TITLE: Transcranial Magnetic Stimulation and Inhibitory Control Training to Reduce Binge Eating: Brain and Behavioral Changes (BE-NEMOIC)

Code: ProyExcel_00776

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Brief Summary: People with BE are characterized by high impulsivity, high levels of craving for high-calorie foods, deficits in inhibitory control, and maladaptive decision making. These characteristics are related, at brain level, to alterations in the activation of areas such as the dorsolateral prefrontal cortex (DLPC) and ventromedial prefrontal cortex (vmPFC) among other brain areas and their connectivity. We propose an intervention that seeks to target these issues. Thus, the present study aims to characterize the effects of neuromodulation with theta burst transcranial magnetic stimulation (iTBS) of the DLPFC or the vmPFC in combination with inhibitory control training to produce brain, cognitive, behavioral changes and modify altered biological parameters in people with BE. Participants will be randomly allocated to one of three groups: 1) a group that will receive active iTBS of the DLPFC, 2) a group that will receive active iTBS of the vmPFC, and 3) an active control group that will receive sham iTBS of the vertex. The three groups will also receive inhibitory control training with a food Go/NoGo paradigm after the iTBS. We hypothesized that neuromodulation with iTBS applied to DLPFC or vmPFC will modify the dynamics of different brain circuits associated with binge eating. Stimulation of the DLPFC and vmPFC in combination with inhibitory control training, will be associated with: (i) decreased appraisal of unhealthy foods, (ii) reduced food craving, (iii) improved eating behavior, (iv) modified brain connectivity and activation both at rest and linked to task performance with food stimuli, (v) a decrease in the frequency and intensity of binge eating, (vi) improved emotional symptoms and emotional eating (depression, anxiety, emotional regulation, emotional eating, reward-related eating, non-homeostatic eating), (vii) improved cognitive abilities (motor and cognitive inhibition, delay of gratification, impulsivity, working memory, cognitive flexibility and decision making), (viii) changes in biological parameters associated to the interventions (blood and microbiota), and (ix) advantages in cost-effectiveness and cost-utility based on economic evaluation analyses.

Comentado [ACR1]: Los 3 grupos entrenan con la FoodT, no? En ese caso, te propongo la redacción alternativa:
1) a group that will receive active iTBS of the DLPFC, 2) a group that will receive active iTBS of the vmPFC, and 3) an active control group that will receive sham iTBS of the vertex. The three groups will also receive inhibitory control training with a food Go/NoGo paradigm after the iTBS.

STARTING HYPOTHESES AND GENERAL OBJECTIVE

HYPOTHESIS: Neuromodulation with theta burst transcranial magnetic stimulation (iTBS) applied to the left dorsolateral prefrontal cortex (DLPFC) or the ventromedial prefrontal cortex (vmPFC) in combination with inhibitory control training with the food Go/NoGo paradigm, will be associated with: (i) decreased appraisal of unhealthy foods, (ii) reduced food craving, (iii) improved eating behavior, (iv) modified brain

connectivity and activation both at rest and linked to task performance with food stimuli, (v) a decrease in the frequency and intensity of binge eating, (vi) improved emotional symptoms and emotional eating (depression, anxiety, emotional regulation, emotional eating, reward-related eating, non-homeostatic eating), (vii) improved cognitive abilities (motor and cognitive inhibition, delay of gratification, impulsivity, working memory, cognitive flexibility and decision making), (viii) changes in biological parameters associated to the interventions (blood and microbiota), and (ix) advantages in cost-effectiveness and cost-utility based on economic evaluation analyses.

GENERAL OBJECTIVE: To determine the effects of neuromodulation with iTBS in DLPFC or vmPFC in combination with inhibitory control training to generate brain, behavioural, emotional, cognitive and biological changes in people with binge eating (BE).

1.1 Specific Aims:

Objective 1: To study the differential effect of iTBS applied to the left DLPFC compared to vmPFC and sham iTBS (applied to vertex), in combination with inhibitory control training, for the treatment of people with binge eating (improvements in frequency and intensity of binge eating, craving, eating behavior, emotional symptoms and emotional eating, cognitive measures and biological parameters).

