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Effect of home-based transcranial direct current stimulation associated with nutritional counseling therapy on clinical and electrophysiological measures in Binge eating disorder: a study protocol for a blind, randomized, controlled clinical trial

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Abstract:

Background: Binge Eating Disorder (BED) is a psychiatric disorder that has several medical and social consequences. Cognitive Behavioral Therapy (CBT) is the reference treatment, but presents significant dropout rates and elevated failure of therapeutic response. Therefore, new therapies targeting Central Nervous System (CNS) modulation, such as transcranial direct current stimulation (tDCS), might improve therapeutical responses, by modulating cognitive control over eating behavior and/or by enhancing inhibitory control due to synergistic action when combined with the current treatments available.

Methods: Women with moderated BED, aged between 18 and 65 years and BMI ≥ 25 Kg/m² will be included. The participants will be divided into one of four groups: (1) Active tDCS; (2) Nutritional Counseling Therapy (NCT); (3) Active tDCS + NCT; (4) Sham tDCS + NCT. The electrodes of the tDCS will be positioned over the right Dorsolateral Pre-Frontal Cortex (DLPFC) - anode and left DLPFC - cathode. The participants will have a weekly appointment for 8 weeks where they will undergo the stimulation and/or the NCT. The groups that have the tDCS therapy will also receive the stimulation at home 4x/week in the first 5 weeks. The follow up is 8 weeks. The primary outcomes are the severity of symptoms, measured by the Binge Eating Scale (BES), and the inhibitory parameters of cortical excitability, measured by Transcranial Magnetic Stimulation (TMS) - Short Intracortical Inhibition (SICI). The secondary outcomes are weight loss, eating behavior, inhibitory control (Go/No-go), parameters of cortical excitability (Intracortical Facilitation (ICF) and cortical silent period (CSP)), and serum levels of leptin.

Discussion: Cumulative research has provided evidence that tDCS improves disordered eating behaviors. Nevertheless, studies investigating the efficacy of long-term tDCS combined to standard treatment to BED are scarce. Based on exciting findings in trials that have associated tDCS and cognitive-behavioral approaches in Major Depressive Disorder (MDD), we hypothesize that the proposed protocol will be able to amplify therapeutical responses by reducing the severity of BED symptoms and enhancing inhibitory pathways assessed by cortical excitability parameters.

Keywords: Binge Eating Disorder; Transcranial direct current stimulation; Cortical Excitability; Nutritional Therapy

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INTRODUCTION

Binge Eating Disorder is a psychiatric disorder defined as recurrent binge eating episodes in the absence of any compensatory method (American Psychiatric Association, 2013). It is the most prevalent eating disorder, accounting for up to 25% of patients who seek medical attention for obesity and up to 75% of those with severe obesity (body mass index (BMI) above 40) (Davis, 2015).

Several biological changes are related to BED, mostly related to altered balance between neural mechanisms related to reward and impaired executive function, such as higher impulsivity/compulsiveness, attention deficits and poor decision-making (Kessler, Hutson, Herman, & Potenza, 2016). In fact, neuroimaging studies have identified reduced activation, mainly in frontal areas such as DLPFC, in individuals with BED in comparison to healthy and obese without BED, which may be partially underlying the impaired impulsivity and the processing of rewards (American Psychiatric Association, 2013). Electrophysiological analysis through electroencephalogram records (EEG) have evidenced changes in resting state on frontal areas in patients with BED compared to patients without BED, as well as attention related to food process, where the beta activity of individuals with BED was positively correlated to BED symptomatology (Blume, Schmidt, & Hilbert, 2019; Imperatori et al., 2015; Tammela et al., 2010).

Another widely electrophysiological measure is the Transcranial Magnetic Stimulation (TMS) that can provide information about the excitability and conductivity of the motor cortex and the functional integrity of intracortical neuronal structures (Kobayashi & Pascual-Leone, 2003), providing measures of intracortical mechanisms of inhibition and facilitation (Rossini, Rosinni, & Ferreri, 2010). However, there are scarce studies in the field of eating disorders, with only one study with anorexia nervosa that showed a diffuse hyperexcitability of the motor cortex and the corticospinal tracts compared to healthy controls (Khedr, El Fetoh, El Bieh, Ali, & Karim, 2014).

Although Cognitive Behavior Therapy (CBT) is the reference treatment, its effectiveness remains unreachable to a substantial group of affected individuals, in part due to significant dropout rates, ranging from 12% up to 34% (Flückiger et al., 2011). Failure of therapeutic response in those who completed the treatment can reach 25 to 40% of patients (Byrne, Fursland, Allen, & Watson, 2011; Fairburn et al., 2015, 2009).

In fact, transcranial direct current stimulation (tDCS) is a noninvasive neuromodulatory technique that is able to improve cognitive control over eating, by modulating Pre-Frontal Cortex regions (PFC), in healthy subjects, overweight adults and eating disorders patients (Gluck, Viswanath, & Stinson, 2017). This procedure modifies cortical excitability through tonic stimulation with weak direct currents between electrodes located on the scalp that de- or hyperpolarizes neuronal resting membrane potentials in cortical areas, leading to long-term potentiation or depression, according to the type of stimulation used (Polanía, Nitsche, & Ruff, 2018). Besides, the use of combined top-down techniques, such as CBT and tDCS have already revealed a synergistic effect in treatment-resistant depression (D'Urso, Mantovani, Micillo, Priori, & Muscettola, 2013; Segrave, Arnold, Hoy, & Fitzgerald, 2014).

Therefore, the refractory nature of BED as well the current insights from its neurobiology support the use of neuromodulatory techniques, such as tDCS, to modulate dysfunctional eating behaviors (Goldman et al., 2011; Val-Laillet et al., 2015). Thus, we have designed a randomized controlled clinical trial with parallel design that aims to test if the treatment with active-tDCS combined with a Nutritional Counseling Therapy (NCT): i) will reduce the severity of BED symptoms, measured by the Binge Eating Scale (BES), ii) enhance the inhibitory parameters of cortical excitability, measured by Transcranial Magnetic Stimulation (TMS) - Short Intracortical Inhibition (SICI).

METHODS

The protocol was revised and approved by the Ethics Committee Board of the Hospital de Clínicas de Porto Alegre (Institutional Review Board IRB 0000921) and the participants will sign the consent form after the screening and before the baseline collection. This trial is currently ongoing and is in the recruitment (screening of the patients) and data collection (protocol application) phases.

Participants

The subjects will be recruited in nutrition, psychology or psychiatric clinics, or by disclosure on social networks. The inclusion criteria are: women, aged between 18 and 65 years, literate, right-handed, with a body mass index $\geq 25 \text{ Kg/m}^2$, who complete the criteria of the V Diagnostic and Statistical Manual of Mental Disorders for Moderate Disorder of Binge Eating (4 to 7 binge eating episodes per week)- diagnosed by a psychiatrist.

