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High definition transcranial pink noise stimulation of anterior cingulate cortex on food craving: An explorative study

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ABSTRACT

Dysfunctional neural activity in the cortical reward system network has been implicated in food addiction. This is the first study exploring the potential therapeutic effects of high definition transcranial pink noise stimulation (HD-tPNS) targeted at the anterior cingulate cortex (ACC) on craving and brain activity in women with obesity who showed features of food addiction (Yale Food Addiction Scale score of $\geq$3). Sixteen eligible females participated in a randomized, double-blind, parallel group study. Participants received six 20-minute sessions of either 1 mA (n = 8) or sham (n = 8) stimulation with HD-tPNS over two weeks. Anode was placed above the ACC (Fz) with 4 cathodes (F7, T3, F8, and T4). Food craving was assessed using the Food Cravings Questionnaire State (FCQ-S) and brain activity was measured using electroencephalogram (EEG). Assessments were at baseline, and two days, four weeks, and six weeks after stimulation. A 22% decrease (mean decrease of −1.11, 95% CI -2.09, −0.14) was observed on the 5-point 'intense desire to eat' subscale two days after stimulation in the HD-tPNS group compared to sham. Furthermore, whole brain analysis showed a significant decrease in beta 1 activity in the ACC in the stimulation group compared to sham (threshold 0.38, p = 0.04). These preliminary findings suggest HD-tPNS of the ACC transiently inhibits the desire to eat and, thus, warrants further examination as a potential tool in combating food craving.

1. Introduction

Obesity continues to be a significant public health concern. In 2014, the World Health Organization (WHO) estimated that 1.9 billion adults were overweight and 600 million were obese globally (World Health Organization, 2016). Efforts to curb the obesity epidemic have not had significant wide-spread success (Mann et al., 2007). Approaches that target the underlying drive to over-eat and enable an individual to exist in an obesogenic environment without overconsumption could be beneficial.

Craving can be defined as the intense persistent desire for a certain stimulus. Studies have shown a strong link between craving and high fat/high sugar foods (Kelley et al., 2002; Kringelbach, O'Doherty, Rolls, & Andrews, 2003). The rewarding properties of certain foods can result in neural activation patterns and specific behaviors seen in other addictions (Pelchat, 2009), as defined by the Diagnostic and Statistical Manual of Mental Disorder- IV (DSM-IV). The Yale Food Addiction Scale (YFAS) is a validated tool used to identify those that display signs of food addiction similar to the DSM-IV characteristics of substance addiction (Gearhardt, Corbin, & Brownell, 2009).

Neuroimaging studies using electroencephalogram (EEG) (De Ridder et al., 2016b; De Ridder, Manning, Leong, Ross, & Vanneste, 2016c) have shown that food craving among individuals with obesity may be associated with abnormal brain activity in multiple interacting brain networks, more specifically the anterior cingulate cortex (ACC) (principal cortical area in the salience network), dorsal medial prefrontal cortex (dmPFC), pregenual anterior cingulate cortex (pgACC), dorsal anterior cingulate cortex (dACC) and precuneus, as well as the parahippocampal area.

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The ACC is involved in craving, both for alcohol, nicotine, cocaine, and food. The areas for food craving and craving for other substances are adjacent in the ACC. Therefore, the ACC could be a good target for neuromodulation in order to decrease food craving in individuals with features of food addiction.

