Medical®). The AE was performed on a treadmill after tDCS, at an intensity of 60-65% of HRmax, repeating the evaluations at the end. Primary outcomes included measures of food intake and perceptions of hunger, satiety and desire. Secondary outcomes were assessed through body composition, biochemical markers (lipid, glycaemic and leptin profile) and maximum oxygen consumption. Results: The tDCS group had lower values of triglycerides and lean mass compared to the other groups. However, in relation to food intake, hunger, satiety throughout the day, and uncontrollable desire to eat, there was no difference between the groups. Conclusions: tDCS alone was able to improve more clinical outcomes such as adipose mass and triglycerides. To our knowledge, to date this is the first study to demonstrate that the association of tDCS with aerobic exercise can improve the symptoms of binge eating in the investigated population. Test record: ReBEC identifier RBR-3d8fd2.

Keywords: Sport medicine, Health, Transcranial direct current stimulation, tDCS, Exercise, Binge eating.

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INTRODUCTION

Binge Eating Disorder (BED) is classified as an Autonomous Eating Disorder (DSM-5) and is characterized by repeated consumption of exceptionally large amounts of food accompanied by a feeling of loss of control during the episode of binge eating (Sena, 2014). This disease is of particular interest due to its frequency in primary care, its link with obesity and its medical and psychiatric comorbidities, leading to a high socioeconomic impact due to the reduction in quality of life and increased use of health services (Higuera-Hernández et al, 2018, Solmi et al, 2018). Its prevalence in the general population is around 1.4%, however this estimate increases substantially among obese individuals without marked gender differences (Burrows et al, 2017). The prevalence is likely to increase, due to the increasing incidence of obesity as well as eating disorders worldwide (Amianto et al, 2015).

Deficiencies in inhibitory control have been considered a transdiagnostic mechanism of maintenance in a variety of clinical conditions, including obesity or BED (Siddiqui et al, 2008, Jáuregui-Lobera and Martínez-Quiñones, 2018). Cognitive control functions allow adaptive behaviour in the context of complex environments and are supported by prefrontal brain networks that can guide attention and influence neural and motor processes, including inhibitory control. This is an important component of cognitive control and refers to the ability to interrupt motor actions already initiated or planned (Siddiqui et al, 2008, Jáuregui-Lobera and Martínez-Quiñones, 2018).

In order to improve cognitive control in several contexts, transcranial direct current stimulation (tDCS) was proposed by directing a weak direct current through the cortical tissue through electrodes on the scalp, where the spontaneous triggering activity caused by a cognitive process may be slightly increased or attenuated, depending on the target brain region and the direct current flow (Wiegand et al, 2019). The positioning of the electrodes is considered an important determinant of the effectiveness of stimulation (Chen et al, 2019). For this protocol, the choice of anodic stimulation in the right CPFDL and cathodic stimulation in the left was based on previous studies that found a significant effect in reducing food intake and the desire for food associated with this position, both in healthy individuals and in individuals with overweight or obese (Fregni et al, 2008). Currently, tDCS has shown promising results as an alternative for the regulation of several clinical conditions, including acting on affective and appetite self-regulation. Therefore, this technique may be a possible approach to regulate food intake in patients with binge eating.

