Prefrontal cortex transcranial direct current stimulation associated with aerobic exercise change aspects of appetite sensation in overweight adults

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Abstract
This study investigated whether transcranial direct current stimulation (tDCS) on dorsolateral prefrontal cortex (DLPFC) isolated or combined with aerobic exercise influenced the desire to eat, hunger, and satiety in overweight subjects. Nine volunteers underwent anodal or sham tDCS (2 mA; 20 min) over DLPFC and isocaloric exercise bouts (70%VO2R; ~200 kcal). The appetite sensations were evaluated by visual analogue scales at four moments: I – Baseline; II – After tDCS; III – Post-Exercise and IV – 30-min Post-Exercise. The tDCS on left DLPFC decreased the desire to eat at baseline (tDCS 26% vs. – 14% Sham). The tDCS associated with exercise had greater suppressing effect in desire to eat compared to either tDCS or exercise alone (DLPFC – 39% vs. – 27% Sham). Moreover, the tDCS associated with exercise decrease hunger (tDCS – 48% vs. 36% Sham) and increased satiety (tDCS 28% vs. 7% Sham) immediately after exercise. The post-exercise 30-min recovery elicited an overall increase in appetite. However the increase in desire to eat and hunger after recovery was lower after tDCS (29% and 13%, respectively) compared to sham stimulation (77% and 113%, respectively). These findings in overweight subjects indicate that the combination of tDCS over DLPFC and aerobic exercise induced greater decrease in appetite sensations compared to anodal tDCS or exercise alone.

Introduction
Obesity is major cardiovascular risk factor for patients with metabolic syndrome (Fontaine, Redden, Wang, Westfall, & Allison, 2003) and has been considered as a global epidemic problem (WHO, 2010). The sedentary lifestyle combined with the increase in food intake, especially high fat, sugar and beverages are in the origin of this phenomenon (Feng, Purser, Zhen, & Duncan, 2011; Wadden, Brownell, & Foster, 2002). Therefore, the process of regulation of food intake in overweight subjects has been widely investigated, especially the mechanism involved in hunger control and satiety signals from peripheral and central pathways (Schwartz, Woods, Porte, Seeley, & Baskin, 2000; Woods, 1991).

Some evidence indicates that the control of food and drug intake are related to hypo- or hyperactivity of the dorsolateral prefrontal cortex (DLPFC) (Boggio, Sultanì, et al., 2008; Uher et al., 2004, 2005) which is associated with decision-making process (Pignatti et al., 2006). It has been shown through functional magnetic resonance imaging (fMRI) that the appetite activates the orbitofrontal and anterior cingulate cortex, and decreased activation of the dorsolateral prefrontal area (Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Uher et al., 2004). In addition, DLPFC has been considered to have a central role in aerobic exercise tolerance (Yanagisawa et al., 2010), with lower cortical activation occurring concomitantly with an impairment in muscular function and fatigue (Rupp & Perrey, 2008).

Transcranial direct current stimulation (tDCS) is a non-invasive method of brain stimulation. This technique uses a weak safety current of 1–2 mA for 3–20 min which may increase (anodal tDCS) or decrease (cathodal tDCS) cortical excitability (Brunoni et al., 2011; Nitsche & Paulus, 2000). It has been demonstrated that high frequency (10 Hz) repetitive transcranial magnetic stimulation (rTMS) and anodal tDCS on the DLPFC decreases the food cravings in healthy women (Fregni et al., 2008; Goldman et al., 2011; Uher et al., 2005). Fregni et al. (2008) and Goldman et al. (2011) applied bilateral DLPFC stimulation and reported that there might be a hemispheric laterality for the appetite sensation and the effects
on the left vs. right cerebral hemisphere could be qualitatively different. Despite of this possibility, the influence of tDCS on the hunger or satiety sensations still needs to be addressed.

On the other hand, several studies have focused on evaluating the effect of physical activity on the body weight management, obtaining positive results for both improvement in energy balance (Saris, 1993; Schoeller, Shay, & Kushner, 1997) and appetite regulation (Cooper et al., 2011; Mayer, Roy, & Mitra, 1956). Aerobic exercise has shown to improve the process of neuroplasticity, optimizing the synaptic transmission and increasing the brain sensitivity to neuropeptides related to satiety (i.e. PYY and leptin) (Ekkekakis, 2009; Ropelle et al., 2010). However, no study so far has verified the acute effects of physical exercise and tDCS used concomitantly in order to modulate appetite sensations. Thus, understanding this possible influence on overweight individuals might indicate a new method to control food intake and body composition management.