Studies assessing the effects of non-invasive neurostimulation using repetitive transcranial magnetic stimulation (rTMS) and transcranial direct stimulation (tDCS) on the dorsolateral prefrontal cortex (DLPFC) to decrease food cravings have shown positive encouraging results (McClelland, Bozhilova, Campbell, & Schmidt, 2013). These findings indicate that overeating could/may be decreased via a top-down approach by modulating the excitability of the DLPFC (perhaps through increasing inhibitory control), and consequently suppressing the reward network involved in food craving (Bravo et al., 2016; Gluck et al., 2015; Ljubisavljevic, Maxood, Bjekic, Oommen, & Nagelkerke, 2016; Potenza & Grilo, 2014). Another approach to combating food craving among individuals with obesity would be to target the desire to eat using a 'bottom-up' strategy, focusing on reducing the salience attached to food and, thus, the urge to eat (De Ridder et al., 2016b). The ACC, a higher-order executive control area of the salience network has been reported to play a role in the pleasurable aspects of food (hedonistic eating) and, thus, influences overeating (Sescousse, Redouté, & Dreher, 2010). Although not in food addicted individuals, it has been shown in a case report that rTMS targeting the ACC induced a three-week reduction in alcohol craving (De Ridder, Vanneste, Kovacs, Sunaert, & Dom, 2011b). Moreover, a following case study reported that an alcohol dependent patient remained free of alcohol intake for more than 18 months after having an electrode implanted over the ACC (De Ridder et al., 2016a). The mechanistic similarities in alcohol and food craving mean that the ACC is a plausible target to curb food craving.

Previous non-invasive neuromodulation studies for food craving have utilized rTMS and tDCS (McClelland et al., 2013). Another technique, transcranial pink noise stimulation (tPNS) has yet to be examined. The use of smaller 'high definition (HD)' electrodes stimulation has an increased spatial specificity compared to traditional larger saline soaked sponge electrodes and is suitable for focal targeting of cortical regions (Datta et al., 2009; Edwards et al., 2013). With regards to pink noise (1/f), it has been postulated that this frequency spectrum resembles the naturally occurring signals in the self-organization of the brain (Van Orden et al., 2003), thus, when applied, may be more effective than standard electrical stimulation parameters. One possible explanation could be that the brain habituates to repetitive electrical parameters that are dissimilar to its own naturally occurring rhythm.

The aim of this study was to explore the effect of HD-tPNS of the ACC on food craving in individuals with obesity with features of food addiction. It was hypothesized that participants undergoing HD-tPNS targeted at the ACC will report decreased food craving compared to participants undergoing placebo tPNS. We further hypothesized that HD-tPNS will, compared to placebo, induce decreased activity in the ACC.

2. Materials and methods

2.1. Participants

Female individuals with obesity (body mass index, BMI $\geq$ 30) between the ages of 20 and 60 years were recruited via advertisement in local newspapers and on notice boards with an invitation to participate in a potential therapeutic method to curb food craving. Interested individuals were invited to the clinic of the University Hospital of Otago, Dunedin, New Zealand for a screening procedure. Inclusion criteria included being right handed and having symptoms of food addiction (score $\geq$ 3 on the YFAS). Exclusion criteria included major weight gain or loss (>5 kg) in the last six months, recent significant head injuries, a history of epilepsy, previous diagnoses with an eating disorder or any psychiatric disorders, or significant current health problems (i.e. diabetes, cancer, heart disease). All participants were fully informed and have given written consent. The study was approved by the Southern District Health Board Ethics Committee (Ref: 15/STH/68), and was in accordance with the Declaration of Helsinki.

2.2. Study design

The study was a six-week, randomized, double-blind, parallel trial. Participants were randomized to either real HD-tPNS or sham HD-tPNS groups. At baseline (T0), food craving was measured using the validated Food Craving Questionnaire (FCQ-S), and resting state brain activity was measured using EEG in an overnight fasting state. Also, at T0, height was measured without shoes to the nearest 0.5 cm using a stadiometer and body weight assessed using a Bioelectric Impedance Analysis (BIA) machine (BC-418, Tanita Co., Tokyo, Japan).

Participants received either real HD-tPNS or sham HD-tPNS three times a week for two weeks, totalling up to six sessions. Assessments were repeated two days after treatment (T1), at week four (T2), and week six (T3) post-treatment after overnight fasting.