Exclusion criteria are: pregnancy, shift workers (defined as working through non-standard daylight hours and/or regular shifts (that is, outside 7 a.m. to 6 p.m. and/or a 7 to 8 hour shift) (Mendoza, 2019), treatment for weight loss in the last 30 days, bariatric surgery and formal contraindication for tDCS (history of stroke, traumatic brain injury, epilepsy or family history of epilepsy, unexplained loss of consciousness, abuse or chemical dependence in the last six months, neurosurgery or presence of metallic implants).

Design overview

The participants will go through a screening and, if the criteria are completed, they sign the consent form and start the baseline phase. After that, they will be randomized to one of the four groups: (1) Active tDCS; (2) Nutritional Counseling Therapy (NCT); (3) Sham tDCS + Nutritional Counseling Therapy (NCT); (4) Active tDCS + Nutritional Counseling Therapy (NCT) (Figure 1).

The randomization table will be generated by a computer program (Randomlogue). The random number codes will be placed in sealed brown envelopes with the patient's entry sequence number on the outside of the envelope. Randomization will be in blocks of 8. A specific person will be designated for this procedure, who has no contact with the recruitment and data collections.

The study will be divided into 5 phases: 1) Baseline: basal data before beginning the treatment; 2) Intensive phase: 20 sessions of tDCS (Monday to Friday) and/or weekly NCT (5 appointments); 3) Maintenance phase: 3 sessions of tDCS (weekly) and/or weekly NCT (3 appointments); 4) Close-out: 1 to 3 days after the session of the treatment and 5) follow up: 8 weeks.

Both participant and researcher responsible by tDCS application will be blinded to the type of stimulation (active or sham) and they will only know the treatment group (tDCS or NCT), since NCT intervention does not allow blinding. However, in order to minimize bias, the personnel responsible for handling

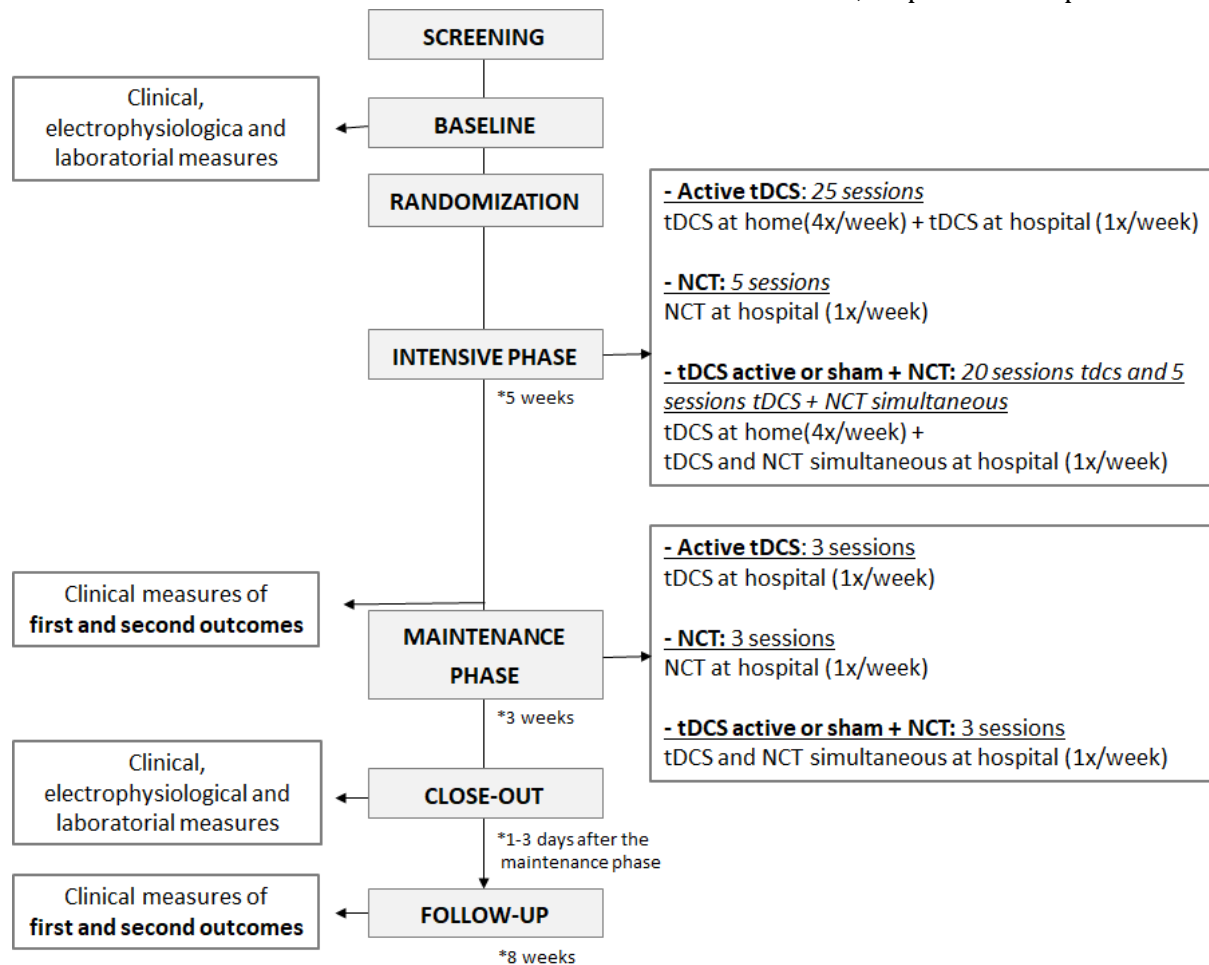


Figure 1. Study Flow. tDCS (transcranial direct current stimulation); NCT (Nutritional Counseling Therapy).

the database will also be blinded to the type of the intervention. Blinding will only be assessed after the end of the data collection. The validity of sham stimulation will be assessed by means of the blinding questionnaire for tDCS after the end of the last session, grading the degree of confidence in the response provided on a visual analog scale (1 - 10).

After completion of the study, blinding will be broken and if there is superiority in any treatment, groups that did not receive it will have the opportunity. Patients will be instructed not to start any new treatment (medication, nutritional and/or psychological) during the research period, but, if necessary, should inform the responsible research staff.

Interventions

tDCS

We will apply home-based tDCS that was developed and validated by the Pain and Neuromodulation Laboratory of the Hospital de Clínicas de Porto Alegre (HCPA) in partnership with the HCPA Biomedical Engineering Laboratory (NCT02408237) (Carvalho et al., 2018). The study protocol is designed to apply 2 mA direct current to the right dorsolateral prefrontal cortex (anode) and to the left dorsolateral prefrontal cortex (cathode) for 20 minutes.