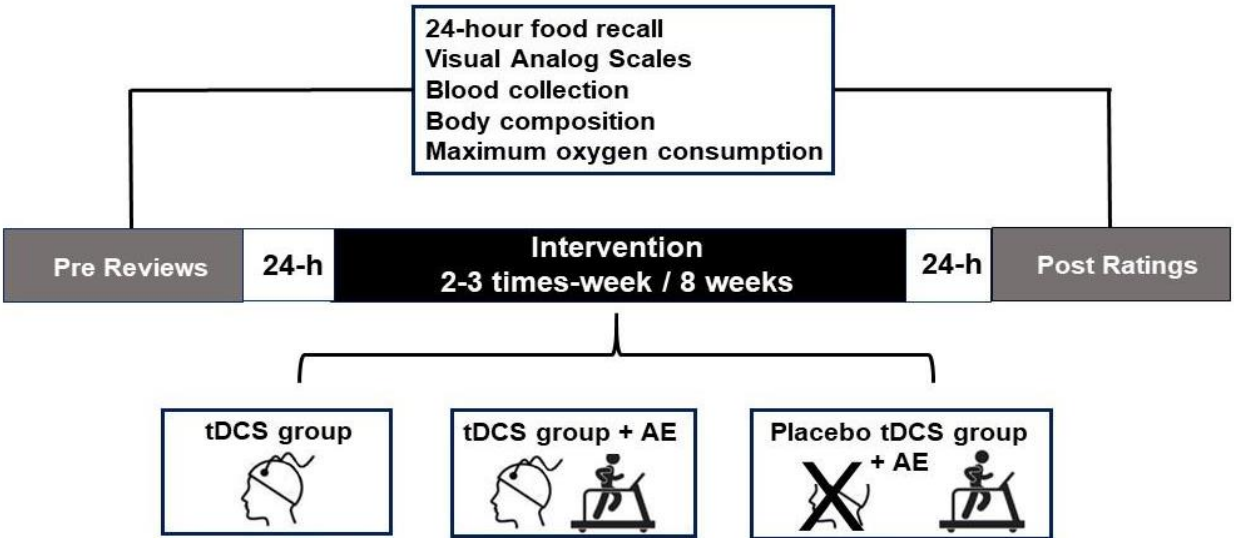
On the other hand, aerobic exercise is related to the improvement of eating habits due to the suppression of hormones linked to satiety, regulating binge eating (Mathisen et al, 2020). In this sense, a reduction in plasma leptin levels is observed after an aerobic exercise program in obese individuals, suggesting a beneficial regulatory effect on appetite (Fedewa et al, 2018). In fact, regular aerobic exercise promotes a protective environment, characterized by a reduction in the chronic inflammatory process of dysfunctional adipose tissue and an improvement in the oxidative capacity of skeletal muscle, reducing in the long run the risk of cardiovascular events (Sloan et al, 2018).

The management of non-pharmacological strategies such as tDCS and aerobic exercise in the treatment of BED, since they act in different mechanisms and do not compete with the combined application of the two therapies, can generate results superior to the isolated use of tDCS. On the other hand, the effect of the combination of the two techniques to date has been investigated only acutely on the sensation of appetite in overweight individuals (Montenegro et al, 2012). Thus, this study aimed to analyse the chronic effects of tDCS associated with aerobic exercise on the control and perception of food intake, satiety, body composition and cardiovascular outcomes in obese adults with BED.

MATERIALS AND METHODS

Experimental study design

The present study is characterized as a randomized, double-blind clinical trial. The study consisted of 20 sessions of active tDCS or placebo in the dorsolateral prefrontal cortex (DLPFC) associated or not with aerobic exercise (AE). Primary outcomes included measures of food intake and perceptions of hunger, satiety and desire. Secondary outcomes were assessed using body composition, biochemical markers (lipid, glycaemic and leptin profiles) and maximum oxygen consumption. All study procedures were approved by the local Research Ethics Committee and the study was registered with RebeC (RBR-3d8fd2). A timeline with the study design is shown in Figure 1.



Note. tDCS -Transcranial direct current stimulation; AE-Aerobic exercise; pl- placebo.

Figure 1. Timeline of the study.

Participants

Participants were recruited through public announcements and asked to complete an electronic questionnaire for initial screening according to the inclusion and exclusion criteria presented in Table 1.

Table 1. Study inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Between 20 and 49 years	Nutritional monitoring or intervention
Grade I overweight or obesity according to WHO criteria (15)	Women intending to become pregnant
	Pregnant or breastfeeding women
Binge eating diagnosis according to DSM-5 criteria (1)	History of severe depression or other serious psychiatric comorbidities
Not having exercised regularly for 6 months	Use of appetite-suppressing drugs
	History of cardiovascular disease
	Renal insufficiency
	Diabetes mellitus
	Inability to exercise

Note. DSM-5 - Diagnostic and Statistical Manual of Mental Disorders); WHO - World Health Organization.