2.3. High definition transcranial pink noise stimulation (HD-tPNS)

Stimulation electrodes were placed to target the ACC (electrode placements: four cathodes: F7, T3, F8, and T4, and one anode at FZ, in accordance with the 10/20 EEG system). The electrical stimulation device (Starstim system- NE neuroelectrics) was set at 1/f (pink) noise spectrum with the direct current offset at 0.

Participants in the treatment group received stimulation at a current strength of 1 mA for 20 min, with 60 s ramp up and ramp down at the beginning and end of each stimulation session, respectively. For sham stimulation, the current was applied for 60 s (ramp up) before terminating to create an identical skin sensation to the treatment group.

2.4. Evaluations

Evaluations were conducted using self-report questionnaires as described below, and EEG.

2.4.1. Screening: Yale Food Addiction Scale (YFAS)

The Yale Food Addiction Scale (YFAS) (Gearhardt et al., 2009) is a well-validated tool consisting of 27 items used to identify those that display signs of dependency towards food similar to the DSM-IV characteristics of substance addiction. The YFAS has a total continuous score of seven and participants who scored three or more were included in the study as showing signs of food addiction.

2.4.2. Primary outcome: Food Craving Questionnaire (FCQ-S)

The validated Food Craving Questionnaire (FCQ-S) (Cepeda-Benito, Gleaves, Williams, & Erath, 2001) was used to assess food cravings occurring 'right now'. Participants were asked to indicate how strongly they disagree or agree with the items on a 5-point scale from 1. Strongly disagree to 5. Strongly agree. The FCQ-S has a total score that ranges from 15 to 75 (mean from one to five), and consists of five subscales: craving as a physiological state, an intense desire to eat, anticipation of a positive reinforcement that may result from eating, lack of control over eating, and anticipation of relief from negative states or feelings as a result of eating.

2.4.3. Secondary outcome: electroencephalogram (EEG) and source localization

Resting state EEG was obtained in a way previously described by the investigators (De Ridder, Vanneste, & Congedo, 2011a; Vanneste, Van de Heyning, & De Ridder, 2011) using the Mitsar-EEG 202 amplifier recorded after overnight fasting. In short, the EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 O2) in the standard 10–20 International placement, referenced to linked ears and impedances were checked to remain below 5 kΩ. Participants were asked to sit upright comfortably in a chair with their eyes closed during the 5-minute recording. Data was resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz, and subsequently transposed into Eureka! Software, plotted and carefully inspected for manual artefact-rejection. Average cross-spectral matrices were computed for bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12.5 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–45 Hz).

Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate the intracerebral electrical sources that generated the activity in each of the eight frequency bands. Technical details of sLORETA and its validity have been previously published (Mulert et al., 2004; Nichols & Holmes, 2002; Pascual-Marqui, 2007a, 2007b; Worrell et al., 2000).

3. Statistical analyses

3.1. Demographic variables and FCQ-S

Independent *t*-test was used to examine differences between the groups for demographic variables and FCQ-S scores. Repeated measures analyses of variance (ANOVA) were conducted with groups as between-subject variable, time as a repeated factor (T0, T1, T2, and T3), and the FCQ-S scores and BMI as dependent variables. Further analysis using pairwise comparison was carried out to test significant differences between the different time points. Where there was a group difference but not a significant difference across time points, analysis of covariance (ANCOVA) was performed using the average of T1, T2, and T3 as a dependent variable, groups as fixed variables, and T0 as covariate. All statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA).

3.2. Whole brain analyses

Resting state whole brain analysis was conducted to obtain an unbiased measure of the effect of HD-tPNS on the brain. This analysis was used to compare differences in whole brain activity between groups at T0, T1, T2, and T3. The sLORETA analysis is a non-parametric, null hypothesis comparison (Nichols & Holmes, 2002). It is based on estimating the empirical probability distribution for max-statistic through randomization. It corrects for multiple testing, and due to its non-parametric nature, does not rely on any assumption of Gaussianity. The significant thresholds of sLORETA's statistical contrast maps were calculated through multiple voxel-by-voxel comparisons. The significance threshold was based on 5000 permutations.