The present study aimed to verify whether the stimulation of the prefrontal cortex with tDCS, associated with exercise practice modulates the hunger, satiety and desire to eat sensations in overweight subjects. We hypothesized that pre- and post-stimulation ratings of hunger, satiety and desire to eat would be influenced by unilateral tDCS. Moreover, aerobic exercise might increase cortical excitability in DLPFC and associated to tDCS should induce a greater decrease in hunger and desire to eat, consequently increasing the satiety sensation in comparison to the sham stimulation.

Methods

Subjects

Nine overweight subjects (5 men and 4 women) volunteered to participate in this study [Median (range); age = 24 (20–32) years; weight = 84.7 (74.6–137.7) kg; height = 173.9 (163.5–184.5) cm; body mass index = 28.2 (25.2–43.5) kg m²]. The women were not taking contraceptive drugs and were not pregnant or menstruating. Exclusion criteria included clinical diagnosis of cardiovascular disease, the use of any medication with potential cardiovascular influence, pregnancy, history of eating disorders, depression and implantation of metal parts. In addition, the participants were fully informed about the procedures and potential risks before giving written consent to take part in the study. This study was approved by the local Institutional Research Ethics Committee.

Experimental design

Each subject visited the laboratory three times on three separate days. Subjects went through two counterbalanced and randomized types (anodal or sham) of unilateral stimulation with tDCS over DLPFC associated with isocaloric exercise bouts. On the first visit, resting VO₂ was determined, anthropometric measurements were taken and familiarization with the electrical stimulation device to minimize errors or discomfort was performed. The subjects were blinded about the stimulation condition. After this a maximal cardiopulmonary exercise test for determining the maximal values of heart rate and VO₂ was performed. The volunteers were instructed to refrain from vigorous activities, tobacco, and ingestion of beverages containing caffeine and alcohol for 24 h prior to each test. A 24-h dietary recall was used to assess the diet intake during the experimental protocol (see Table 1).

On the second and third visits the participants performed two isocaloric exercise bouts separated by 48–120-h interval to avoid carry-over effects from the previous stimulation (Iyer et al., 2005; Montenegro et al., 2011). In both exercise bouts the participants initially remained seated at rest during 10 min in a quiet room with low lights, controlled temperature (21–22 °C), and humidity (65–70%). Afterwards either anodal or sham tDCS was applied in a counterbalanced random order over DLPFC [2 mA during 20 min]. After the end of the stimulus the participants remained seated for another 10 min and performed the isocaloric exercise bouts (70%VO₂R; ~200 kcal). Immediately after that, the participants underwent a recovery period of 30 min. The measures of subjective appetite sensations, including hunger, satiety and desire to eat, were performed in four different moments: pre- and post-tDCS, immediately after the end of the exercise and after 30 min of post-exercise recovery. Adequate hydration was provided during the experimental protocol. All measurements took place 2–3 h after lunch, between 2:00 and 5:00 P.M.

Evaluation of subjective appetite sensation

The appetite sensation was evaluated by indicators of hunger, satiety and desire to eat. The ‘hunger’ sensation is related to an uneasy feeling occasioned by the lack of food and the need of specific nutrients and energy. On the other hand, the ‘desire to eat’ sensation can be defined by the urge to consume any foods and can be influenced by many external and internal physiological variables (i.e. emotional factors, time of day, availability and palatability of foods, and threats from the environment), regardless of the actual need of nutrients and presence of hunger sensation. The previous validated (Flint, Raben, Blundell, & Astrup, 2000; Mattes, 1990; Siew et al., 2009; Stubbs et al., 2000) visual analogue scale (VAS) was applied in four different moments: (1) pre (Baseline); (2) Post-tDCS (After tDCS); (3) post-exercise (Post-Exercise), and (4) 30 min post-exercise (30-min Post-Exercise). The subjects answered five questions assessing subjective hunger, satiety, and desire for food: (1) How hungry do you feel now? (2) How satisfied do you feel now? (3) Would you like to eat something sweet? (4) Would you like to eat something salty? (5) Would you like to eat something savory? The answers should be within a range between 0 and 100. The VAS was applied in a double-blind fashion.