Screening, randomization and general procedures

Evaluation procedures

Participants who met the inclusion criteria in the screening were invited to perform the initial assessment, where they signed the informed consent form. For the initial evaluation, they were instructed to perform an eight-hour fast and to prepare for the analysis of body composition, such as suspending calcium medications 24 hours before and not undergoing physical training on the day of the evaluation. Initial assessments included: blood collection, body composition assessment (Dual-Energy X-ray Absorptiometry-DXA), maximum oxygen consumption test (VO_{2peak}), food intake through the 24-hour food recall, visual analogue scales to assess hunger and satiety throughout the day, hunger at the time of testing and uncontrollable desire to eat. An independent researcher randomly designated the treatment condition of each subject by drawing envelopes. Thus, participants were randomized into three experimental groups: (1) active tDCS only - tDCS group, (2) active tDCS with AE- tDCS + AE group and (3) placebo tDCS with AE- tDCSpl + AE group. In the tDCS group, the subjects were submitted to 20-minute tDCS sessions. In the tDCS + AE group, the participants were submitted to 20-minute tDCS sessions and then performed an aerobic exercise protocol for another 20 minutes. In the tDCSpl + AE group, the subjects were submitted to 20 minutes of tDCS, but it remained active for 30 seconds and then the current was blocked, and the individuals performed the aerobic exercise protocol for another 20 minutes. For all groups, the intervention lasted 8 weeks with a frequency of twice in the first four weeks and three times in the subsequent weeks, with at least 24-hour interval between sessions, totalling 20 sessions. The study was blinded to participants and evaluators.

Biochemical markers

Venous blood samples were drawn in anticoagulant tubes containing 4 mL EDTA after an overnight fast of at least eight hours. The tubes were centrifuged, and plasma aliquots were frozen at -80ºC for further analysis. Glucose levels (mg / dL), total cholesterol (mg / dL), high-density lipoprotein-HDL (mg / dL), triacylglycerol (mg / dL) and glycated haemoglobin (%) were measured using an automatic analyser (Cobas C111, Roche Diagnostics, Basel, Switzerland), while low-density lipoprotein-LDL was calculated using the Friedewald equation. Plasma levels of insulin (µUI / mL) and leptin (ng / dL) were determined by ELISA, according to the manufacturer's instructions (BosterBio, Pleasanton, USA).

Body composition

Dual Energy Radiological Absorptiometry (DXA) was performed in the initial evaluation on an 8-hour fast. DXA performed cross-sectional analyses of the entire body, at intervals of 1 cm from head to toe, and based on its results, lean mass, adipose mass, body fat percentage and total densitometry - bone mineral density (BMD) could be quantified. For the day of the assessment, the subjects were instructed to wear light clothing, which allows for an adequate scan of body composition. After the exam, the participants received a standard meal before starting the other assessment protocols.

Assessment of food intake, hunger at the time of testing, hunger and satiety throughout the day and uncontrollable desire to eat

Food consumption was assessed by means of a 24-hour recall, with all food consumed in the 24 hours prior to the assessment being recorded, including the type of food and the amount consumed. Food intake was assessed 24 hours before the start of the protocol and 24 hours after the last session of the experimental protocol. The total energy (Kcal) and the composition of macronutrients: carbohydrates, proteins and lipids (g) of the intake were calculated using the Dietbox® program. Hunger and satiety throughout the day and desire were measured twice (pre- and post-interventions) with a subjective visual analogue scale (VAS) that ranged from 0 to 10. Hunger at the time of the test was assessed in the same way, however, on a scale that ranged from 0 to 7.

Maximum oxygen consumption

The participants' VO_{2peak} and maximum heart rate (HRmax) were determined using an incremental exercise test on a treadmill (Inbramed, Porto Alegre / Brazil). The test started with a 5min warm-up (from 3 to 5 km / h, increasing 0.5 km / h each min, up to 5 min), followed by increases of 2% in the inclination every min, maintaining a constant speed of 5 km / h throughout the test. To be considered a maximal stress test, participants should have met at least two of the following criteria: (1) HRmax predicted by age, (2) respiratory exchange ratio (RER) ≥1.1, (3) subjective perception of effort ≥ 17 (Borg scale 6-20), (4) signs of muscle fatigue, such as loss of motor coordination. Ventilatory parameters were measured continuously, breath by breath, using an open circuit spirometry system (Quark CPET, Cosmed Italy) calibrated according to the manufacturer's instructions before each test day. HR was also measured continuously using chest strap telemetry (Polar Electro Oy, Kempele, Finland). VO_{2peak} was identified as the highest VO_2 value in a trend line plotted against time. Participants were verbally encouraged to make the maximum effort during the test (Rodrigues-Krause et al, 2018).

tDCS procedures

Participants were instructed not to eat at least two hours before the intervention, which they hoped to increase the degree of desire during the tDCS session.

tDCS therapy system targeting CPFDL: The transcranial direct current stimulator- tDCS 1x1, model no. 1300A (Soterix Medical®). The direction to the stimulation site was performed from the anode or cathode positioned in area F3 or F4 according to the international electroencephalogram (EEG) system 10-20. This method of locating the CPFDL was previously used in studies with tDCS (Martin et al, 2018). The reference electrode was positioned in the contralateral supraorbital region.