Objective 2: To characterize the effects of neuromodulation with iTBS of DLPFC or vmPFC, in combination with inhibitory control training to modify brain connectivity and activation both at rest and linked to task performance with food stimuli with functional magnetic resonance imaging (fMRI).

Objective 3: To determine the relationship of biological parameters obtained in blood, saliva, urine and faeces, as well as candidate genes, with neuropsychological variables (depression, anxiety, stress, emotional regulation, emotional eating, craving, motor and cognitive inhibition, food valuation, delay of gratification, impulsivity, working memory, flexibility and decision making) and brain neuroimaging (activation, gray and white matter volume, connectivity).

Objective 4: To analyze the economic evaluation of the cost-effectiveness and cost-utility of combined training (neuromodulation with iTBS and inhibitory control training)

in people with BE, and to analyze the budgetary impact of the program if it was implemented in the public health system.

1. METHODOLOGY

1.1. Design: Randomized controlled trial of parallel groups.

1.2. Participants:

Sample size and statistical power:

Previous research has reported small effect sizes pre-post transcranial magnetic stimulation for changes in binge eating (Dunlop et al., 2015; Van den Eyden, 2010), food craving (Claudino et al., 2010; Van den Eyden, 2012; Sutoh et al., 2015), mood (Van den Eyden, 2012) or brain changes (Hanlon et al., 2013). Using G*Power, we calculated the sample size considering the statistical method (inter- and intra-subject repeated measures ANOVA models), the number of groups (g=3), number of measurements (3), a small effect size (*f*=0,15) and assuming an alpha level of 0.05 and a power of 0.95, the resulting sample size was 141 participants. However, considering that, so far, no study has conducted a treatment based on the combination of iTBS and cognitive training, and especially considering that the studies do not perform post-treatment follow-ups, we have opted for a conservative estimate, increasing the number of participants to be included in the study to 150 to guarantee statistical power.

Participants:

Participants (N=150) will be randomly allocated to three groups: (i) group 1 (active stimulation of the DLPFC with iTBS and inhibitory control training) n=50; (ii) group 2 (active stimulation of the vmPFC with iTBS and inhibitory control training) n=50; group 3 (active control group of sham iTBS and inhibitory control training) n=50.

Comentado [ACR2]: and inhibitory control training (no?

People between 18 and 60 years old will be candidates to participate in the study, with proficiency in the Spanish language, a range of BMI between 20 and 39.9 kg/m2, two or more binge eating episodes in the past month assessed with the Binge Eating Scale (BES), and right lateral dominance to avoid differential effects due to cortical hemispheric specialization. All candidates will be screened for medical and psychological disorders and excluded if they have: (i) traumatic, digestive, metabolic or systemic disorders that

affect the central nervous system, autonomic or endocrine; (ii) psychopathological disorders or presence of severe symptoms in the Depression Anxiety and Stress Scale-21 (DASS-21); (iii) eating disorders other than Binge Eating Disorder, or severe or extreme Binge Eating Disorder (8 or more binges per week); (iv) contraindication for performing functional magnetic resonance imaging (pregnancy, metal implants, etc) or iTBS (tinnitus, dizziness, surgical interventions, diseases or drugs that affect the central nervous system, etcetera).

Sampling context:

The recruitment will be carried out through poster, brochures, social media, and the web of the project.

Randomization and blinding:

Computerized randomization will be performed by one of the principal investigators. The psychologists that conduct the assessments (screening, evaluation sessions and follow-up) will be blinded to the group allocation during the whole project. Moreover, all participants will be blind to their condition. Also, the people who perform the statistical analyses will be blind to the condition of the groups, through the coding of the interventions. Only the therapist performing the interventions will not be blind to the allocation of the participants.

1.3. Interventions:

Pre-treatment interventions.

First, all participants will participate in a group briefing informational session about the study. Also, informative videos and brochures will be provided.

Neurocognitive interventions. Duration: 2 weeks of 5 daily sessions of about 10-15 minutes. Sessions have two parts:

- Part 1. Three minutes of neuromodulation with iTBS (in the DLPFC for group 1, in the vmPFC for group 2, in the vertex for group 3). The whole process of iTBS includes 3 minutes of stimulation and the time devoted to coil location, reception and farewell. This part lasts around 10 minutes.