- Active tDCS: anodic current of 2mA (fade in/out: 10 seconds) for 20 minutes.
- Sham tDCS: the placement of the electrodes for sham stimulation will be exactly the same as the active ETCC; however, after 20 seconds, stimulation automatically turns off.

Patients will undergo training on day 1 of the survey and will do 20 stimulation sessions at home (4 days/week – except weekends) + 1x/week at the hospital. After finalizing this phase, patients will perform 3 weekly stimulations at the hospital (1x/week), for a total of 28 sessions per patient. The device presents safety features for adjustment of the tolerability and resistance intensity, ending the session if necessary and blocking the next session for 20h, avoiding excessive use (Carvalho et al., 2018).

Nutritional Counseling Therapy

The program is based on psychoeducational and cognitive-behavioral techniques, acting directly on dysfunctional eating attitudes (McElroy, Guerdjikova, Mori, Munoz, & Keck, 2015; Murphy, Straebler, Cooper, & Fairburn, 2010). Weekly presential meetings will be held, with the first meeting lasting 1 hour in person and the subsequent meetings lasting 20 minutes using a video during the outpatient consultation. After each session, patients will have 20 minutes to answer questions. They will have weekly exercises related to the topic. The topics and the exercises are detailed in **Table 1**.

tDCS + NCT

The patient will perform tDCS at home, which can be active or sham, according to the protocol described above. Furthermore, tDCS + NCT will be undergone simultaneously during the outpatient consultation session for 8 weeks.

Week	NCT topic	NCT Exercise
1	Psychoeducation on BED and tDCS Expectations/motivations with treatment	None
2	Identification of feelings and emotions and how they interfere with our diet	Food record: Food, feeling of hunger, satiety, emotions related to food
3	Neurophysiology of eating	Guided food record review
4	Beliefs	Record of Dysfunctional Thoughts
5	Trigger situations + Mindful eating	Mindful eating
6	Organizing the food routine	Goals related to food routine
7	Coping card	Coping card
8	Relapse prevention and closure	Maintenance plan

Table 1. Detailed Nutritional Counseling Therapy (NCT) protocol. BED (binge eating disorder); tDCS (transcranial direct current stimulation).

Outcomes

The primary outcomes will be the reduction on the severity of symptoms of binge eating, measured by the BES and the measure of cortical inhibition, evaluated through TMS (SICI). The secondary outcomes will be i) clinical: Weight, waist circumference and measures of eating behavior (TFEQ-21) and eating attitudes (FCQ); ii) Electrophysiological: Measurements of cortical excitability (TMS: ICF and silent period); Inhibitory control (Go/No-go task); iii) Laboratorial: serum leptin.

Measures

All measures will be examined by the same evaluator to reduce variability and will be evaluated at the baseline and close-out phases, except the psychiatric interview that will be measured only at baseline. The clinical measures of the first and second outcomes (BES, TFEQ-21 and FCQ) will be evaluated at intermediary and follow-up phases. Measures of accompanying and anthropometric measures will be evaluated weekly throughout all of the phases, as represented in **Figure 2** and **Figure 3**.

Clinical

Demographic questionnaire:

To assess general health information, such as use of medications, previous psychological or nutritional therapy, and educational level.

Confounding variables:

Psychiatric disorders, sleep quality, depressive symptomatology, central sensitization, anxiety and physical activity were selected as confounding variables and they will be assessed through the corresponding questionnaires: Structured Clinical Interview for DSM-5 Clinician Version (SCID-5-CV); Pittsburgh Sleep Quality Index (PSQI) (Bertolazi et al., 2011); Beck Depression Inventory II (BDI - II) (Gomes-Oliveira, Gorenstein, Neto, Andrade, & Wang, 2012); Brazilian Portuguese-Central Sensitization Inventory (BP-CSI) (Caumo et al., 2017); State-Trait Anxiety Inventory (STAI) (Balle et al., 2010); International Physical Activity Questionnaires-Long form (IPAQ-L) (Craig et al., 2003).