Active tDCS: tDCS was administered at 2mA for 20 minutes, configuring the treatment session.

Placebo tDCS: the placebo system used in this study was that of the equipment itself, in which the sensation of active tDCS is imitated during the initial 30 seconds and subsequently blocked.

Virtual reality environment: using virtual reality glasses (Oculus®), structured exposure of images of food that usually cause cravings (sweet, salty, fatty) was used simultaneously with the tDCS session.

Aerobic exercise protocol

The aerobic exercise was performed on a treadmill (BF 601-Oneal) immediately after each tDCS session for the tDCS + AE group. The training started with five minutes of warm-up at a comfortable speed on the treadmill. Subsequently, aerobic exercise was performed with intensity related to the percentage of VO_{2peak} and monitored throughout the session by a frequency meter and subjective scale of perceived exertion (Borg Scale 6–20) (Howley et al, 1995). In the first four weeks, individuals performed 20 minutes with intensity of 60-65% of HRmax and subjective perception of effort from 12 to 14. In the following four weeks, individuals performed 20 minutes with intensity of 70-75% of HRmax and perception subjective effort from 13 to 15. At the end of each session, five minutes of stretching for the lower limbs were performed.

Sample calculation

The sample size calculation was based on the article by Lapenta et al (2014), which verified the effect of two sessions of tDCS (active or placebo) on calorie intake. The program used for the calculation was G * Power 3.1.9.2®, with $\alpha = 0.05$, $1-\beta = 0.8$ and effect size (f) = 1.0, totalling 30 participants, divided into three groups (10 per group).

Statistical analysis

Due to sample losses, only two individuals completed the intervention protocol in the tDCSpl + AE group. This sample made it impossible to execute any hypothesis test and, therefore, it was excluded from the research, leaving only two groups for the analyses. The verification of the normality of the distribution occurred by the Shapiro-Wilk test considering the data of the initial evaluation of the whole sample, complementarily the test was carried out with the sample divided according to the experimental groups and generated QQ graphs in order to investigate fragile violations of the normality in the groups. The descriptions and test hypotheses followed what was proposed in Field (2009) and Ulbricht, Ripka and Beraldo (2016). Thus, measures of mean ± standard deviation and median (interquartile range) are used. Intergroup comparisons were performed using the independent t test and the Mann-Whitney test. Intergroup comparisons were performed using the dependent t test and the Wilcoxon sign rank test. All tests have their effect size expressed by Pearson's r and their interpretation according to Santo and Daniel (2015). This was obtained through the one proposed by Rosenthal (1991) for the independent and dependent t tests. For the Mann-Whitney test, the equation proposed by Wendt (1972) was used, while the one indicated by Kerby (2014) was used to test the Wilcoxon signal stations. All hypothesis tests were performed using SPSS v.21.0 software, as well as descriptive statistics. Effect sizes were calculated in Microsoft Excel 2010. The level of significance was set at .05.

RESULTS

Characteristics of the participants

At the end of the eight weeks, 16 individuals (93.6% women) completed the 20 intervention sessions in the tDCS (n = 09) and tDCS + AE (n = 07) groups. The sample was aged 35.88 ± 7.99 years, weighed 82.23 ± 10.67 kg and BMI was 30.31 ± 2.43 kg / m².

Food intake

Food intake, according to the 24-hour recall, is shown in Table 2. Significant intra-group reductions were observed for carbohydrates and proteins in the tDCS group and lipids in the tDCS + AE group. Although the total energy reduction in the tDCS + AE group was not significant, it presented a moderate effect size. In intergroup comparisons, no significant differences were observed.

Table 2. Analysis of the chronic effect of interventions on food intake (n = 16).

Variables	Group	Pre	Post	Intergroup comparisons	Intragroup comparisons	
				p-value	*p*-value	Effect size (R)
Energy (Kcal)	tDCS	1776.2±443.6	1411.5±774.5	.70	.10	0.55
	tDCS+AE	1706.3±466.3	1277.5±476.5		.06	0.69
Carbohydrates (g)	tDCS	227.7±62.6	169.8±97.0	.98	.05*	0.63
	tDCS+AE	203.6±48.9	169.0±52.3		.20	0.50
Proteins (g)	tDCS	77.8±25.3	61.5±27.2	1.00	.02*	0.72
	tDCS+AE	77.6±30.1	61.5±37.2		.26	0.45
Lipids (g)	tDCS	61.7±20.1	54.0±35.7	.26	.53	0.23
	tDCS+AE	64.4±27.2	38.2±22.7		.05*	0.71

*Note. tDCS-Transcranial direct current stimulation; AE-Aerobic exercise. *p ≤ .05.*

Table 3. Analysis of the chronic effect of interventions on visual analogue scales of hunger, satiety and uncontrollable desire to eat (n = 16).