- Part 2. Inhibition training with the Food Trainer app (Lawrence et al., 2018). In this task participants are instructed to touch green circled items as quickly as possible, but to withhold their response and not to press on the red circled items. Some images are food (high-calorie and low-calorie), some non-foods. Participants earn points for correct tap responses and lose points for incorrect tap responses. Participants can choose which food categories they would like to train to resist, and those high-calorie foods are always paired with the no-go signal (red circle).

Comentado [ACR3]: Es importante ponerlo si el número de palabras lo permite (pero lo pongo sobre todo para no olvidarlo después en la descripción de la app en artículos, porque es un aspecto que indica una posible fuente de motivación para algunas personas que se retan a sí mismas en los juegos)

1.4. Outcome measures:

1. *Main outcome measures (pre and post-treatment, follow-up)*

Comentado [MOU4]: ALFON: he repensado y cambiado esto. Revísalo a ver qué te parece. No le veía mucho sentido a tener los cambios en neuroimagen como medida de resultado principal…

a) Binge eating symptoms: The Binge Eating Scale (BES) (Escrivá-Martínez et al., 2019) is a self-administered questionnaire composed of 16 items: eight items that describe behavioral manifestations (for example, eating fast or consuming large amounts of food) and eight items on associated feelings and cognitions (for example, fear of not stopping eating). Each item has a response range from 0 to 3 points (0 = no severity of the symptom, 3 = serious problems on the symptom).

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

b) Food craving. The Food Craving Questionnaire Stait-reduced (FCQ-S-r; Meule, et al., 2014) will be administered to obtain the total score, indicative of the craving state at the time of the evaluation.

Comentado [MOU5]: Estaba incluido el craving rasgo, pero no lo hemos utilizado previamente, y no sé si tiene mucho sentido incluirlo. ¿Habíamos hablado en algún momento te incluirlo y a mí se me ha pasado? Esto es muy posible…

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

2. *Secondary outcomes.*

2.1. *Changes in neuroimaging measures.*

a) Brain connectivity at rest: For acquisitions at rest, participants are instructed to remain still, with their eyes closed and as relaxed as possible, trying not to think about anything for 6 minutes. Seed-based

connectivity analysis will be performed, with the stimulated regions (DLPFC and vmPFC) as a reference. Thus, changes in functional connectivity between these regions and the rest of the brain can be observed.

Comentado [ACR6]: Revisar la redacción de la frase, porque "this way" me parece un poco raro. La he separado en dos

It will be measured in Pre-treatment (week 2) and post-treatment assessments (week 5).

b) Food Go/No-go Paradigm (Lawrence et al., 2018). The task consists of touching as quickly as possible the items marked with a green circle and not responding to those marked with a red circle. It contains images of high-calorie and low-calorie foods, and non-food neutral images. This inhibitory control task will parallel the one that participants train during the intervention, with the same images and procedure. Activation during Go and No-go items will be calculated according to the type of images (high calorie and low-calorie foods).

It will be measured in Pre-treatment (week 2) and post-treatment assessments (week 5).

c) Food decision making. The task of Neveu et al. (2018) will be used. It consists of three blocks (palatability, health benefits and decision making). Participants respond on a 5-point Likert scale how healthy (block 1) and palatable (block 2) they consider different foods. In the third block, choices are made between a reference food (selected from foods rated as neutral in blocks 1 and 2) and an alternative food. These forced binary choices provoke cognitive conflicts when the reference food is more palatable than the alternative food and the alternative food is healthier than the reference food and vice versa. Reaction time, impulsivity and control of the choices will be measured.

It will be measured in Pre-treatment (week 2) and post-treatment assessments (week 5).