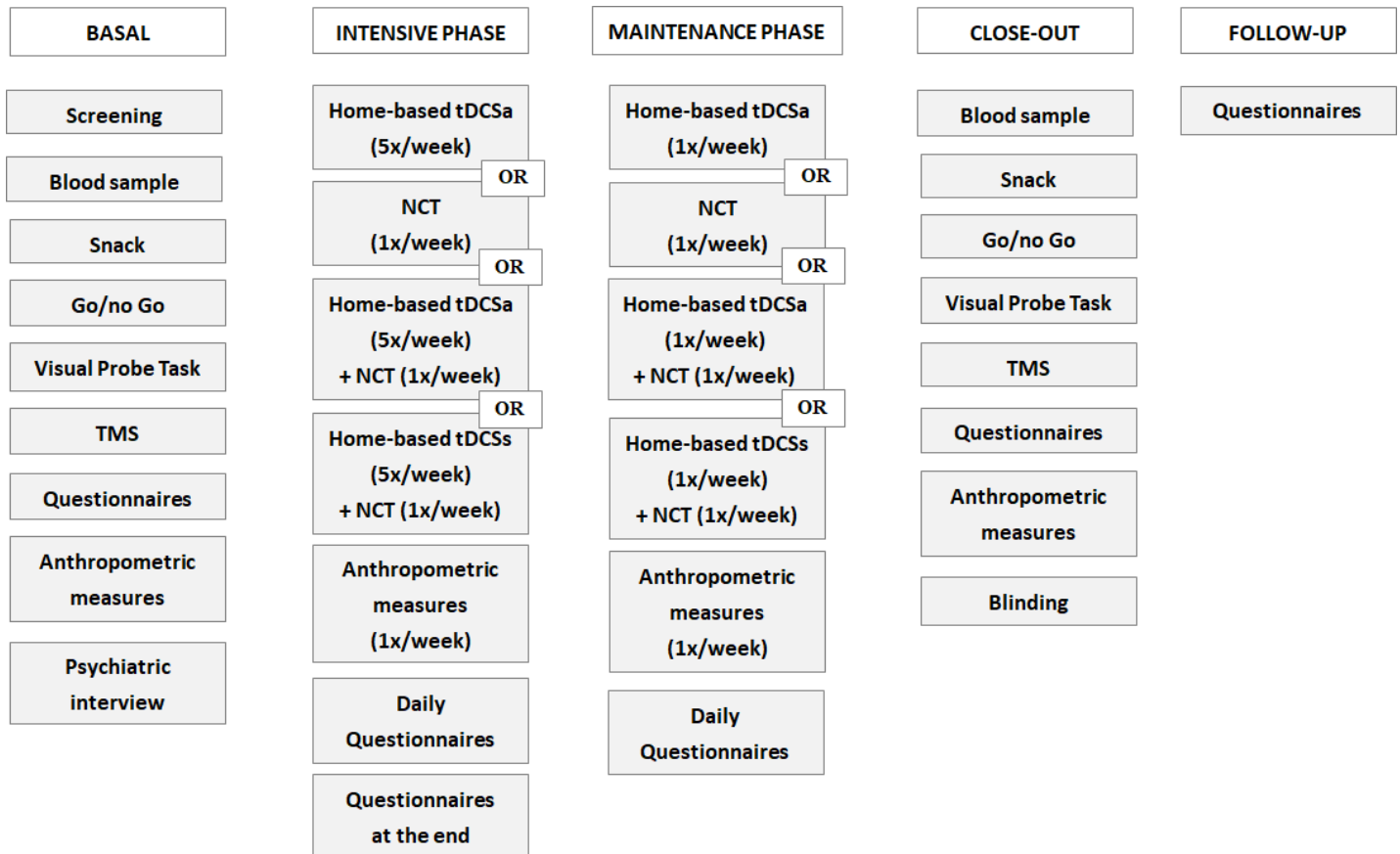


Figure 2. Assessment sequence according to study phase. tDCSa (active transcranial direct current stimulation); tDCSs (sham transcranial direct current stimulation); NCT (Nutritional Counseling Therapy); TMS (Transcranial Magnetic Stimulation).

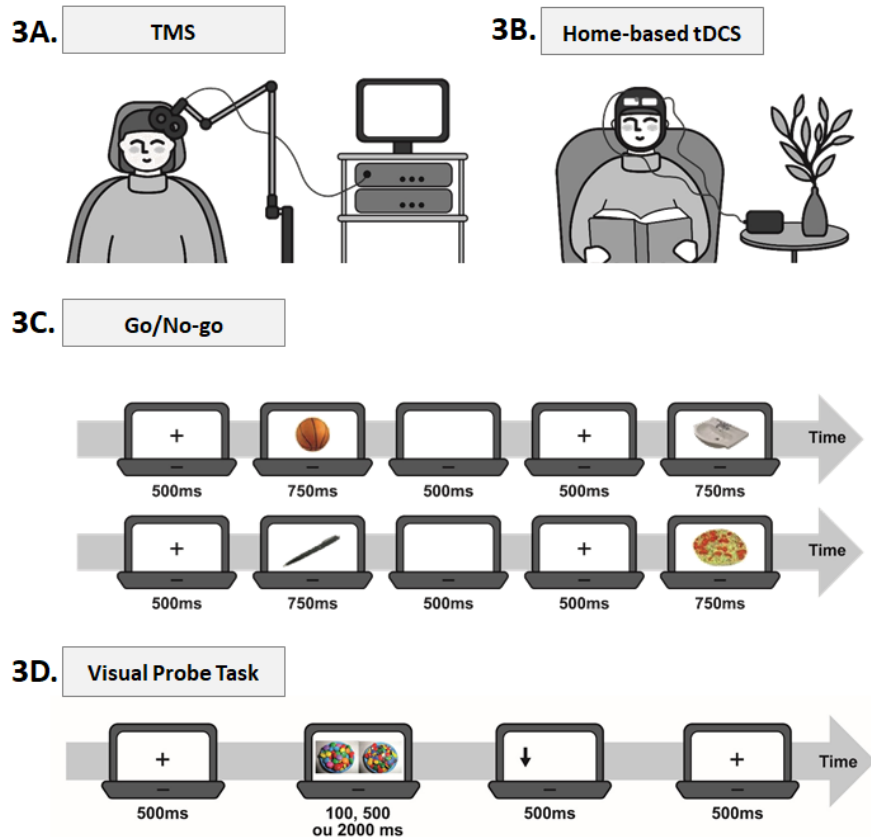


Figure 3. Home-based tDCS stimulation, neurophysiological assessment and test paradigms. (3A) Transcranial Magnetic Stimulation (TMS) parameters will be assessed at baseline and close-out phases. (3B) Home-based transcranial direct current stimulation (tDCS) protocol: The sessions will be executed 5 times/week (4 times at home and 1 time at hospital). (3C) Go/No-go paradigm: A total of 200 randomized trials will be presented (neutral and food stimuli) in a ratio of 80% 'go' and 20% 'no - Go'. The time of each image is specified above. The participants have to press the keyboard space bar whenever a target (Go) stimulus is presented. (3D) Visual Probe task: Two paired similar images will be presented (food and related to food stimuli). Each time is specified in the figure above. The participants will be instructed to press in the keyboard the direction of the narrow.

Anthropometric measurements:

Body weight, height, BMI and waist circumference. Obesity and overweight will be classified according to WHO criteria (WHO, 2000). Abdominal circumference will be measured in centimeters at the point of greatest circumference, using a non-stretchable measuring tape.

Three-Factor Eating Questionnaire - 21 (TFEQ-21):

Access three dimensions of human eating behavior. Cognitive Restriction is characterized as limiting food intake to control weight; Uncontrolled Eating is a tendency to lose control over eating due to hunger or when exposed to external environments (eg, hyperpalatable food), even in the absence of physiological hunger; Emotional Eating is a susceptibility to eat in response to emotional stress or negative mood. The score corresponds to a converted scale, ranging from 0 to 100 to each domain, where higher scores are equivalent to more dysfunctional behavior (de

Medeiros, Yamamoto, Pedrosa, & Hutz, 2016; Stunkard & Messick, 1985).

Binge Eating Scale (BES):

Measures the severity of binge eating (BE). It is composed of 16 items, 8 that describe behavioral manifestations and 8 on associated feelings and cognitions. The score range from 0 to 46 points, where a score of less than 17 points indicates minimal BE behavior; a score between 18 and 26 points indicates moderate BE, and a score of more than 27 points indicates severe BE (Freitas, Lopes, Coutinho, & Appolinario, 2001; Gormally, Black, Daston, & Rardin, 1982).

State and Trait Food Cravings Questionnaires (FCQ):

The FCQ explore about cravings, urges or desires for one or more specific types of food. The Food Cravings Questionnaire-State (FCQ-S) investigates state

dependent food craving and consists of 15 questions, grouped into five dimensions. The score corresponds to the sum of the scores (1 'Strongly Agree' to 5 'Strongly Disagree') and can vary from 15 to 75 (Cepeda-Benito et al., 2000; Queiroz de Medeiros, Campos Pedrosa, Hutz, & Yamamoto, 2016). The Food Cravings Questionnaire-Trait (FCQ-T) identifies patterns related with food-craving behavior and consists of 39 questions, divided into nine dimensions. The score corresponds to the sum of the scores (1 'never or not applicable' to 6 'always') and can vary from 39 to 234 (Cepeda-Benito et al., 2000; Queiroz de Medeiros et al., 2016).