Maximal cardiopulmonary exercise test

A maximal cardiopulmonary exercise test was performed on cycle ergometer (CatEye EC-1600, CatEye™, Tokio, Japan) using an individualized ramp protocol. The protocol was designed to make the duration of the testing protocol to fall within the range of 8–12 min. The workload increments were individualized to elicit the subject’s limit of tolerance within the duration of the test. A non-exercise model developed to estimate the cardiorespiratory capacity of healthy subjects was applied (Matthews, Heil, Freedson, & Pastides, 1999) to estimate the VO₂max and the final power was calculated using the specific ACSM (2009) equation. The mean ± SD predicted final power was 278 ± 63 W and the power of 0 and 25 W were used, respectively, for the 5-min warm-up period and for the initial test workload. The cadence was set at 55 revs min⁻¹ throughout the test.

Table 1

<table>
<thead>
<tr>
<th>Nutrient Intake</th>
<th>24-h Dietary Recall</th>
<th>Sham Condition</th>
<th>Mean (SD)</th>
<th>Anodal tDCS</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>2863.0 (570)</td>
<td>2663.0 (470)</td>
<td></td>
<td></td>
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<tr>
<td>Protein (g)</td>
<td>125.0 (56.1)</td>
<td>95.0 (36.1)</td>
<td></td>
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<tr>
<td>Carbohydrate (g)</td>
<td>403.2 (170.1)</td>
<td>333.2 (150.1)</td>
<td></td>
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<tr>
<td>Fat (g)</td>
<td>101.8 (37.8)</td>
<td>81.8 (27.8)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg)</td>
<td>691.7 (467.3)</td>
<td>641.7 (454.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiber (g)</td>
<td>26.3 (12.7)</td>
<td>14.3 (8.7)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Isocaloric exercise bouts

Based on the HR\textsubscript{max} and VO\textsubscript{2,max} obtained in the ramp protocol, and on the values of resting heart rate and resting VO\textsubscript{2}, the values corresponding to 70% of oxygen uptake reserve (VO\textsubscript{2R}) were calculated to determine the intensity of the two isocaloric exercise bouts. The energy expenditure was calculated individually from the net VO\textsubscript{2} (Swain, 2000). In addition, the time to achieve 200 kcal for 70%VO\textsubscript{2R} was calculated. The net VO\textsubscript{2} values expressed in ml kg\(^{-1}\) min\(^{-1}\) were converted to L min\(^{-1}\) and then to kcal min\(^{-1}\). Each exercise bout was preceded by a 5-min warm-up at 0 W and free rest min\(^{-1}\), and was followed by a 30-min recovery at sitting rest. The absolute VO\textsubscript{2} values obtained from the equation of xVO\textsubscript{2R} were used to calculate the associated cycling power using the ACSM metabolic equation: \(\text{VO}_2 = \frac{1}{2} \times \text{mass} \times \text{power} \times \text{BW}^{-1}\). Where power is in W and BW the body weight is in kilograms (ACSM, 2009). Expired gases were collected during the exercise bouts via the metabolic cart using a Hans Rudolph face mask (Hans Rudolph™ Inc., Kansas City, MO, USA). The exercise bout ended when the subject had achieved a total caloric expenditure of 200 kcal.

The oxygen uptake (VO\textsubscript{2}), pulmonary ventilation (V\textsubscript{E}), carbon dioxide output (VCO\textsubscript{2}), and heart rate (HR) were calculated, averaged, and recorded every 30 s. Gas exchanges were determined using a VO2000 analyzer (Medical Graphics™, Saint Louis, MO, USA) and heart rate using a cardiotachometer (Polar® RS-800ccx, Kempele, Finland). The gas analyzers were calibrated with a certified standard mixture of oxygen and carbon dioxide, balanced with nitrogen. The flows and volumes of the pneumotachograph were calibrated with a syringe graduated for 3 L capacity (Hans Rudolph™, Kansas, MO, USA). The system was calibrated before each test according to the manufacturer’s guidelines.

Transcranial direct current stimulation (tDCS)

The electric current was applied using a pair of sponges soaked in saline solution (140 mMol of NaCl dissolved in Milli-Q water) involving both electrodes (35 cm\(^2\)) (Nitsche & Paulus, 2000). The electrodes (anodal and cathodal) were connected to a constant current stimulation device with three power batteries (9 V) presenting a maximal output of 10 mA. The batteries were regulated by a digital multimeter (EZA EZ 984, China) with a standard error of ±1.5%.

For the anodic stimulation on left DLPFC, the anode was placed over F3 area according to the international EEG 10-20 system. The cathode was placed over the supraorbital contralateral area (Fp2) and fixed by elastic bands. The electrodes were placed in the same position of the anodal stimulation to perform the sham condition. However, the stimulator was turned off after 30 s, which has been reported as ineffective stimulation (Gandiga, Hummel, & Cohen, 2006). Thus, the subjects reported to feel a tingling or itching sensation coming from the initial electrical stimulation, but they did not receive any further current. This procedure allowed the subjects to remain ‘blind’ for the type of stimulation received during the test and to assure a sham control effect (Boggio, Rigonatti, et al., 2008).