2.2. Changes in eating behavior (pre, post and follow-up)

a) Diet information during the last year (pre-treatment), two last weeks (post-treatment) and tree last months (follow-up) will be collected through the Food

frequency questionnaire (CFA; validated by Vioque et al., 2013) with 52 items in which participants must record quantities of all the foods and drinks they had consumed during those periods. These data will be transformed into the number of total calories ingested, as well as the number of calories from fats, carbohydrates, and sugars.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

2.3 Changes in emotional symptoms and emotional eating (pre, post and follow-up)

a) The Depression Anxiety Stress Scale-21 (DASS-21) (Daza et al., 2002) is a dimensional, self-report scale that was designed to measure the negative emotional states of depression, anxiety, and stress (we will only use the stress and anxiety scales). Each scale contains seven items designed to assess the symptoms of interest. Scores for the scales are calculated by aggregating the scores for the relevant items. Responses are rated on a 4-point scale. Participants are asked to endorse how much the item applied to them over the past week.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

b) Depression symptoms will be measured with the BDI-II (Sanz and Vázquez, 2011). This scale is a widely used 21-item self-report inventory measuring the severity of depression. It has also been used in numerous treatment outcome studies.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

c) Emotion Regulation Questionnaire (ERQ; Gross & John, 2003): It is a self-report consisting of 10 items to examine different emotion regulation strategies. The instrument has two modalities of emotional regulation strategies, called cognitive reassessment and emotional suppression.

This will be measured in Pre-treatment assessment (week 2), post-treatment

assessment (week 5) and follow-up (week 17)

d) Emotional eating. Coping subscale of the Palatable Eating Motives Scale (PEMS; Burgess et al., 2014): Score on 4 items that evaluate the intentionality for eating palatable foods to face negative emotions.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

e) Reward-related eating. Reward-Based Eating Scale (RED; Mason et al., 2017): Score on this scale with 13 items that evaluate worries about foods, losing intake control and absence of satiety.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

f) Non homeostatic eating. Dutch Eating Behavior Questionnaire (DEBQ; Van Strien et al., 1986): Score on this questionnaire that assesses restrictive eating behaviors related to external cues and emotional states.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

1.2. Changes in cognitive measures (pre, post, follow-up)

a) Motor inhibition: The Food Trainer app will be used to measure reaction times for go and no-go items according to the type of images (high-calorie and low-calorie foods), as well as the commission errors (see Lawrence et al., 2015).

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17).

b) Cognitive inhibition. The Food Stroop Task (Davidson & Wright, 2002) will be used to measure the interference of food-related words on the performance of a Stroop task. Participants are asked to name the colour in which a word is printed, ignoring the word itself (which describes a different colour), and the speed of naming the appropriate colour is calculated; a bigger latency is thought to represent bigger interference from task-irrelevant information, that is, the meaning of the

Comentado [MOU7]: Incluir esto en los otros ensayos clíncios!

Comentado [MOU8R7]:

word.

Comentado [ACR9]: Si sobran palabras esta descripción se puede quitar porque es una tarea archiconocida, pero añadir lo de arriba me parece más importante que describir la prueba que la conoce todos, pero no sabrán en qué consiste la aplicación al mundo de la comida.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

c) Inhibition and activation systems. Sensitivity to punishment and reward. Punishment Sensitivity and Reward Sensitivity Questionnaire (PSRSQ; Torrubia et al., 2001): Score on this questionnaire with 48 dichotomous response items (Yes/No). The instrument has two subscales of 24 items each: The Punishment Sensitivity subscale, related to the inhibition behavioral system; and the Reward Sensitivity subscale, related to the activation behavioral system of Gray's theory.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

d) Delay of gratification: Score on the questionnaire Food Delay Discounting (Food DD) will be used to measure the sensitivity relative to immediate rewards versus higher value rewards delayed at different time intervals with the k parameter (Kirby et al., 1999).