Disordered Eating Attitude Scale (DEAS):

Assesses the individual's eating attitudes. It is a 25-item questionnaire. The questions are distributed in five subscales: (1) Relationship with food; (2) Concerns about eating and body weight gain; (3) Restrictive and compensatory practices; (4) Feelings toward eating; and (5) Idea of normal eating. Higher scores mean worse eating attitude. The result corresponds to the sum of the scores (1 to 6) and can vary from 37 to 190 (Alvarenga, Scagliusi, & Philippi, 2010).

Perception of hunger, feeling of hunger, satiety and appetite to specific (sweet and savory) and unspecific foods:

10-point numerical rating scale [from 0 (any desire or need to eat) to 10 (very prominent desire or need to eat)], according to a previous protocol (Jauch-Chara et al., 2014).

Feeling of loss of control on eating:

10-point numerical rating scale [from 0 (any loss of control) to 10 (loss of total control)]. Filled daily.

Number of binge-eating episodes:

Patients must fill in the number of episodes of binge eating daily.

Food pattern questionnaire:

Evaluates food consumption indicators considered markers of healthy and unhealthy eating patterns. The score corresponds to the frequency of consumption (Brasil, 2017).

Electrophysiological measures

Transcranial Magnetic Stimulation:

TMS is a measure of the excitability and conductivity of corticospinal motor pathways. We will use a MagProX100 stimulator with a figure-eight coil

(MagVenture Company, Lucernemarken, Denmark) over the left primary motor cortex (M1) and surface electromyography electrodes placed on the right first dorsal interosseous (FDI) muscle and its tendon.

The following parameters will be evaluated: Motor threshold (MT), in which the resting motor threshold is defined as the minimal intensity that produces a motor evoked potential >50 μ V in 5 of 10 trials in a relaxed muscle (Radhu et al., 2013), followed by single-pulse TMS with an intensity of 130% of MT to record 10 motor evoked potential (MEP); and Cortical Silent Period (CSP), recorded in milliseconds (ms) using an intensity of 120% of MT during FDI muscle activity measured on a dynamometer set to approximately 25% of the maximal force. The average of 10 sequential measures will be recorded. The TMS protocol, to measure SICI and ICF, will use a total of 30 randomized paired-pulse trials, 10 for each measure (SICI, ICF, and control stimuli) with an interstimulus interval (ISI) to evaluate the SICI equal to 2ms and 12ms for ICF respectively, with the first individual conditioning stimulus set at 80% of the MT, while the test stimulus being set at 130% (Kujirai et al., 1993; Pascual-Leone, Valls-Solé, Wassermann, & Hallett, 1994).

Physiologically, each TMS parameter has a specific translation: CSP appear to be assessing GABA-B receptor-mediated inhibitory neurotransmission (Radhu et al., 2013); Short Intracortical Inhibition (SICI) associated to GABA-A receptor-mediated inhibitory function (Radhu et al., 2013); and Intracortical Facilitation (ICF) originates from excitatory postsynaptic potentials transmitted by N-methyl-D-aspartate (NMDA) glutamate receptors (Radhu et al., 2013).

Go/No-go paradigm:

Performed to assess the response inhibition. Designed and run using E-Prime™ software (Psychology Software Tools, Inc., Sharpsburg, PA, USA) and the images from the Bank of Standardized Stimuli (BOSS) (Brodeur, Dionne-Dostie, Montreuil, & Lepage, 2010). In the neutral-based task, the target (Go) stimulus will be toiletries images, while the non-target (No-go) stimulus images of sports equipment. In the food-based task, the target (Go) stimulus was images of neutral office supplies; while the non-target (No-go) stimulus was the images of high-fat and/or high-sugar foods. Patients will be instructed to look at a fixation cross in the center of the screen and afterwards an image will be shown (for 500 ms), they'll be instructed to answer as fast as possible by pressing the keyboard space bar whenever

a target (Go) stimulus was presented (80% of trials) and not answer to an infrequently presented nontarget (No-go stimulus (20% of trials). The interstimulus interval (ISI) is 1,000ms (trial length=1,500ms). The presentation order will be fully counterbalanced. The measure of interest is the number of commission errors (the number of incorrect answers performed during the No-go trials) (Price, Lee, & Higgs, 2016). The entire task consisted of 200 trials divided into two 100 trial runs and the last 750ms/each.

Visual Probe Task:

Used as a measure of attentional bias. Paired images will be simultaneously displayed side-by-side on a computer screen, where one is related to the target (pictures of food) and the other to the control (very similar to the target but not food related). After 100, 500 or 2000ms the images will randomly disappear and an arrow will be exhibited (500ms), and the participants will have to point in the keyboard the direction of the arrow. The arrow switches the target and the control images by 50%. Therefore, the shorter the reaction time when the arrow replaces the stimuli, the higher is the attentional bias to the stimulus tested (pictures of food) (Deluchi, Costa, Friedman, Gonçalves, & Bizarro, 2017).

Laboratory Measures

Blood samples will be collected in the morning (8-11 a.m.) after a 12-h fasting period. The blood samples will be placed in plastic tubes with separator gel and centrifuged for 10 minutes at 4.500 rpm at 4°C. Serum will be stored at -80°C. Serum mediator concentrations will be determined for Brain-derived Neurotrophic Factor (BDNF), which plays an important role in the regulation of neuronal survival, growth and differentiation (Merighi et al., 2008), and a predictor of tDCS therapeutic response (Brietzke et al., 2020) and leptin, which is an anorectic peptide hormone that regulates the function of the autonomic system and the energy balance both on homeostatic and hedonic systems (Brandão et al., 2010).

Adverse effects

In order to assess potential adverse effects of tDCS, a standard tDCS Side Effects Questionnaire will be used (Carvalho, 2018).

Treatment compliance

The adherence of tDCS treatment will be defined as the performance of at least 95% of the proposed sessions. The percentage of completed sessions will be calculated

after the report has been generated by the software analysis of tDCS at the end of the treatment. This software allows users to extract the recorded sessions, providing data concerning all the sessions performed, including the duration of stimulation, the current intensity applied and the contact impedance of each session (Carvalho, 2018).

As tDCS, the adherence of NCT treatment will be considered as the accomplishment of at least 95% of the proposed tasks. NCT compliance will be assessed through the confirmation of prescribed tasks that shall be delivered during the weekly schedule appointments.

Statistical procedures

Sample size

Due to the lack of studies that associate tDCS with NCT in individuals with BED, we will conduct a pilot study with 10 patients in each group (n=40). Afterwards, this will be evaluated by a blinded technician who will analyze the data, accepting a 0.05 type I error chance and a 90% power (beta = 0.1).

Data analysis

The data entry will be conducted by two blinded researchers who will perform range checks for data values. The distribution of variables will be described as mean and standard deviation or frequency and proportion, when applicable. The comparison between groups of means of the variables will be carried out using one-way ANOVA or ANCOVA, when the variables show normal distribution or equivalent test for non-statistical parametric, if the normality criteria are violated.