4. Results

4.1. Demographic variables and baseline FCQ-S

Fifty-two individuals responded to the advertisement and were screened for the study. Of the 52 female participants, 21 did not have YFAS scores of more than three. Eight participants had a BMI of less than 30, two had a history of epilepsy, one was bipolar, and two lost more than 5 kg in the past six months. Of the 18 participants who were eligible for the study, two dropped out at baseline. The final sample consisted of 16 participants who were randomized to either real HD-tPNS ($n = 8$) or sham HD-tPNS ($n = 8$). At T0, there were no significant differences in age, weight, height, BMI, YFAS scores, and FCQ-S scores between the two groups (Table 1).

4.2. FCQ-S over time

There were no significant interactions between time and group for total FCQ-S score and the subscales, as well as BMI (Table 2).

For the 'intense desire to eat' subscale, further exploration of the data was performed using analysis of covariance (ANCOVA) with the average of T1, T2, and T3 as the dependent variable, the groups as fixed variables, and T0 as a covariate. This additional analysis was conducted because of a significant group difference $F(1, 14) = 6.33$, $p < 0.05$ but no significant difference between T1, T2, and T3 for the 'an intense desire to eat' subscale (Table 2).

Results indicated a significant difference between the two groups $F(2, 13) = 6.06$, $p = 0.029$ (Fig. 1). In other words, after the treatment period, the real HD-tPNS group had a 22% reduction (mean decrease of −1.11 (95% CI -2.09, −0.14), $p = 0.029$ points) on the intense desire to eat subscale compared to the sham group. The intense desire to eat subscale had a possible mean range score of 1–5.

4.3. Adverse effects and integrity of tPNS blinding procedure

At the end of each stimulation session, participants were asked if they experienced any adverse effects using the questionnaire outlined by Brunoni et al., 2011. No adverse effects were noted aside from a slight itching sensation under the electrodes at the beginning of stimulation.

At T1 (first follow-up upon completion of treatment), participants were asked 'Which condition do you think you received?' All participants guessed 'real treatment'. When asked to elaborate, women attributed the itching sensation at the beginning of the stimulation to real tPNS. This suggests that the ramp in period of the sham stimulation provoked skin sensations that were similar to active stimulation.

4.4. Whole brain between groups

There were no significant differences in resting state whole brain analysis between sham and real HD-tPNS groups at T0, T2, and T3. At T1 (1–2 days post), there was a significant decrease in beta 1 activity in the ACC, specifically the dorsal ACC, in the real HD-tPNS group compared to the sham group after correcting for multiple comparisons (Fig. 2).

5. Discussion

This was the first study to examine the effect of high definition transcranial pink noise stimulation (HD-tPNS) targeting the ACC on food craving in female individuals with obesity who show signs of food addiction. There was a significant transient (1 month) reduction in the 'intense desire to eat' scale following HD-tPNS stimulation. Findings of this study are consistent with results from non-invasive and invasive stimulation reports for alcohol addiction (De Ridder et al., 2011b; De Ridder et al., 2016a). Together, these studies uphold the theory that food and alcohol addiction share common pathological brain activity. The ACC seems to play a crucial role in this 'addictive network', and stimulation of this region appear to have an inhibitory effect on craving.

Table 1
Baseline demographic and behavioral variables for HD-tPNS and sham HD-tPNS groups.