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

e) Self-reported impulsivity. Impulsive behavior scale (UPPS-P; Lyman et al., 2006, Spanish adaptation by Verdejo-García et al., 2010). This scale evaluates five personality factors that can trigger impulsive behaviours: negative and positive urgency, lack of premeditation, lack of perseverance and sensation seeking.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

f) Working Memory: In the N-back Task (Kirchner, 1958) participants are presented with a series of visual stimuli and are asked for each stimulus whether it matches a stimulus 1, 2 or 3 trials before (depending on the block). The task requires a cascade of cognitive processes: it requires encoding and a temporary

storage of each stimulus n of the stimulus sequence in WM and a continuous updating of incoming stimuli. At the same time, irrelevant items must be inhibited, and the currently irrelevant items abandoned from WM. It will be assessed using an 'efficiency score' which incorporates accuracy and reaction times.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

g) Cognitive Flexibility: The Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948) is a neuropsychological measure that requires examinees to accurately sort every response card with one of four stimulus cards through the feedback (right or wrong) given to them based on a rule. The test consists of two card packs having four stimulus cards and 64 response cards in each. Each card measures 7×7 cm, and there are various geometric shapes in different colors and numbers.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

h) Decision making: The Iowa Gambling Task (IGT; Bechara et al. 1994): This task assesses real-world decision-making in a lab setting. Participants start with $2000 and aim to maximize profit over 100 trials by selecting cards from four decks. Decks A and B yield $100 per draw but result in a net loss of $250 after 10 selections, making them "disadvantageous" and risky. Decks C and D yield $50 per draw but lead to a net gain of $250 after 10 selections, making them "advantageous". Favorable task performance requires subjects to forgo potentially large immediate rewards in exchange for small long-term rewards to avoid larger losses.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

2. Screening and descriptive measures:

a) Sociodemographic (age, education, sex, socioeconomic variables) and clinical variables to consider exclusion and inclusion criteria.

Measured at Pre-treatment assessment (week 2).

b) Beck Depression Inventory (BDI-II, Sanz and Vázquez, 2011): For assessing depression symptoms this scale is a widely used 21-item self-report inventory measuring the severity of depression in adolescents and adults.

c) Depression Anxiety and Stress Scale-21 (DASS-21; Antony et al., 1998): Scores on the subscales that evaluate anxiety and stress.

d) Questionnaire on Eating and Weight Patterns-5 (QEWP-5; Yanovski et al., 2015): Score on the items of the questionnaire, which is adapted to DSM-5 criteria. It will be used to exclude people with binge eating problems and bulimia.

Measured at Pre-treatment assessment (week 2).

e) Motivation to change. The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES 00; Vieira da Silva et al., 2019): Score in this questionnaire about motivation to change adapted to excess weight. It has 18 items that score readiness to change in people with abusive food use.

f) Previous treatment history: Pharmacological, nutritional, psychological treatments, etc.

3. Measures to calculate cost effectiveness, cost utility and budget impact analysis:

a) SF-36 Quality of Life Questionnaire: Total score on this questionnaire will be used to estimate the quality of life in terms of utility. The utility will be estimated based on the tariff validated for Spain (Abellán-Perpignan et al., 2012).

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17)

b) Years of life adjusted for quality (QALY). The QALY is the most used measure in economic evaluation. It is a measure composed of years of life and profits (collected from the SF-36) that reflect the quality of life of the population under study. This measure will be used in the cost-utility analysis of the intervention.

c) Changes in binge eating assessed with the Binge Eating Scale will be used to calculate the cost-effectiveness of the interventions, recorded both at baseline session and at 3-month follow-up.

d) Intensity of food craving-state, assessed with the FCQ-S-r (Meule, et al., 2014) will be used for the calculation of the cost-effectiveness of the interventions, recorded both at baseline session and at 3-month follow-up.

e) Cost of health resources that the participants spend (visits to primary care, urgencies, hospital admissions, and medicines consumed).

f) Cost of time spent by the staff in charge of the iTBS sessions. A professional with the category of Area Specialist Physician (FEA) of Clinical Psychology for each training session, with 10 minutes per session for 10 days. The hourly cost will be collected according to the remuneration of the staff of health centers and institutions of the Andalusian Health Service.

Comentado [MOU10]: Esto es así ahora, no? IMPORTANTE CAMBIARLO EN LOS OTROS PROTOCOLOS, SI NO ESTÁ HECHO YA

g) Cost of time spent by the staff in charge of the cognitive training sessions. A professional with the category of Area Specialist Physician (FEA) of Clinical Psychology for each cognitive training session, with 10 minutes per session for 10 days. The hourly cost will be collected according to the remuneration of the staff of health centres and institutions of the Andalusian Health Service.

h) Cost of fMRI and iTBS equipment for assessment and brain stimulation sessions.