The differences within the variables will be obtained through ANOVA, controlled for variables that can be considered confounders. In addition, we intend to assess possible correlations between additional clinical variables between groups. In the event of patient withdrawal or loss, the analysis of the results will be made by ITT (intention to treat): if the loss occurs in the intervention group, in evaluation of outcomes will be considered the worst result, that is, that there was no improvement in that case. If the loss occurs in the placebo group, the best outcome will be considered, that is, there was an improvement in the assessed outcome.

The study protocol was written in accordance with Standard Recommendations for Interventional Trials (SPIRIT) guidelines.

DISCUSSION

To our knowledge, this is the first study to investigate the benefits of repetitive tDCS sessions over the right DLPFC associated with NCT in BED patients, on the severity of the symptoms and inhibitory cortical parameters. Studies in healthy populations indicate that tDCS is able to positively influence cognitive functions, involving the regions of the Pre-Frontal Cortex (CPF), which is relevant to CBT. (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016). Specifically, it has been shown that tDCS can improve the use of reevaluation strategies and cognitive control techniques necessary for emotional regulation (Bajbouj et al., 2018). Segrave et al (2014) in a sample of patients with Major Depression Disorder (MDD) found that the group using the combined tDCS + CBT therapy had a sustained antidepressant response at follow-up (3 weeks), whose magnitude was greater than that observed immediately after completion treatment (Segrave et al., 2014).

Several studies provide preliminary evidence to suggest that neurostimulation has the potential to alter disordered eating behaviors, food intake and body weight after one or more tDCS sessions aimed at enhancing both right and left DLPFC activity in lean, overweight/obese and BED individuals (Dendy, Stinson, Guerithault, & Gluck, 2019; Burgess et al., 2016). However, fewer studies have examined the efficacy of TDCS over the longer term (Dendy et al., 2019) and none have associated this promising treatment with the existing reference treatment, so there are still several gaps that need to be explored, such as patient selection, intervention parameters, treatment goals and how to optimize existing protocols (Dalton, Bartholdy, Campbell, & Schmidt, 2018)

Thus, this protocol was designed to include a total of 28 anodal tDCS sessions over the right DLPFC associated to a NCT. Our hypothesis is that therapeutic approaches aimed at modulating the CNS, such as tDCS, may have a beneficial effect on the neurobiology of the processes that govern these disorders, thus adding to the effects of CBT and amplifying the therapeutic response.

This study presents an important contribution to the field because, to the best of our knowledge, is the first to combine the reference treatment (Cognitive-Behavioral approaches through nutritional counselling therapy) to neuromodulation of DLPFC using tDCS technique in the treatment of BED. Other strengths of this protocol are the long-term treatment and the home-based tDCS design, which are critical to assure behavioral changes, improve treatment compliance and

feasibility. On the other hand, this protocol may have some limitations. Due to the nature of NCT, patients and the researcher responsible for applying NCT will be aware of this treatment, which compromises a double-blind design. However, we determined appropriate measures to minimize the possible biases arising from this limitation: the research team responsible for outcome measures and data analysis will be blinded to the intervention performed.

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Declaration of conflict of interest:

The authors declare that there is no financial or other relationship, which might lead to conflicts of interest to any of the following arrangements: financial relationship to the work; company employees; company consultants; company stockholders; members of a speaker's bureau or any other form of financial compensation. FF is the editor-in-chief of the

Principles and Practice of Clinical Research journal and WC is an associate editor. Therefore, they excused themselves from the peer-review process and followed the journal guidelines for peer-reviewing when an editor co-authors a manuscript. They did not influence the editorial process and final publication decision.