Variables	Group	Pre	Post	Intergroup comparisons	Intragroup comparisons	
				p-value	*p*-value	Effect size (R)
Visual analogue scale of hunger and satiety throughout the day						
Upon waking	tDCS	5.0 (1.5-9.0)	9.0 (4.5-9.5)	.38	.13	0.64
	tDCS+AE	5.0 (2.0-5.0)	8.0 (3.0-9.0)		.14	0.73
Before lunch	tDCS	5.0 (2.5-5.5)	5.0 (4.5-7.0)	.63	.12	0.58
	tDCS+AE	2.0 (2.0-3.0)	5.0 (3.0-6.0)		.04*	0.86
3 hours after lunch	tDCS	5.0 (3.5-7,0)	6.0 (5.0-7.5)	.33	.46	0.33
	tDCS+AE	4.0 (2.0-5.0)	7.0 (5.0-9.0)		.03	1.00
Before dinner	tDCS	2.0 (0.5-4.5)	5.0 (4.5-7.0)	.06	.02*	1.00
	tDCS+AE	1.0 (1.0-2.0)	4.0 (3.0-5.0)		.02*	1.00
3 hours after dinner	tDCS	7.0 (3.0-9.0)	8.0 (6.5-9.5)	.55	.05*	0.78
	tDCS+AE	5.0 (2.0-7.0)	9.0 (7.0-9.0)		.03*	1.00
At bedtime	tDCS	7.0 (4.5-9.0)	9.0 (8.0-10.0)	.91	.07	0.72
	tDCS+AE	7.0 (2.0-10.0)	9.0 (8.0-10.0)		.13	0.64
Visual analogue scale for hunger assessment						
At the time of testing	tDCS	2.0 (1.0-4.0)	3.0 (1.0-3.5)	.70	.93	0.04
	tDCS+AE	1.0 (1.0-2.0)	3.0 (1.0-3.0)		.10	1.00
Visual analogue scale of uncontrollable desire to eat						
Candy	tDCS	5.0 (0.0-9.0)	3.0 (0.5-5.0)	.63	.21	0.50
	tDCS+AE	8.0 (5.0-9.0)	3.0 (0.0-7.0)		.14	0.73
Salty	tDCS	8.0 (3.5-10.0)	5.0 (3.0-9.5)	.67	.73	0.14
	tDCS+AE	7.0 (6.0-8.0)	7.0 (5.0-9.,0)		.67	0.18
Tasty	tDCS	9.0 (3.5-10.0)	4.0 (2.5-7.5)	.22	.31	0.43
	tDCS+AE	8.0 (8.0-10.0)	6.0 (5.0-9.0)		.12	0.71
Fatty	tDCS	5.0 (0.5-9.5)	1.0 (0.0-2.5)	.34	.04*	0.86
	tDCS+AE	4.00 (2.0-8.0)	3.0 (0.0-5.0)		.14	0.80

*Note. tDCS-Transcranial direct current stimulation; AE-Aerobic exercise. *p ≤ .05.*

Assessment of hunger and satiety throughout the day

The tDCS group showed a significant increase in satiety only in the moments before dinner and three hours after dinner, while the tDCS + AE group in the moments: before lunch, three hours after lunch, before dinner and three hours after dinner (Table 3). There were no significant intergroup differences.

Assessment of hunger at the time of testing

There were no statistically significant differences in any of the groups (p > .05) (Table 3).

Assessment of uncontrollable desire to eat (desire for food)

There was less of an uncontrollable urge to eat fatty foods only in the tDCS group. Regarding intergroup comparisons, no significant differences were observed (Table 3).

Biochemical analyses

The tDCS group showed a significant reduction in the plasma concentration of HDL-cholesterol and a significant increase in the concentration of insulin, while in the tDCS + AE group, no significant differences

were observed after the intervention (Table 4). In the intergroup comparison, significant differences were observed in the concentration of triglycerides, with the tDCS group showing lower triglyceride values (Table 4).

Table 4. Analysis of the chronic effect of interventions on biochemical markers, body composition and maximum oxygen consumption (n = 16).