4. Biological samples Collection

Comentado [MOU11]: Incluir los cambios que ha hecho aquí Alfon en el protocolo InhibE

Biological samples will be collected and deep-frozen (in the freezers that the researchers have at their disposal in the CIMCYC) until mass analyses are performed at the end of the project.

a) Blood. Fasting blood tests will determine estradiol, progesterone, cortisol, leptin, adiponectin, TSH, thyroxine, triiodothyronine, ghrelin, glucagon, GLP-1, PYY (3-36), glucose, triglycerides, insulin, TNF-alpha, CRP, andIL-6. In addition, genetic analysis will be performed by sequencing candidate genes. A total of 10 ml of blood will be collected and centrifuged to separate the plasma from the rest

and stored at -80ºC.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17).

b) Saliva. Saliva samples for oral microbiota analysis will be collected using three swabs (right cheek, left cheek, tongue) that will be stored at -80ºC.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17).

c) Feces. Participants will collect fecal samples and 1.5 g of the top layer will be stored in tubes at -80ºC for microbiota analysis.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17).

d) Urine. Samples for proteomics analysis will be collected in plastic bottles, centrifuged and stored at -80ºC.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 5) and follow-up (week 17).

2. PROCEDURE

Assessments will be delivered online through Lime Survey and Milliseconds platforms. Inclusion and exclusion criteria will be checked through the data collected in a questionnaire of sociodemographic and clinical variables. Further, psychopathology exclusion criteria will be tested with three questionnaires to measure depression, anxiety, and stress symptoms as well as severity of binge eating episodes (BDI, DASS-21 and QEWP-5), and a short clinical interview by phone and/or information requested by email in those cases where there are doubts about any of the aspects collected through the online instruments.

All candidates who meet the criteria will attend an information meeting about the project in which they will receive written and oral information and will be asked for their informed consent. Then, participants will be randomly assigned to groups before the pre-treatment assessment sessions. A simple randomization will be performed by generating

Comentado [ACR12]: Se debería poner, aunque sea entre paréntesis, a través de MIllisecond y cuestionarios en la plataforma Limesurvey para dar fiabilidad

Comentado [MOU13R12]: Hacerlo también en los otros protocolos.

Comentado [ACR14]: Pregúntale a Andrea como lo ha puesto finalmente porque hay que poner el método concreto de aleatorización

five-letter codes with *Calculado.net* and randomizing the codes into three different groups using *Rafflys*. The three groups of the study will complete all the evaluations, as well as the follow-up (see below). What will differentiate the groups will be, therefore, the stimulation area: active iTBS applied to the DLPFC with inhibitory control training vs. active iTBS applied to the vmPFC with inhibitory control training vs. sham iTBS applied to the vertex with inhibitoty control training. At the end of the project, if one treatment is more effective, the other two groups will be offered the complete treatment sessions.

Comentado [ACR15]: Revisar esto si el grupo sham tb recibe foodT

Comentado [MB16R15]: Sí, también recibe

Informative and assessment sessions will be developed in groups of 4-6 people through the platform GoogleMeet. iTBS sessions will be administered individually. If a participant misses a session, it will be rescheduled for the beginning of the next week at a similar time. There will be at least 10 experimental groups of DLPFC stimulation intervention combined with inhibitory control training (50 participants), 10 experimental groups of vmPFC stimulation intervention combined with inhibitory control training (50 participants), and 10 active control groups of sham stimulation (50 participants). The program will comprise 5 weeks including two assessments (pre- and post-treatment), ten intervention sessions (two weeks of 5 daily sessions), as well as the information session. Also, a follow-up will be conducted 3 months after treatment (see below). Assessment sessions will last about 2 hours while intervention sessions will be approximately 10 to 20 minutes. Sessions will consist of the following:

1) **Informative session (session 1; week 1):** For the participants to understand the foundation of the intervention they will be informed about the aims, basis of the project and the procedure of the research. They will be provided written informed consent as well. At the end of this session, participants will be asked for their informed written consent.