Variable	Sham HD-tPNS	Real HD-tPNS	P value
Age	41.1 (12.7)	38.4 (11.3)	0.655
Weight	111.1 (37.4)	114.7 (17.8)	0.805
Height	165.0 (5.2)	169.5 (7.6)	0.189
BMI	40.4 (11.2)	39.8 (4.9)	0.899
YFAS	4.8 (1.4)	5.4 (1.6)	0.418
FCQ-S			
Total	3.24 (0.87)	3.63 (0.37)	0.261
Craving as a physiological state	3.08 (1.08)	3.08 (0.89)	1.000
An intense desire to eat	3.75 (0.71)	3.88 (0.84)	0.751
Anticipation of a positive reinforcement that may result from eating	3.08 (1.22)	3.67 (0.50)	0.231
Lack of control over eating	3.25 (1.14)	4.13 (0.80)	0.096
Anticipation of relief from negative states or feelings as a result of eating	3.04 (0.81)	3.42 (0.46)	0.273

Table 2
Descriptive statistics for the Food State Craving Questionnaire (total and subscales) and body mass index at baseline and at the different time points as well as results from repeated measures ANOVA analyses.

Variables	Sham HD-tPNS (mean, SD)				Real HD-tPNS (mean, SD)				Repeated measures ANOVA		
	Time 0	Time1	Time 2	Time 3	Time 0	Time 1	Time 2	Time 3	Time	Group	Time x Group
FCQ-S											
Total	3.24 (0.87)	3.19 (0.76)	3.13 (0.70)	3.08 (0.71)	3.63 (0.37)	3.05 (0.50)	2.89 (0.77)	2.84 (0.86)	$F(2, 27) = 4.26^{*}$ linear $F(1,14) = 5.48$	$F(1,14) = 0.03$	$F(2,27) = 2.11$
Craving as a physiological state	3.08 (1.08)	3.17 (0.87)	3.29 (1.05)	3.25 (1.15)	3.08 (0.89)	2.96 (1.16)	2.75 (1.29)	2.58 (1.38)	$F(2, 27) = 0.16$	$F(1,14) = 0.60$	$F(2, 42) = 0.66$
An intense desire to eat	3.75 (0.71)	3.58 (0.79)	3.54 (0.47)	3.79 (0.85)	3.88 (0.84)	2.75 (0.79)	2.46 (1.39)	2.29 (1.41)	$F(2, 27) = 3.53$	$F(1,14) = 6.33^{*}$	$F(2, 27) = 2.93$
Anticipation of a positive reinforcement that may result from eating	3.08 (1.22)	3.17 (1.27)	3.04 (0.81)	2.75 (0.81)	3.67 (0.50)	3.29 (0.72)	3.50 (0.78)	3.33 (1.22)	$F(2,27) = 0.73$	$F(1,14) = 1.30$	$F(2, 27) = 0.44$
Lack of control over eating	3.25 (1.14)	2.75 (0.64)	2.83 (0.80)	2.75 (1.04)	4.13 (0.80)	3.00 (0.67)	2.92 (0.78)	2.88 (1.01)	$F(2,32) = 8.15^{**}$ linear $F(1,14) = 9.57$	$F(1,14) = 0.88$	$F(2,32) = 1.58$
Anticipation of relief from negative states or feelings as a result of eating	3.04 (0.81)	3.29 (0.86)	2.96 (0.81)	2.83 (0.93)	3.42 (0.46)	3.25 (0.56)	2.83 (0.87)	3.13 (1.06)	$F(3,38) = 2.1$	$F(1,14) = 0.13$	$F(3,38) = 0.92$
BMI	39.9 (5.0)	39.9 (5.0)	39.7 (5.0)	39.7 (5.1)	40.4 (11.2)	40.5 (11.1)	40.3 (11.1)	40.1 (11.1)	$F(3, 42) = 0.77$	$F(1, 42) = 0.03$	$F(3, 42) = 0.68$

$^{*}p < 0.05$, $^{**}p < 0.01$. Time 0 = baseline, Time 1 = 1–2 days post, Time 2 = 2 weeks post, Time 3 = 4 weeks post.

