Tittle: Inhibitory Control Training and Transcranial Magnetic Stimulation for Treating People with Excess Weight: Behavioural and Brain Changes (InhibE).

Code: SICEIA-2024-000656

Date: February 7th, 2025

Brief Summary: People with excess weight (EW) 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 the brain level, to alterations in the activation of areas such as the dorsolateral prefrontal cortex (DLPFC) and its connectivity. We propose an intervention that seeks to target these issues. Thus, the present study aims to characterize the effects of neuromodulation with intermittent theta burst transcranial magnetic stimulation (iTBS) of the DLPFC alone and in combination with inhibitory control training to produce brain, cognitive, behavioral changes and modify altered biological parameters in people with EW. Participants will be randomly allocated to one of three groups: 1) a group that will receive active iTBS of the DLPFC together with inhibitory control training with the food Go/No-go paradigm, 2) a group that will receive active iTBS of the DLPFC, and 3) a control group that will receive sham iTBS. We hypothesize that the combined intervention will obtain better results that the neuromodulation alone, and that both interventions, compared to sham iTBS, will achieve: (i) decreased body mass index, (ii) decreased craving, (iii) modified brain connectivity and activation both at rest and linked to task performance with food stimuli, (iv) improved anthropometric measures (waist circumference and waist-to-hip and waist-to-height ratios), (v) improved eating and exercise behaviors (decreased caloric intake and increased frequency and time of physical activity), (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 (plasma and microbiota), and (ix) advantages in cost-effectiveness and cost-utility based on economic evaluation analyses.

STARTING HYPOTHESES AND GENERAL OBJECTIVE

HYPOTHESIS: Neuromodulation with intermittent theta burst transcranial magnetic stimulation (iTBS) applied to the left dorsolateral prefrontal cortex (DLPFC) in combination with inhibitory control training with the food Go/No-go paradigm will be associated with (i) decreased BMI, (ii) decreased craving, (iii) modified brain connectivity and activation both at rest and linked to task performance with food stimuli, (iv) improved anthropometric measures (waist circumference and waist-to-hip and waist-to-height ratios), (v) improved eating and exercise behaviors (decreased caloric intake

increased frequency and time of physical activity), (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 (plasma 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 left DLPFC alone and in combination with inhibitory control training to generate brain, behavioural, emotional, cognitive and biological changes in people with excess weight (EW).

1.1. Specific Aims:

Objective 1:) To determine the effectiveness of iTBS of the DLPFC as an add-on to the treatment as usual (TAU: diet and exercise) for the treatment of people with excess weight (improvements in BMI, craving, anthropometric measures, food and exercise behaviours, emotional symptoms and emotional eating, cognitive measures and biological parameters).

Objective 2: To study the effectiveness of combining iTBS and inhibitory control training compared to iTBS alone (both as an add-on to TAU), for the treatment of EW (using the same parameters before)

Objective 3: To characterize the effects of neuromodulation with iTBS of DLPFC alone and 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 4: 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, grey and white matter volume and connectivity).

Objective 5: To analyse the economic evaluation of the cost-effectiveness and cost-utility of combined training (neuromodulation with iTBS and inhibitory control training) in people with EW, and to analyse the budgetary impact of the program if it were to be implemented in the national health system.

2. METHODOLOGY

2.1. Design: Randomized controlled trial of parallel groups.

2.2. Participants:

Sample size and statistical power:

The sample size was calculated using the G*Power 3.1 tool G-Power v3.1.9.7 (Heinrich Heine University Düsseldorf, Düsseldorf, Germany). To do so, we relied on the only study to date that has analysed changes in BMI in people with obesity after the administration of 4 rTMS sessions over 2 weeks, which found a small effect size (Cohen's d= 0.31) (39). Thus, considering a small effect size for conducting ANOVAs (f= 0.15), the minimum recommended sample size to reach a power of 0.95 and alpha level of 0.05 to calculate the interaction model of the three groups (combined intervention vs. neuromodulation alone vs. sham iTBS) and three repeated measures were 141 (47 participants per group).

Participants

Participants: Participants (N=141) will be randomly allocated to three groups: (i) group 1 (combined intervention: active stimulation of the DLPFC with iTBS and inhibitory control training) n=45; (ii) group 2 (active stimulation of the DLPFC with iTBS) n=45; group 3 (control group of sham iTBS) n=45.