Comentado [ACR17]: No se les da información de las bases en las que se fundamenta el proyecto?

2) **Pre-treatment assessment (session 2 and 3; week 2):** All participants will complete, in session 1, the following instruments to assess the main and secondary outcomes, and the exploratory and economic measures: WCST, Food Go/NoGo, IGT, Stroop, Food DD, N-Back, CFA, DASS-21, BDI-II, PEMS, RED, DEBQ, PSRSQ, ERQ, UPPS-P, SF-36, SOCRATES 00, QEWP-5, sociodemographic questionnaire and questions about used health resources. Also, all participants will undergo the fMRI session (session 2) and biological sample collection (blood, saliva,

feces and urine).

3) **Intervention sessions (sessions 4 to 13; weeks 3 and 4):** Intervention will consist of five weekly individual sessions for two weeks, with a 10-20-minute total duration each. The stimulation parameters are based on the protocols for the application of iTBS in people with food intake problems, by Barone et al., (2023), and following international safety recommendations (Rossi et al., 2009; 2021). The procedure in the three groups consists of:

i) Localization of the stimulation area by T1 sequence structural neuroimaging images using the Brainsight software for the correct placement of the stimulation coil: in the active stimulation groups it will be the left DLPFC area (x -37, y -34, z 78) corresponding to F3 position on the 10-20 EEG system (based on Beam, 2009) or he vmPFC area (x -24, y 66, z 12) corresponding to FP1 position on the 10-20 EEG system (Chen et al., 2021). In the control group it will be the vertex (x 0, y-34, z 78), an area without cognitive effects after stimulation but matching the sensory effects (Kalla et al., 2009).Stimulation with iTBS for 3 minutes with parameters of: 50 Hz frequency, number of pulses 3; number of bursts 10; cycle duration 8 seconds; number of cycles 20; burst frequency 5 Hz; and total number of pulses 600. The stimulation intensity will be maintained at 30% of the stimulator's maximum output.

ii) Cognitive inhibitory control training (10 minutes): It will be performed with the Food T app (Lawrence et al., 2018), for 10 minutes and will be applied immediately after the iTBS, taking advantage of its time of maximum brain potentiation (Huang et al., 2005). In this application, the task consists of touching as quickly as possible the items that appear surrounded with a green circle, and not responding to the items surrounded by a red circle. Some images correspond to food and others are not related to food. Participants can select the categories of the images they want to train, which should correspond to the foods used for binge eating (candy/gummies, cakes, chocolate, cookies, alcohol, chips, bread, cheese, fast food - burgers, take-out food -, sweet sodas, meat, pizza). Inhibitory control training consists of pairing high-calorie foods 100% of the time7 with the no-go signal.

4) **Post-treatment assessment (session 14 and 15, week 5):** To evaluate the effectiveness of the interventions, BMI and craving (FCQ-T/S-r) will be registered (main outcomes), and the following instruments will be administered to obtain the secondary outcomes; WCST, Food Go/NoGo, IGT, Stroop, Food DD, N-Back, CFA, DASS-21, BDI-II, PEMS, RED, DEBQ, PSRSQ, ERQ, UPPS-P, SF-36 and questions about used health resources. Also, fMRI and biological samples of the pre-treatment assessment will be repeated.

5) **Follow-up (sessions 16; week 15):** Follow-up at 3 months after the intervention will include the following measures: WCST, Food Go/NoGo, IGT, Stroop, Food DD, N-Back, CFA, DASS-21, BDI-II, PEMS, RED, DEBQ, PSRSQ, ERQ, UPPS-P, SF-36, and interview about used health resources sociodemographic questionnaire and questions about used health resources and collection of biological samples and anthropometric measures to obtain the main and secondary outcome measures. Every month after the end of the treatment, participants will be contacted by email and mobile message to maintain adherence.

Participants will be instructed to eat two hours before all evaluations (pre- and post-treatment, and the follow-up) and iTBS sessions. All the assessments will be carried out at the same hour.