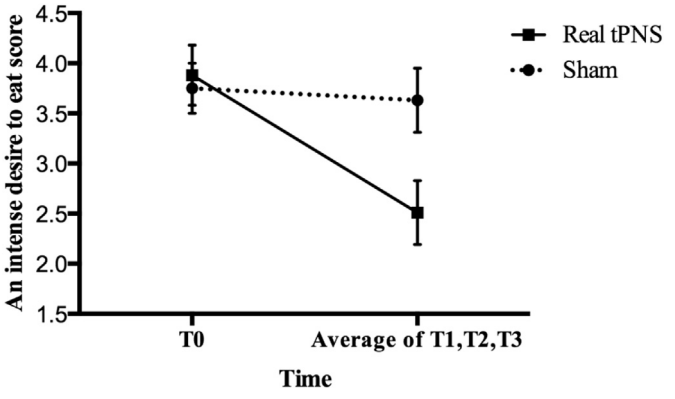

Fig. 1. Changes in an intense desire to eat subscale before and after real/sham HD-tPNS using an average score for Time 1, 2 and 3 as the outcome.

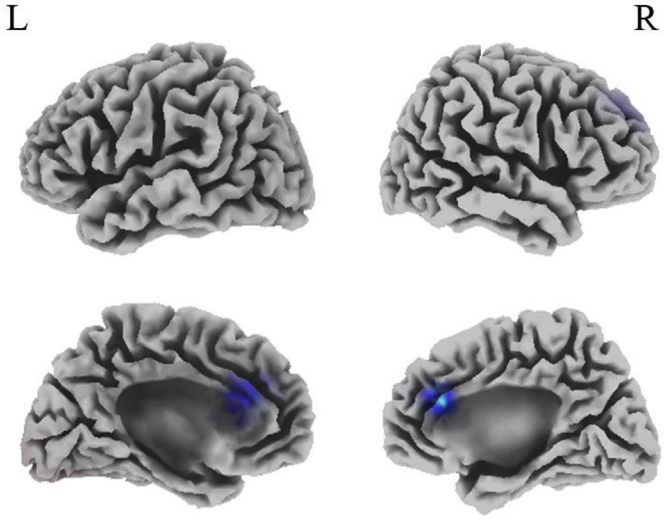

Fig. 2. Significant decrease ($p = 0.04$) in beta 1 activity in the anterior cingulate cortex in the real HD-tPNS group compared to sham HD-tPNS at T1 (1–2 days after HD-tPNS).

Neuroimaging research have revealed that brain circuits implicated in addiction involve regions governing motivation, reward, and decision making (De Ridder et al., 2016b; Kuhn & Gallinat, 2011). Previous studies using non-invasive neuromodulation (TMS, tDCS) targeting the DLPFC reported positive short- and longer-term outcomes on self-reported food craving (Gluck et al., 2015; Ljubisavljevic et al., 2016; Potenza & Grilo, 2014). The current study expands on prior results by showing that similar to the 'top-down' approach, the 'bottom-up' strategy of combating food craving can induce immediate (2 days after HD-tPNS)

suppression of desire to eat, which persists for up to a month post treatment.

A recently published study (Ljubisavljevic et al., 2016) reported that neuromodulation of the DLPFC with tDCS decreased total score for state-dependent craving by 4% in normal and overweight young adults. Although our study did not show a significant reduction in total score for state craving, changes on this scale over time were noted to be linear with a downward trend in the real HD-tPNS group compared to the sham group. It is noteworthy that the relatively small sample size ($n = 16$) in our study may have limited the power of the study and possibly affected its external validity. This is the first study attempting to decrease food craving in female individuals with obesity using HD-tPNS targeting the ACC, a key hub of the salience network. Considering the positive results from this study, it would, therefore, be a worthwhile exercise to conduct a larger intervention trial to confirm these preliminary findings.