Variables	Group	Pre	Post	Intergroup comparisons	Intragroup comparisons	
				p-value	*p*-value	Effect size (R)
Biochemical analyses						
Glucose	tDCS	101.5±11.7	97.2±7.6	.24	.15	0.49
(mg/dL)	tDCS+AE	92.6±5.8	88.5±5.5		.37	0.37
Insulin	tDCS	20.4(17.6-31.2)	34.7(25.0-45.,4)	.27	.03*	0.82
(µUI/mL)	tDCS+AE	23.7(15.3-42.2)	27.6(21.9-31.6)		.87	0.07
Glycated	tDCS	5.9±0.2	5.75±0.22	.46	.27	0.39
haemoglobin (%)	tDCS+AE	5.9±0.2	5.7±0.2		.12	0.60
Total cholesterol	tDCS	175.5±37.7	177.3±36.1	.77	.83	0.08
(mg/dL)	tDCS+AE	197.2±34.1	181.7±17.1		.24	0.47
Triglycerides	tDCS	101.4(49.1-144.1)	84.6(53.2-115.9)	.05	.21	0.47
(mg/dL)	tDCS+AE	116.5(100.9-120.7)	160.1(112.7-176.0)		.31	0.43
LDL-cholesterol	tDCS	95.9±31.7	106.4±33.6	.80	.24	0.41
(mg/dL)	tDCS+AE	112.5±26.3	102.4±23.3		.14	0.57
HDL-cholesterol	tDCS	58.1±9.6	51.5±10.5	.93	.01*	0.81
(mg/dL)	tDCS+AE	47.4±14.0	50.9±15.9		.62	0.21
Leptin	tDCS	20.7±7.8	21.7±9.6	.59	.74	0.12
(ng/mL)	tDCS+AE	28.4±15.0	25.1±15.6		.48	0.29
Body composition						
Body mass	tDCS	78.5±9.4	78.4±7.6	.08	.94	0.03
(Kg)	tDCS+AE	87.0±10.9	86.9±10.2		.83	0.09
BMI	tDCS	29.7±2.6	29.4±2.1	.09	.48	0.26
(Kg/m²)	tDCS+AE	31.2±2.0	31.1±1.6		.87	0.07
Total fat mass	tDCS	43.8(42.8-45.3)	44.2(43.7-44.7)	.52	.44	0.29
(%)	tDCS+AE	44.6(42.7-46.1)	45.0(42.4-45.0)		.74	0.14
Fat mass	tDCS	48.1±5.1	33.8±5.3	.40	.00*	0.99
(Kg)	tDCS+AE	46.4±7.2	36.3±6.4		.03*	0.75
Lean Mass	tDCS	49.7±3.1	41.4±3.7	.02*	.00*	0.84
(Kg)	tDCS+AE	44.5±6.2	49.8±7.3		.20	0.51
Total densitometry	tDCS	1.2±0.1	1.2±0.1	.12	.48	0.25
– BMD (g/cm²)	tDCS+AE	1.3±0.1	1.3±0.1		.94	0.03
Maximum oxygen consumption test						
VO_{2peak}	tDCS	30.5±5.7	33.9±6.0	.87	.04*	0.67
(mL/kg/min)	tDCS+AE	31.5±5.6	33.4±4.8		.40	0.35
Absolute VO_2	tDCS	2380.2±382.1	2527.3±488.4	.08	.06	0.61
(mL/min)	tDCS+AE	2764.0±663.6	3009.7±547.1		.25	0.46
Maximum heart	tDCS	177.1±16.8	183.2±7.4	.47	.22	0.43
Rate (bpm)	tDCS+AE	177.1±14.0	179.1±13.9		.68	0.17

*Note. tDCS-Transcranial direct current stimulation; AE-Aerobic exercise; LDL-cholesterol- Low density lipoproteins; HDL-cholesterol- High density lipoproteins; BMI-Body Mass Index; BMD-Bone mineral density; VO_2peak-Peak oxygen volume; VO_2 absolute-Volume of absolute oxygen. *p ≤ .05.*

Body composition (DXA)

A significant reduction in adipose mass was observed for both groups and a reduction in lean mass only in the tDCS group (Table 4). In the intergroup analysis, significant differences were observed only for lean mass, with the tDCS group showing lower values for this variable.

Maximum oxygen consumption and maximum heart rate (FCM)

VO_{2peak} increased significantly only in the tDCS group, with no significant difference being observed in the intergroup comparison (Table 4). For FCM, no significant intra and intergroup differences were observed.