REFERENCES

- Alvarenga, M. dos S., Scagliusi, F. B., & Philippi, S. T. (2010). Development and Validity of the Disordered Eating Attitude Scale (Deas). *Perceptual and Motor Skills*, 110(2), 379–395. <https://doi.org/10.2466/pms.110.2.379-395>.
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). <https://doi.org/https://doi.org/10.1176/appi.books.9780890425596>.
- Bajbouj, M., Aust, S., Spies, J., Herrera-Melendez, A.-L., Mayer, S. V., Peters, M., ... Padberg, F. (2018). PsychotherapyPlus: augmentation of cognitive behavioral therapy (CBT) with prefrontal transcranial direct current stimulation (tDCS) in major depressive disorder—study design and methodology of a multicenter double-blind randomized placebo-controlled trial. *European Archives of Psychiatry and Clinical Neuroscience*, 268(8), 797–808. <https://doi.org/10.1007/s00406-017-0859-x>.
- Balle, M., Chachamovich, E., Paz, M., Hidalgo, L., Lucena, I., & Caumo, W. (2010). Evaluation of the structure of Brazilian State-Trait Anxiety Inventory using a Rasch psychometric approach. *Journal of Psychosomatic Research*, 68(3), 223–233. <https://doi.org/10.1016/j.jpsychores.2009.09.013>.
- Bertolazi, A. N., Fagundes, S. C., Hoff, L. S., Dartora, E. G., da Silva Miozzo, I. C., de Barba, M. E. F., & Menna Barreto, S. S. (2011). Validation of the Brazilian Portuguese version of the Pittsburgh Sleep Quality Index. *Sleep Medicine*, 12(1), 70–75. <https://doi.org/10.1016/j.sleep.2010.04.020>.
- Blume, M., Schmidt, R., & Hilbert, A. (2019). Abnormalities in the EEG power spectrum in bulimia nervosa, binge-eating disorder, and obesity: A systematic review. *European Eating Disorders Review*, 27(2), 124–136. <https://doi.org/10.1002/erv.2654>.
- Brandão, P. P., Garcia-souza, E. P., Neves, F. A., Jose, M., Sichiari, R., Moura, E. G. De, ... Moura, A. S. (2010). Leptin/adiponectin ratio in obese women with and without binge eating disorder. *Neuro Endocrinol Lett*, 31(3):353-8. PMID: 20588239.
- Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância de Doenças e Agravos não Transmissíveis e Promoção da Saúde. (2017) *Vigitel Brazil 2016: surveillance of risk and protective factors for chronic diseases by telephone survey: estimates of sociodemographic frequency and distribution of risk and protective factors for chronic diseases in the capitals of the 26 Brazilian states and the Federal District in 2016.* / Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância de Doenças e Agravos não Transmissíveis e Promoção da Saúde. – Brasília: Ministério da Saúde. 160p.: il. ISBN 978-85-334-2479-1.
- Brietzke, A. P., Zortea, M., Carvalho, F., Sanches, P. R. S., Silva, D. P. J., Torres, I. L. da S., ... Caumo, W. (2020). Large Treatment Effect With Extended Home-Based Transcranial Direct Current Stimulation Over Dorsolateral Prefrontal Cortex in Fibromyalgia: A Proof of Concept Sham-Randomized Clinical Study. *The Journal of Pain*, 21(1–2), 212–224. <https://doi.org/10.1016/j.jpain.2019.06.013>.
- Brodeur, M. B., Dionne-Dostie, E., Montreuil, T., & Lepage, M. (2010). The bank of standardized stimuli (BOSS), a new set of 480 normative photos of objects to be used as visual stimuli in cognitive research. *PLoS ONE*, 5(5). <https://doi.org/10.1371/journal.pone.0010773>.
- Burgess, E. E., Sylvester, M. D., Morse, K. E., Amthor, F. R., Mrug, S., Lokken, K. L., ... Boggiano, M. M. (2016). Effects of transcranial direct current stimulation (tDCS) on binge-eating disorder. *International Journal of Eating Disorders*, 49(10), 930–936. <https://doi.org/10.1002/eat.22554>.
- Byrne, S. M., Fursland, A., Allen, K. L., & Watson, H. (2011). The effectiveness of enhanced cognitive behavioural therapy for eating disorders: An open trial. *Behaviour Research and Therapy*, 49(4), 219–226. <https://doi.org/10.1016/j.brat.2011.01.006>.
- Carvalho, F., Brietzke, A. P., Gasparin, A., dos Santos, F. P., Verdelino, R., Ballester, R. F., ... Caumo, W. (2018). Home-Based Transcranial Direct Current Stimulation Device Development: An Updated Protocol Used at Home in Healthy Subjects and Fibromyalgia Patients. *Journal of Visualized Experiments*, (137). <https://doi.org/10.3791/57614>.
- Caumo, W., Antunes, L. C., Elkfury, J. L., Herbstrith, E. G., Sipmann, R. B., Souza, A., ... Neblett, R. (2017). The central sensitization inventory validated and adapted for a Brazilian population: Psychometric properties and its relationship with brain-derived neurotrophic factor. *Journal of Pain Research*, 10(1), 2109–2122. <https://doi.org/10.2147/JPR.S131479>.
- Cepeda-Benito, A., Gleaves, D. H., Williams, T. L., & Erath, S. A. (2000). The development and validation of the state and trait food-cravings questionnaires. *Behavior Therapy*, 31(1), 151–173. [https://doi.org/10.1016/S0005-7894\(00\)80009-X](https://doi.org/10.1016/S0005-7894(00)80009-X).
- Craig, C. L., Marshall, A. L., Sjöström, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., ... Oja, P. (2003). International physical activity questionnaire: 12-Country reliability and validity. *Medicine and Science in Sports and Exercise*, 35(8), 1381–1395. <https://doi.org/10.1249/01.MSS.0000078924.61453.FB>.
- D’Urso, G., Mantovani, A., Micillo, M., Priori, A., & Muscettola, G. (2013). Transcranial direct current stimulation and cognitive-behavioral therapy: Evidence of a synergistic effect in treatment-resistant depression. *Brain Stimulation*, 6(3), 465–467. <https://doi.org/10.1016/j.brs.2012.09.003>.
- Dalton, B., Bartholdy, S., Campbell, I. C., & Schmidt, U. (2018). Neurostimulation in Clinical and Sub-clinical Eating Disorders: A Systematic Update of the Literature. *Current Neuropharmacology*, 16(8), 1174–1192. <https://doi.org/10.2174/1570159X1666618010811532>.
- Davis, C. (2015). The epidemiology and genetics of binge eating disorder (BED). *CNS Spectrums*, 20(6), 522–529. <https://doi.org/10.1017/S1092852915000462>.
- de Medeiros, A. C. Q., Yamamoto, M. E., Pedrosa, L. F. C., & Hutz, C. S. (2016). The Brazilian version of the three-factor eating questionnaire-R21: psychometric evaluation and scoring pattern. *Eating and Weight Disorders*, 22(1), 169–175. <https://doi.org/10.1007/s40519-016-0256-x>.
- Dedoncker, J., Brunoni, A. R., Baeken, C., & Vanderhasselt, M.-A. (2016). A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. *Brain Stimulation*, 9(4), 501–517. <https://doi.org/10.1016/j.brs.2016.04.006>.
- Deluchi, M., Costa, F. S., Friedman, R., Gonçalves, R., & Bizarro, L. (2017). Attentional bias to unhealthy food in individuals with severe obesity and binge eating. *Appetite*, 108, 471–476. <https://doi.org/10.1016/j.appet.2016.11.012>.
- Dendy, R., Stinson, E. J., Guerithault, N., & Gluck, M. E. (2019). Brain Stimulation to Modulate Food Intake and Eating Behavior. *Current Diabetes Reports*, 19(12), 152. <https://doi.org/10.1007/s11892-019-1250-2>.
- Fairburn, C. G., Bailey-Straebl, S., Basden, S., Doll, H. A., Jones, R., Murphy, R., ... Cooper, Z. (2015). A transdiagnostic comparison of enhanced cognitive behaviour therapy (CBT-E) and interpersonal psychotherapy