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 25 and 39.9 kg/m^2 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 affectthe central

nervous system, autonomic or endocrine, (ii) cardiovascular or any other disorders that prevent physical exercise; (iii) psychopathological disorders or presence of severe symptoms in the Depression Anxiety and Stress Scale-21 (DASS-21); (iv) eating disorders; (v) contraindication for performing functional magnetic resonance imaging (pregnancy, metal implants, etc.) or TMS (tinnitus, dizziness, surgical interventions, trauma, diseases or drugs that affect the central nervous system).

Sampling context:

The recruitment will be carried out through posters, brochures, social media, and the project website.

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.

2.3. Interventions:

Pre-treatment sessions: information, dietary plus physical guidelines (all groups):

First, all participants will participate in a group briefing informational session about the procedure and rationale of the study that will last about an hour. Also, informative videos and brochures will be provided. There will be two 90-minute sessions afterwards given by a nutritionist and personal trainer respectively to provide individualized diet and physical exercise instructions to all participants.

Neurocognitive intervention

Duration: 2 weeks of 5 daily sessions.

Part 1 (all groups). Three minutes of neuromodulation with iTBS (in the DLPFC for the groups 1 and 2; in the vertex for the 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 (more details below).

Part 2 (group 1). Immediately after the iTBS, only the combined intervention group will also receive a 10-minute inhibition training with the Food Trainer app in their smartphones (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 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.

2.4. Outcome measures:

1. Main outcome measures

- Change in BMI. Weight for BMI calculation (kg/m2) will be obtained with a digital weight (TANITA Corporation of America Inc., Arlington Heights, IL), and height with a measuring rod (SECA Tape Measure 206).

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18)

- Change in food Craving. The Food Craving Questionnaire Stait-reduced (FCQ-S-r; Meule, et al., 2014) will be administered to obtain a total score indicative of craving status at the time of assessment.

This will be measured in Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18)

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. Resting brain connectivity will be the main outcome measure. The images obtained in this way allow us to study the resting connectivity of the different brain networks. Specifically, seed-based connectivity analysis will be performed, in which taking the stimulated region (DLPFC) as a reference. Thus, changes in functional connectivity in this region and the rest of the brain can be observed.

It will be measured in Pre-treatment (week 2) and post-treatment assessments (week 6).

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 6).

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 6).

2.2 Changes in anthropometric measures

a) Waist-to-height ratio (WHtR): Participants should stand with heels close together and trunk erect, and put the tape measure around the waist, just above the navel, to measure the waist circumference in centimeters. The height in centimeters will be measured with a measuring rod (SECA Tape Measure 206). The WHtR is determined by dividing the waist circumference by the height.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

2.3 Changes in eating and physical activity behaviours

a) Eating behaviour: 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.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

b) The International physical activity questionnaire (IPAQ) (Craig et al., 2003) asks about physical activity related to work, activity at home, free time and determines the degrees of physical activity based on the metabolic equivalents (MET) consumed during said activity.

c) Exercise adherence. The following question will be asked using a visual analogue scale (VAS): *In the last 2 weeks or 3 months, to what extent did you follow the exercise guidelines given to you by the programme's physical trainer?* (0 = I did not follow the exercise recommendations at all; 100 = I absolutely followed the exercise recommendations.

a) d) Adherence to diet. The following question will be asked using a visual analogue scale (VAS): *In the last 2 weeks or 3 months, how well did you follow the dietary guidelines given by the nutritionist in the programme* (0 = I did not follow the diet at all; 100 = I followed the diet absolutely).

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

2.4 Changes in emotional symptoms and emotional eating

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 state 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.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

b) Depression symptoms will be measured with the Beck Depression Inventory (BDI-II, Sanz and Vázquez, 2011 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.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

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.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

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.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

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.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

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

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

2.4 Changes in cognitive measures (cognitive and motor inhibition, delayed gratification, impulsivity, working memory, cognitive flexibility and decision making).

a) Motor inhibition: The Food Trainer app reaction time for the high-calorie and low-calorie foods paired with the go and the no-go signal will be measured. The average reaction time for Go and No-go items will be calculated 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 6) and follow-up (week 18).