Importantly, the resting state brain activity results of this study are notable. The significant decrease in beta 1 activity in the ACC, specifically the dorsal region (dACC), at T1 (1–2 days after HD-tPNS) in the real HD-tPNS group compared to the sham group provides an objective measure for the efficacy of HD-tPNS in supressing beta activity in the dACC. It has been previously shown that in the dACC, individuals with obesity, compared to their lean counterparts, show elevated beta oscillations, a frequency involved in the processing of an individual's existing state (De Ridder et al., 2016b). Namely, this could hypothetically suggest that among individuals with obesity, the state of being obese is the default neurobiological reference or homeostatic set point (De Ridder et al., 2016c) and lasting suppression of beta activity in the dACC could potentially reset the system to within normal homeostatic parameters.

Although the present results support the use of HD-tPNS in the treatment for food craving, it would be premature to conclude that pink noise is more effective than standard electrical modulation in suppressing food craving transiently. This study was not designed to investigate the underlying mechanism of the long-term action of pink noise. Pink noise (1/f) has a decreasing power spectral density as the frequency increases. It has been previously shown that pink noise plays an important role in many biological and physiological processes (e.g. heart rate variability, respiratory intervals) (Sejdić & Lipsitz, 2013). Studies have also reported on the importance of pink noise in maintaining the stability of neural networks (Aquino, Clausznitzer, Tollis, & Endres, 2011) and the amplification of information transfer between brain regions (Li, Wang, & Hu, 2007). Thus, stimulation of brain regions using pink noise may have therapeutic potential.

Consistent with a previous tDCS trial targeting the DLPFC (Ljubisavljevic et al., 2016), preliminary results from this study did not show significant differences in BMI between sham and real tPNS. Nonetheless, a previous study (Gluck et al., 2015) reported that anodal tDCS compared to cathodal tDCS induced more weight loss in obese individuals. One possible explanation for lack of efficacy in regards to weight loss in our study could be the stimulation parameters. Indeed, the transient electrophysiological effect (i.e., changes in beta 1 activity only at T1) observed in this study suggests that different HD-tPNS parameters or prolonged therapy may be necessary for larger reductions in food craving to translate to weight change.

A limitation of the study is the lack of dietary assessment (i.e., food diaries, dietary recalls). Considering that this is the first HD-tPNS study, we were concerned of the possibility that food monitoring would affect subjective reporting of food craving and eating behavior. However, results showed that all study participants thought they were in the real stimulation group. Thus, we could infer in future studies that knowledge of food monitoring will have a similar influence on both the sham and real HD-tPNS groups.

Our findings showed a significant decrease in both groups over time for total score and 'lack of control over eating'. Given the double-blind design of the trial and encouraging results of the integrity of the blinding procedure, the placebo effect could be a result from expectation of a therapeutic benefit (i.e., participants in the sham group thinking they were receiving real stimulation). This issue is often observed in non-invasive stimulation studies (Schambra, Bikson, Wager, DosSantos, & DaSilva, 2014).

A main strength of the study is the use of high definition (HD) stimulation. Compared to conventional saline soaked sponge electrodes, HD small gel electrodes provide more precise targeting of cortical structures (Villamar et al., 2013). The use of traditional sponge electrodes can result in the possibility of stimulating nearby brain areas while HD stimulation have shown to restrict the electric flow to a limited region (Borckardt et al., 2012; Villamar et al., 2013). Another strength of the study is that the versatility of a parallel group design means that there is no risk of a cross-over effect or likelihood of unblinding of both the participants and researchers. Moreover, given the high participant burden of this trial, the parallel design allowed for a shorter trial period.

In conclusion, these preliminary findings showed that HD-tPNS stimulation of the ACC can suppress food craving in individuals with obesity who show signs of food addiction. This supports the potential use of HD-tPNS stimulation on ACC as a potential therapeutic tool to combat food craving and obesity. Further research is needed to assess the long term-benefits of this procedure in a larger group of individuals.

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