4. DATA ANALYSIS PLAN

Once the preliminary analyses for the detection of possible errors in the recording of the data have been carried out, exploratory and descriptive analyses will be performed to study the distribution of the variables and the presence of outliers. The inferential statistics applied will be in accordance with the characteristics of the data obtained (distribution of the data, qualitative/quantitative nature of the data, etc.) and with the hypotheses put forward in the study. Models of repeated measures mixed models will be performed (3 groups X 3 moments). Furthermore, planned analysis will compare the groups that received the combined interventions (1. DLPFC, iTBS and inhibitory control training, or 2. vmPFC, iTBS and inhibitory control training) with each other, and with the Sham stimulation and inhibitory control training group on the other hand. Both Intention to Treat (efficiency) and per protocol (effectiveness) analysis will be conducted. Appropriate corrections to control for multiple comparisons will always be

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Comentado [ACR18]: Sham iTBS. Añadir control inhib si es necesario

considered.

- **For objective 1,** Repeated measures mixed models (Gueorguieva & Krystal, 2004) will be conducted, using improvements in frequency and intensity of binge eating, craving, eating behavior, emotional symptoms and emotional eating, cognitive measures and biological parameters The independent variables will be the type of treatment: combined treatment (active iTBS with inhibitory control training) and sham stimulation. Effect sizes will be calculated for between-group and within-group comparisons.

- **For objective 2,** the fMRI data will be analyzed following different approaches. Prior to the statistical analyses, the functional MRI images will be preprocessed using the Statistical Parametric Mapping (SPM12) program running on the MATLAB mathematical tool (version R2018a). The independent variables will be the type of treatment: combined treatment (active iTBS with inhibitory control training), and sham stimulation.

  The images of the resting task will be analyzed following a double approach. On the one hand, an independent component analysis (ICA) will be performed, which will allow comparing the different brain networks, as a whole, between the groups, with special interest in those that have been shown to be altered in the binge eating population. On the other hand, seed-based connectivity analyses will be performed, in which changes in functional connectivity between DLPFC and vmFPC, and the rest of the brain can be observed. The two functional tasks will be analyzed to assess the brain activity associated with food inhibitory control and decision-making processes, as well as the brain connectivity of various regions of interest, using a psycho-physiological interactions (PPI) analysis. All these analyses will be performed with the SPM12 program. For the study of DTI images, the FSL program will be used to establish the integrity of the white matter of the different groups by evaluating the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) maps. Effect sizes will be calculated for between-group and within-group comparisons.

- For objective 3, Exploratory analyses will be carried out with plasma, genetic, proteomic and microbiota variables. Correlations and regression analysis will be conducted to determine the relation between the biological parameters and the

neuropsychological and neuroimaging variables.

- **For objective 4,** Incremental cost-effectiveness (ICER) and incremental cost-utility (ICUR) ratios will be calculated as the difference in costs and effectiveness (binge eating and QALYs, respectively) for the 3 groups. All analyses will be performed according to the CHEERS Consolidated Health Economic Evaluation Reporting Standards methodological recommendations (Husereau et al., 2013) and the guidelines developed for Spain (López-Bastida et al., 2010).

  The health system perspective will be used, including only direct costs. If we find significant differences in baseline utility values, a bivariate regression analysis will be performed to adjust these data. The uncertainty of the results (ICER and ICUR) will be carried out through various deterministic sensitivity analyses (SA) to assess variability of the parameters included in the analyses, and for the ICUR a probabilistic SA will also be carried out using non-parametric bootstrapping methods of 1000 iterations (Luce et al., 2001) that will allow the cost-effectiveness plane and the acceptability curve to be represented. For this purpose, the suggested cost-effectiveness threshold for Spain of 20,000 euros per QALY will be taken as a reference (Vallejo-Torres et al., 2018). Finally, the budgetary impact (IB) will estimate the change in the budget of the public health system that would result from the iTBS and the inhibitory control training, based on the estimated costs of the alternatives compared and the estimated number of patients expected to benefit from the intervention. Univariate and multivariate SA will also be carried out to analyze different budget scenarios according to a possible variation in the variables of cost and number of beneficiary patients.