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 word.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

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 behavioural system; and the Reward Sensitivity subscale, related to the activation behavioural system of Gray's theory.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

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

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

e) Self-reported impulsivity. Impulsive behaviour scale (UPPS-P; Lyman et al., 2006, Spanish adaptationby 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.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

f) Working Memory (WM): N-back Task (Kirchner, 1958) In this task participants see 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.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

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 colours and numbers.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

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". Favourable task performance requires subjects to forgo potentially large immediate rewards in exchange for small long-term rewards to avoid larger losses.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

3. 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) Health Resources Questionnaire: For assessing the use of the health system and health complaints in the last weeks.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

c) 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.

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

e) 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).

f) 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.

g) Stigma: Participants will answer whether they have experienced stigma (yes/no) because of their weight (Himmelstein et al., 2017) and a VAS scale from 0 to 100 where they can rate the degree to which they have experienced it.

Measured at Pre-treatment assessment (week 2).

h) Previous treatment history: Participants will be asked what treatments they have undergone to date to try to lose weight, as well as the number of times they have tried such treatments (pharmacological, nutritional, psychological, etc.).

Measured at Pre-treatment assessment (week 2).

5. 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).

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

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) BMI will be used for the calculation of the cost-effectiveness of the interventions, recorded both at baseline session and at 3-month follow-up.

d) Intensity of food craving -status, 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 TMS sessions. A professional with the category of Area Specialist Physician (FEA) of Clinical Psychology for each training session, with 3 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.

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 TMS equipment for assessment and brain stimulation sessions.

6. Biological samples Collection

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 to determine the following variables: Estradiol; Progesterone; Cortisol; Leptin; High molecular weight adiponectin; Thyroid stimulating hormone; Thyroxine; Triiodothyronine; Ghrelin; Glucagon; Glucagon-like peptide-1; Peptide YY (3-36); Glucose; Triglycerides; Insulin; Tumor necrosis factor alpha; C-reactive protein; Interleukin-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. The two separate phases will be stored at -80ºC.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

b) Saliva. Storage of saliva to analyse the oral microbiota. Three swabs will be used (one for the right cheek, one for the left cheek and one for the tongue), which will be introduced into the tube and stored at -80ºC.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

c) Faeces. Storage of faeces for gut microbiota analysis. Each participant will collect his/her sample in a plastic jar. Around 1-1.5 g of the top layer of the sample will be stored at -80ºC.

Measured at Pre-treatment assessment (week 2), post-treatment assessment (week 6) and follow-up (week 18).

d) Urine. 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 6) and follow-up (week 18).

3. 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 binge eating and bulimia (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 five-letter codes with *Calculado.net* and randomizing the codes into three different groups using *Rafflys*. The three groups of the study (interventions and control) will complete all the pre and post assessments, as well as the follow-up (see below). What will differentiate the groups will be, therefore, the treatment: active iTBS applied to the DLPFC plus inhibitory control training vs. active iTBS only applied to the DLPFC vs. sham iTBS applied to the vertex. If the combined treatment is effective, groups 2 and 3 will be offered the complete treatment sessions (without the assessment components) at the end of the 3-month follow-up.

Informative and evaluation sessions will be developed in groups of 4-6 people. 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 8 experimental groups of DLPFC stimulation intervention combined with inhibitory control training (45 participants), 8 experimental groups of DLPFC stimulation intervention alone (45 participants) and 8 control groups of sham iTBS (45 participants). The program will comprise 6 weeks including two assessments (pre- and post-treatment), ten intervention sessions (two weeks of 5 daily sessions), as well as the information and the diet and physical exercise sessions. Also, a follow-up will be conducted 3 months after treatment (see below). Assessment sessions will last about 2 hours while intervention sessions will between 10 and 20 minutes depending on the group. 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.

2. **Pre-treatment assessment (session 2, 3 and 4; 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, IPAQ, DASS-21, BDI-II, PEMS, RED, DEBQ, PSRSQ, ERQ, UPPS-P, SF-36, SOCRATES 00, QEWP-5, sociodemographic questionnaire, another one about used health resources, stigma and previous treatments questions. Also, all participants will undergo the fMRI session (session 2) and biological sample collection (blood, saliva, feces and urine) and anthropometric measures to calculate BMI, WC, WHR and WHtR (session 3).