DISCUSSION

This is the first study to investigated whether tDCS in DLPFC with virtual reality associated with aerobic exercise can reduce food intake and improve symptoms of hunger, satiety and desire for food, in individuals with binge eating. After 20 experimental sessions, it was observed that both intervention protocols (tDCS alone or with exercise) were not able to reduce caloric intake, the same observed in a study conducted by Ljubisavljevic et al (2016).

A recent study showed that obese individuals who received anodic tDCS from the left CPFDL had a tendency to lower caloric intake and weight loss than with cathodic tDCS (Gluck et al, 2015, Heinitz et al, 2017), a protocol similar to that used in our study. On the other hand, in the present study, significant reductions were observed in proteins and carbohydrates consumption of for the tDCS group and of lipids for tDCS + AE, with no intergroup difference. It is known that stimulation of the prefrontal cortex can stimulate dopaminergic pathways by regulating food intake through appetitive motivational processes (Nitsche et al, 2006), thus being able to be related to the reduction in the consumption of two groups of macronutrients in the tDCS group. In a study by Evero et al (2012), magnetic resonance was used to verify the effect of exercise in brain regions related to food reward, activation of DLPFC was not observed during aerobic exercise. The authors suggest that exercise decreases neural activity in regions that are not necessary for maintaining that effort. This may explain why the tDCS + AE group showed a reduction in only one of the macronutrients, while the isolated tDCS reduced consumption by two.

The hunger measured at the test did not show a significant change in both groups, however, the measurements at this moment cannot represent the usual time of greatest hunger of the participants. At the same time, in the uncontrollable urge to eat, a reduction was observed only for fatty foods in the tDCS group. Fregni et al. (2008), also observed a significant reduction in the desire for food using the same positioning of the electrodes adopted in this protocol. Studies show that there may be a hemispheric laterality to the desire for food; and it can be speculated that the effects of left versus right stimulation may be qualitatively different (Goeders, 2002; Wang et al, 2004; Wang et al, 2006). Considering that the right hemisphere can suppress the desire to eat in general (or hunger), the left hemisphere can have a selective effect on the desire for food and decrease the desire for specific foods (Fregni et al, 2008). The tDCS + AE group, on the other hand, may not have improved in this parameter precisely because of the selectivity of activation of the brain regions during exercise, causing brain regions related to the desire for food to be less activated during exercise (Goeders, 2002).

There were no significant intergroup differences in the analysis of satiety throughout the day. However, significant reductions were seen in both groups post-intervention. Although hunger and satiety appear to be regulated by the hippocampus (Davidson et al, 2010), and it has connections with the prefrontal cortex, this area is a deep subcortical structure, and perhaps the tDCS was not able to modulate the neuronal activity of

this area (Lang et al, 2005) or the intensity and duration of the protocol applied in this study was insufficient to modulate it (Montenegro et al, 2012). On the other hand, the evidence that investigates the chronic effects of aerobic exercise on hunger parameters is quite conflicting. Some studies have shown that hunger increases after aerobic training (King et al, 2009; Caudwell et al, 2013; Martins et al, 2010), others have not reported any changes (Martins et al, 2013; Morishima et al 2014; Martins et al, 2007), or have shown a reduction in hunger (Guelfi, Donges and Duffield, 2013). Despite the lack of consensus, it has been suggested that chronic exercise alters the sensitivity of the appetite control system by regulating the urge to eat, causing an increase in satiety (King et al, 2009; Martins et al, 2010). This is corroborated by evidence that suggests that hunger and ad libitum energy intake are reduced after consuming a high, but not low energy density meal, in individuals undergoing a structured physical training program (Martins et al, 2013; Martins et al, 2007). In our study, the little effect of tDCS on regions that regulate satiety associated with the effect that exercise has on this parameter by other physiological routes, may partly explain the best results in the tDCS + AE group for satiety throughout the day.