- in the treatment of eating disorders. *Behaviour Research and Therapy* (Vol. 70). Elsevier Ltd. <https://doi.org/10.1016/j.brat.2015.04.010>.
- Fairburn, C. G., Cooper, Z., Doll, H. A., O'Connor, M. E., Bohn, K., Hawker, D. M., ... Palmer, R. L. (2009). Transdiagnostic Cognitive-Behavioral Therapy for Patients With Eating Disorders: A Two-Site Trial With 60-Week Follow-Up. *American Journal of Psychiatry*, 166(3), 311–319. <https://doi.org/10.1176/appi.ajp.2008.08040608>.
- Flückiger, C., Meyer, A., Wampold, B. E., Gassmann, D., Messerli-Bürge, N., & Munsch, S. (2011). Predicting Premature Termination Within a Randomized Controlled Trial for Binge-Eating Patients. *Behavior Therapy*, 42(4), 716–725. <https://doi.org/10.1016/j.beth.2011.03.008>.
- Freitas, S., Lopes, C. S., Coutinho, W., & Appolinario, J. C. (2001). Translation and adaptation into Portuguese of the Binge-Eating Scale. *Rev Bras Psiquiatr*, 23(4), 215–220. <https://doi.org/10.1590/S1516-44462001000400008>.
- Gluck, M. E., Viswanath, P., & Stinson, E. J. (2017). Obesity, Appetite, and the Prefrontal Cortex. *Curr Obes Rep*, 6(4):380-388. <https://doi.org/10.1007/s13679-017-0289-0>.
- Goldman, R. L., Borckardt, J. J., Frohman, H. A., O'Neil, P. M., Madan, A., Campbell, L. K., ... George, M. S. (2011). Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. *Appetite*, 56(3), 741–746. <https://doi.org/10.1016/j.appet.2011.02.013>.
- Gomes-Oliveira, M. H., Gorenstein, C., Neto, F. L., Andrade, L. H., & Wang, Y. P. (2012). Validation of the Brazilian Portuguese Version of the Beck Depression Inventory-II in a community sample. *Revista Brasileira de Psiquiatria*, 34(4), 389–394. <https://doi.org/http://dx.doi.org/10.1016/j.rbp.2012.03.005>.
- Gormally, J., Black, S., Daston, S., & Rardin, D. (1982). The assessment of binge eating severity among obese persons. *Addictive Behaviors*, 7(1), 47–55. [https://doi.org/10.1016/0306-4603\(82\)90024-7](https://doi.org/10.1016/0306-4603(82)90024-7).
- Imperatori, C., Fabbriatore, M., Farina, B., Innamorati, M., Quintiliani, M. I., Lamis, D. A., ... Speranza, A. M. (2015). Alterations of EEG functional connectivity in resting state obese and overweight patients with binge eating disorder: A preliminary report. *Neuroscience Letters*, 607, 120–124. <https://doi.org/10.1016/j.neulet.2015.09.026>.
- Jauch-Chara, K., Kistenmacher, A., Herzog, N., Schwarz, M., Schweiger, U., & Oltmanns, K. M. (2014). Repetitive electric brain stimulation reduces food intake in humans. *American Journal of Clinical Nutrition*, 100(4), 1003–1009. <https://doi.org/10.3945/ajcn.113.075481>.
- Khedr, E. M., El Fetoh, N. A., El Bieh, E., Ali, A. M., & Karim, A. A. (2014). Altered cortical excitability in anorexia nervosa. *Neurophysiologie Clinique/Clinical Neurophysiology*, 44(3), 291–299. <https://doi.org/10.1016/j.neucli.2014.08.002>.
- Kessler, R. M., Hutson, P. H., Herman, B. K., & Potenza, M. N. (2016). The neurobiological basis of binge-eating disorder. *Neuroscience & Biobehavioral Reviews*, 63, 223–238. <https://doi.org/10.1016/j.neubiorev.2016.01.013>.
- Kobayashi, M., & Pascual-Leone, A. (2003). Transcranial magnetic stimulation in neurology. *Lancet*, 2(3), 145–156. [https://doi.org/10.1016/s1474-4422\(03\)00321-1](https://doi.org/10.1016/s1474-4422(03)00321-1).
- Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., ... Marsden, C. D. (1993). Corticocortical inhibition in human motor cortex. *The Journal of Physiology*, 471(1), 501–519. <https://doi.org/10.1113/jphysiol.1993.sp019912>.
- McElroy, S. L., Guerdjikova, A. I., Mori, N., Munoz, M. R., & Keck, P. E. (2015). Overview of the treatment of binge eating disorder. *CNS Spectrums*, 20(6), 546–556. <https://doi.org/10.1017/S1092852915000759>.
- Mendoza, J. (2019). Food intake and addictive-like eating behaviors: Time to think about the circadian clock(s). *Neuroscience & Biobehavioral Reviews*, 106, 122–132. <https://doi.org/10.1016/j.neubiorev.2018.07.003>.
- Merighi, A., Salio, C., Ghirri, A., Lossi, L., Ferrini, F., Betelli, C., & Bardoni, R. (2008). BDNF as a pain modulator. *Progress in Neurobiology*, 85(3), 297–317. <https://doi.org/10.1016/j.PNEUROBIO.2008.04.004>.
- Murphy, R., Straebler, S., Cooper, Z., & Fairburn, C. G. (2010). Cognitive behavioral therapy for eating disorders. *Psychiatric Clinics of North America*, 33(3), 611–627. <https://doi.org/10.1016/j.psc.2010.04.004>.
- Pascual-Leone, A., Valls-Solé, J., Wassermann, E. M., & Hallett, M. (1994). Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain*, 117(4), 847–858. <https://doi.org/10.1093/brain/117.4.847>.
- Polanía, R., Nitsche, M. A., & Ruff, C. C. (2018). Studying and modifying brain function with non-invasive brain stimulation. *Nature Neuroscience*, 21(2), 174–187. <https://doi.org/10.1038/s41593-017-0054-4>.
- Price, M., Lee, M., & Higgs, S. (2016). Food-specific response inhibition, dietary restraint and snack intake in lean and overweight/obese adults: A moderated-mediation model. *International Journal of Obesity*, 40(5), 877–882. <https://doi.org/10.1038/ijo.2015.235>.
- Queiroz de Medeiros, A. C., Campos Pedrosa, L. F., Hutz, C. S., & Yamamoto, M. E. (2016). Brazilian version of food cravings questionnaires: Psychometric properties and sex differences. *Appetite*, 105, 328–333. <https://doi.org/10.1016/j.appet.2016.06.003>.
- Radhu, N., de Jesus, D. R., Ravindran, L. N., Zanjani, A., Fitzgerald, P. B., & Daskalakis, Z. J. (2013). A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders. *Clinical Neurophysiology*, 124(7), 1309–1320. <https://doi.org/10.1016/j.clinph.2013.01.014>.
- Rossini, P. M., Rosinni, L., & Ferreri, F. (2010). Transcranial Magnetic Stimulation: A Review. *IEEE Engineering in Medicine and Biology Magazine*, 29(1), 84–96. <https://doi.org/10.1109/memb.2009.935474>.
- Segrave, R. A., Arnold, S., Hoy, K., & Fitzgerald, P. B. (2014). Concurrent cognitive control training augments the antidepressant efficacy of tDCS: A pilot study. *Brain Stimulation*, 7(2), 325–331. <https://doi.org/10.1016/j.brs.2013.12.008>.
- Stunkard, A. J., & Messick, S. (1985). The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *Journal of Psychosomatic Research*, 29(1), 71–83. [https://doi.org/10.1016/0022-3999\(85\)90010-8](https://doi.org/10.1016/0022-3999(85)90010-8).
- Tammela, L. I., Pääkkönen, A., Karhunen, L. J., Karhu, J., Uusitupa, M. I. J., & Kuikka, J. T. (2010). Brain electrical activity during food presentation in obese binge-eating women. *Clinical Physiology and Functional Imaging*, 30(2), 135–140. <https://doi.org/10.1111/j.1475-097X.2009.00916.x>.
- Val-Laillet, D., Aarts, E., Weber, B., Ferrari, M., Quaresima, V., Stoeckel, L. E., ... Stice, E. (2015). Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity. *NeuroImage: Clinical*, 8, 1–31. <https://doi.org/10.1016/j.NICL.2015.03.016>.
- WHO. (2000). Obesity: preventing and managing the global epidemic. World Health Organization.