### Statistical analyses

The Shapiro Wilk and Levene tests were used to assess data normality and homogeneity. Data sphericity was verified using the Mauchly’s test and the Greenhouse–Geisser correction was applied whenever necessary. A repeated measures 2-way ANOVA (stimulation × moment) was used to compare the scores of subjective appetite obtained in different conditions. Tukey post-hoc tests were applied to determine pair wise differences when significant F ratios were obtained. In all cases, a probability level of \(P < 0.05\) was adopted for statistical significance. The same statistical software was used for all calculations (Statistica 6.0; StatSoft™, Tulsa, OK, USA).

### Results

The statistical power of the repeated measures ANOVA model, within-between groups interaction, was determined using the GPower version 3.1.2 (Universität Kiel, Kiel, Germany) and considering the following parameters: effect-size = 3.0; \(\alpha\) error probability = 0.05; number of groups = 2; number of measurements = 13; correlation among repeated measures = 0.5; nonsphericity correction = 1. The actual power for \(N = 9\) was 0.835, which is slightly acceptable for the type II error.

Table 1 presents the nutrient intakes estimated from the 24-h dietary recalls in both tDCS conditions. Table 2 presents the actual values obtained for the peak power cycling and exercise test duration produced by the ramp protocols. The time to achieve 200 kcal in exercise bouts fell within the range of 22–28 min (mean ± SD: 25 ± 3 min) in sham condition, and 23–27 min (mean ± SD: 25 ± 2 min) in anodal tDCS. The length of the exercise did not differ between both conditions (\(P > 0.05\)).

Figure 1A presents the mean of percentage change in desire to eat ratings. Significant decrease was found when comparing the desire to eat in baseline with the assessment immediately after anodal tDCS (\(P = 0.05\)) and Post-Exercise (\(P = 0.04\)). Hence the anodal tDCS was sufficient to decrease the desire to eat, but the combination of anodal tDCS and exercise increased such suppressing effect after the exercise end. In both sham and anodal tDCS conditions, the VAS scores for the desire to eat were significantly higher after 30 min of post-exercise recovery, compared to data obtained either after tDCS or immediately post-exercise (sham and anodal tDCS; \(P = 0.002\); \(P = 0.019\), respectively), which suggests that a 30-min recovery following the aerobic bout elicited an increase in the appetite sensation.

The VAS scores on the sensations of hunger and satiety are shown in Fig. 1B and C. Within-group comparison revealed that the subjective feelings of hunger in the sham condition were
Higher between the moments 30-min Post-Exercise than other moments analyzed. However, in anodal tDCS, the subjective feelings of hunger showed significant differences between 30-min Post-Exercise vs. Post-Exercise (P = 0.01) and Baseline vs. Post-Exercise (P = 0.02) assessments. The same results were observed for the subjective scores of satiety in sham condition. But, only in anodal tDCS, were found significant difference between the moments 30-min Post-Exercise vs. Post-Exercise (P = 0.04), which suggests that after 30-min recovery following the aerobic bout in anodal tDCS elicited a lower decrease in satiety sensation than in sham condition.

Discussion

The present study aimed to verify whether tDCS on prefrontal cortex isolated or combined with an aerobic exercise bout would modulate the desire to eat, as well hunger and satiety sensations in overweight subjects. The main results were: (i) The anodal
unilateral tDCS on left DLPFC decreased the desire to eat at rest; (ii) The anodal tDCS associated with aerobic exercise enhanced the appetite suppressing effect in desire to eat compared to either anodal tDCS or physical exercise isolated effects; and (iii) The appetite sensation throughout recovery period was influenced by anodal tDCS associated with aerobic exercise bout.

We were able to find only two studies that have addressed the effect of tDCS applied over the DLPFC on subjective appetite control (Fregni et al., 2008; Goldman et al., 2011). Both studies investigated the effect of anodal bilateral tDCS on the desire to eat in healthy subjects, and showed that tDCS could influence the appetite regulation. However, these studies did not observe the anodal tDCS effect on hunger and satiety sensations. To the best of our knowledge, this is the first study to investigate the effect of tDCS associated with acute physical activity on subjective appetite sensations in overweight humans. Some recent studies reported that the application of rTMS and anodal tDCS (10 Hz and 2 mA for 20 min, respectively) on the DLPFC may be an effective technique to decrease the desire to eat (Fregni et al., 2008; Goldman et al., 2011; Uher et al., 2005). Unfortunately, these studies enrolled subjects with a wide age range with different body composition, which are potentially confounding factors. In contrast, subjects in the present study had similar physical characteristics [age within 20–30 years; BMI higher than 24.9 kg m²].