Regarding biochemical markers, improvements were observed on cardiovascular outcomes in the tDCS group. A preliminary study identified changes in the intestinal microbiome in an overweight individual who underwent multiple sessions of tDCS (Artifon et al, 2020). It is possible that changes in the microbial composition may reduce intestinal permeability and, consequently, systemic inflammation, as well as contribute to the synthesis of neurotransmitters promoted by the intestinal ecosystem, which, in turn, could justify the change in cardiovascular markers and assist in the treatment of obesity and other relevant chronic diseases (Artifon et al, 2020; Peirce and Alviña, 2019). On the other hand, it has been reported that responses to plasma cholesterol are not always achieved with physical training and are especially difficult to demonstrate in previously sedentary women (Artifon et al, 2020), a predominant sample in our study. In addition, it has been observed that the main effect of exercise on plasma cholesterol is an increase in HDL-C as a result of resistance training related to increased activity of lipoprotein lipase (LPL) and triglyceride catabolism. This may justify the fact that we did not observe differences in these individuals, mainly due to the fact that we adopted an aerobic exercise protocol. A meta-analysis (Peirce and Alviña, 2019) demonstrated that long-term simultaneous exercise programs (aerobic and resistance) generate more significant improvements in LDL cholesterol, as well as in total cholesterol. Thus, it is believed that eight weeks of exclusively aerobic exercises were not enough to observe improvements in these markers. These findings suggest that this population requires interventions for longer periods so that significant changes in lipid variables can occur (Peirce and Alviña, 2019; Haskell, 1984).

Likewise, the tDCS group presented a large body mass decrease, which can lead to an insulin / glycemia imbalance, as well as an increased consumption of foods with a high glycaemic index, an uncontrolled factor in our study. In the tDCS + AE group, the effect of insulin-independent exercise on blood glucose favours the maintenance of insulin levels even with weight loss. Many studies have examined changes in two tonic appetite suppressants, leptin and insulin in response to physical training. These generally report reductions in leptin after aerobic and resistance training (Morishima et al, 2014; Guelfi, Donges and Duffield, 2013), while the findings for insulin are more variable, with some studies showing a reduction (Morishima et al, 2014; García-Hermoso et al, 2018) and other studies showing no change (Martins, Truby and Morga, 2007; Guelfi, Donges and Duffield, 2013) after exercise protocol. Studies suggest that leptin is released in the brain at an increased rate in obese humans, in which there is also activation of brain serotonergic and neuropeptide Y mechanisms (Fragala et al, 2014).

In the analysis of body composition, significant reductions were observed in both groups on fat mass. For lean mass, there was a decrease only in the tDCS group. This may have occurred mainly due to the fact that

in the context of weight loss, exercise strategies play a role in maintaining lean mass, even when the strategies used are predominantly aerobic (Rosenkilde et al, 2013). A significant change in VO_{2peak} was observed in the tDCS group. VO_{2peak} is a direct predictor of mortality, proving to be more effective than other risk factors (Swift et al, 2018). The increase in VO_{2peak} in the tDCS group is possibly attributed to the reduction in body mass found in this group (Δ -11%), since it is relativized by the total body mass, which is evidenced when observing that the absolute VO_2 did not present differences. Obesity and the autonomic nervous system are intrinsically related, demonstrating that a 10% increase in body weight is associated with a decline in parasympathetic tone, accompanied by an increase in average heart rate and, conversely, heart rate decreases during the reduction of weight. There is little data on the metabolic and autonomic effects of weight loss on the autonomic nervous system in obese individuals (Ross et al, 2016).

As eating behaviour is an important component that can increase adherence to prescribed diets, we believe that the potential of tDCS and aerobic exercise to modulate eating behaviour can contribute to better adherence to dietary treatment and, therefore, to weight loss and better quality of life. The present study has some limitations, the small sample size may have limited the inference of the data, in addition to the reduced number of experimental sessions associated with the short duration of the exercise protocol, which may have interfered with the observed results. However, the originality of the study and the reliability of the measures carried out in this work add relevant and reliable data to the literature.

CONCLUSION

The results of the present study demonstrate that multiple sessions of tDCS and simultaneous visual stimulation combined with aerobic exercise, reduced food intake and the uncontrollable desire to eat certain food groups, as well as reduced the perception of hunger by increasing satiety. On the other hand, isolated tDCS was able to improve more clinical outcomes such as adipose mass and VO_{2peak}. To our knowledge, to date this is the first study to demonstrate that the association of tDCS with aerobic exercise can improve the symptoms of binge eating in the investigated population.

AUTHOR CONTRIBUTIONS

Milena Artifon - project development and article writing. Gabriel Mayer Tossi - data collection and article writing. Nathália Griebler - data collection and article writing. Pedro Schestatsky - project development and article review. Francesco Boeno - data collection and article writing. Cesar Moritz - data collection and article writing. Juliana Lopes Teodoro - data collection and article writing. Lucas Beraldo - data collection and article writing. Lauren Naomi Adachi - data collection and article review. Álvaro Reischak de Oliveira - project development and article review. Caroline Pietta-Dias - project development, guidance and article review.

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