3. **Nutrition and exercise session (session 5; week 3):** Participants will receive information on healthy nutritional (Ph.D. Nutritionist) and physical exercise (Ph.D. Sports Science professional) habits. In addition, they will receive individualized diet and physical exercise guidelines, and will be able to consult any doubts to both professionals through WhatsApp groups.

4. **Intervention sessions (sessions 6 to 15; weeks 4 and 5)**: 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:

A. 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 group 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). 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).

B. Stimulation using an intermittent active TBS with Megastim Rapid 2 magnetic stimulator and figure-8-coil iTBS applied 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.

C. 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 app, 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 with the no-go signal.

5. Post-treatment assessment (session 16; week 6): 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, IPAQ, DASS-21, BDI-II, PEMS, RED, DEBQ, PSRSQ, ERQ, UPPS-P, SF-36 and a questionnaire about used health resources. Also, fMRI and biological samples of the pre-treatment assessment will be repeated.

6. Follow-up (sessions 17; week 18): Follow-up at 3 months after the intervention will include the following measures: WCST, Food Go/NoGo, IGT, Stroop, Food DD, N-Back, CFA, IPAQ, DASS-21, BDI-II, PEMS, RED, DEBQ, PSRSQ, ERQ, UPPS-P, SF-36, sociodemographic questionnaire and a questionnaire 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

The inferential statistics will be applied in accordance with the characteristics of the data obtained, including the distribution of the data, its qualitative and quantitative nature, and so forth. Furthermore, the inferential statistics will be conducted in alignment with the hypotheses proposed in the study.

Objectives 1 and 2 will be addressed using repeated measures mixed models with BMI, craving, cognitive skills, and intake and exercise behaviours serving as dependent variables. The independent variables will be the type of treatment: iTBS vs. sham for objective 1; iTBS vs. combined training vs. sham iTBS for objective 2. Also, planned combined training group vs. sham iTBS will be conducted. Effect sizes will be calculated for between-group and within-group comparisons. Mediation and/or moderation analysis will be conducted to investigate the influence of baseline characteristics including cognition, emotional symptoms, emotional eating, motivation, clinical variables, and adherence to diet and physical exercise on the intervention outcome measures. Additionally, potential differences in programme outcomes will be examined based on sex and weight classification (overweight and obesity, including type I and type II).

To achieve the third objective, fMRI data will undergo analysis using various approaches, following pre-processing with the Statistical Parametric Mapping (SPM12) program in MATLAB (R2018a). Resting-state images will be analysed using two methods: independent component analysis (ICA) to compare brain networks, especially those altered in individuals with excess weight, and seed-based connectivity analyses to observe functional connectivity changes in specific regions. The two functional tasks will assess brain activity related to food evaluation, decision-making, and connectivity in regions of interest via psycho-physiological interaction (PPI) analysis. All analyses will be performed in SPM12. DTI images will be analyzed using the FSL program to assess

white matter integrity through fractional anisotropy (FA) and apparent diffusion coefficient (ADC) maps.

In order to address the fourth objective, exploratory analyses will be carried out with plasma, genetic, proteomic and microbiota variables. Correlations and regression analysis will be conducted in order to determine the relation between the biological parameters and the neuropsychological and neuroimaging variables.

For objective 5, incremental cost-effectiveness (ICER) and cost-utility (ICUR) ratios will be calculated based on costs and outcomes (excess weight and QALYs) across the three groups, following CHEERS guidelines and Spanish standards. The healthcare system perspective will be adopted, focusing on direct costs. If baseline utility values show significant differences, bivariate regression will adjust the data. Deterministic sensitivity analyses (SA) will assess parameter variability, and probabilistic SA using non-parametric bootstrapping (1,000 iterations) will evaluate ICUR uncertainty, with results presented as cost-effectiveness planes and acceptability curves. Spain's cost-effectiveness threshold of €20,000 per QALY will guide interpretations. Budget impact (IB) analysis will estimate public healthcare costs for cognitive training and TMS implementation, considering the estimated patient population. Univariate and multivariate sensitivity analyses will examine how variations in cost and patient numbers influence cost-effectiveness.

All analyses will be conducted following an intention to treat (ITT) strategy and per protocol (PP) analysis. Appropriate corrections to control for multiple comparisons will always be considered.