The results in our overweight group demonstrated that the desire to eat was suppressed at rest due to the 20-min unilateral anodal tDCS. The possible underlying mechanisms for such suppressing effect are probably related to an increase in left DLPFC and decrease in right orbitofrontal cortex activity, since previous research have shown that obese subjects may have greater neuronal activity in the orbital and anterior cingulated cortex, as well DLPFC hypo-activation (Uher et al., 2004). Actually the use of unilateral tDCS over left DLPFC allowed placing the reference electrode over the supraorbital contralateral cortex, which may have elicited a decrease in the orbital cortex activity.

It has been suggested (Fregni et al., 2008) that a unilateral electrode montage over DLPFC would not be effective to induce changes in the subjective desire to eat, since this sensation would rely on the cross-cortical activity of both cerebral hemispheres. Our results do not concur with this idea, since the unilateral tDCS over left DLPFC was effective to modulate the desire to eat. Despite the hunger sensation in sham condition throughout 30-min post-exercise reached higher scores and the satiety sensation reached lower scores than anodal tDCS, it is worthy to mention that this appetite sensations were not affected by the tDCS. This result was somewhat expected, because hunger and satiety signals seem to be regulated by the hippocampus (Davidson et al., 2009). Although the hippocampus has connections with the prefrontal cortex, this area is a deep subcortical structure, and perhaps the tDCS was not capable to modulate the neuronal activity of this area (Lang et al., 2005) or the tDCS intensity and duration applied in this experimental protocol was insufficient to modulate the hippocampus. The mechanisms underlying the DLPFC neuronal activity, as well the compensatory mechanisms induced by tDCS in overweight subjects are still unclear, and certainly warrant future research.

Other important finding was that the anodal tDCS combined with the aerobic exercise bout enhanced the appetite suppressing effect compared to the electrical stimulation or physical exercise alone. Nonetheless no significant difference between the sham and anodal tDCS conditions was detected in hunger and satiety sensations. It was expected that immediately after the aerobic exercise the overweight subjects would be hungrier and less satisfied than in the pre-exercise resting assessment. However, such increase in the appetite sensation was detected only 30 min following the exercise end. Moreover, the increase in hunger sensation after 30 min following the exercise end seemed to be attenuated when the anodal tDCS was applied. This behavior concurred with some previous (Durrant, Royston, & Wloch, 1982; Stubbs et al., 2002) – but not all (Doucet, St-Pierre, Almeras, & Tremblay, 2003; King, Hester, & Gately, 2007) – research advocating that there would be an acute suppressive effect of moderate to high intensity exercise bouts on the appetite sensations.

The main limitation of the present study is due to the lack of intermediary assessments of the appetite sensations. We were able to detect a suppressing effect of tDCS on the desire to eat immediately after the exercise. After 30 min such sensation increased to values higher than pre-exercise baseline. However it was not possible to determine whether the suppressing effect remained just for a few minutes or lasted during almost half an hour. The potential duration of the appetite suppressing effect due to tDCS must be addressed in future research. Another limitation is the low statistical power due to the small number of subjects, which may have masked possible significant differences (type II error associated with an effect-size higher than 2.5). Future studies with greater samples and using techniques to detect the brain areas involved in the observed task are, for that reason, necessary.

The fact that specific cortical areas activated by tDCS have been not controlled is another limitation. Since brain areas responsible for the appetite control have been well described, such control would allow a better understanding of the mechanisms underlying the observed effects on the appetite sensations. It is also worthy to mention that a potential confounding factor was the need of food intake standardization within the experimental protocol. The subjects were instructed not to change their diet habits and responded to a 24-h dietary recall, but there was no strict control of the caloric intake.

In conclusion, the application of unilateral anodal tDCS over left DLPFC combined with aerobic exercise of moderate intensity was able to modify the appetite responses. The combination of tDCS and exercise induced greater decrease in the desire to eat compared to either anodal tDCS or exercise bout alone. However such suppressing effect occurred immediately after the exercise performed and was lost after 30 min of post-exercise recovery. Additional research should be encouraged to ratify these results and to help clarifying the mechanisms stimulating appetite and the possible effect of tDCS on its control.

References


