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Intermittent theta burst stimulation (iTBS) and inhibitory control training for excess weight treatment: study protocol for a randomized controlled trial (InhibE)

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Abstract

Background The prevalence of excess weight has increased globally. Despite interventions include targeted goals on essential aspects such as physical activity and diet, their long-term effectiveness remains limited. Research highlights that eating behaviour is influenced by impulsive processes, especially in the context of a food-rich environment. Inhibitory control has been identified as a key factor in regulating eating behaviour. Neuroscience approaches, including inhibitory control training and non-invasive neuromodulation of brain regions such as the dorsolateral prefrontal cortex, show promise in improving eating behaviour when used in addition to conventional intervention for weight management. This parallel group, randomized, controlled trial aims to study the efficacy of neuromodulation with iTBS as an add-on to the weight loss treatment as usual (TAU: diet and exercise), alone and in combination with inhibitory control training, for excess weight treatment.

Methods and analysis 141 people with excess weight will be randomized into three groups: combined intervention (inhibitory control training + iTBS), iTBS and sham iTBS. The three groups will receive individualized diet and physical exercise guidelines (TAU). The interventions will comprehend ten sessions along two weeks. The main outcome measure will be the Body Mass Index change. Secondary outcomes include changes in brain connectivity and activation using fMRI, cognitive measures, eating and physical exercise behaviours, anthropometric and biological measures. Assessments will be carried out before the intervention, after the intervention and 3 months after the intervention. In addition, data on the use of the health system will be collected to analyse the cost-effectiveness and the cost-utility of the intervention.

Discussion Findings of this study will expand the available evidence on cognitive interventions to improve eating behaviour in people with excess weight.

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Trial registration The trial has been registered at www.clinicalTrials.gov under the number NCT06668077 on the 11th of February 2025 named Inhibitory Control Training and iTBS for Excess Weight Behavioral and Brain Changes (InhibE). Any relevant modification to the protocol will be reflected in the clinical trial registry in www.clinicalTrials.gov.

Keywords Excess weight, Obesity inhibitory control training, Neuromodulation, iTBS

Introduction

Over the past three decades, there has been a marked global rise in the prevalence of excess weight (EW: overweight and obesity), which has emerged as the main risk factor for premature mortality associated with lifestyle [1]. Currently, approximately 60% of the global population show EW [2], and this figure is anticipated to continue rising [3].

While the reasons for weight gain are varied and complex, an upsurge in unhealthy overeating in a food-rich environment [4] and more sedentary lifestyles [1] are key factors to understand EW increase. Therefore, treatment as usual (TAU) for weight management interventions focus on increasing physical activity and reducing caloric intake [5]. Researchers, health professionals, psychologists, and policymakers have developed a wide range of interventions aimed at improving diet and physical activity [6]. Typically, these interventions range from providing information on healthy eating and exercise [7], developing drug treatments [8] or bariatric surgery [9], strategies such as stimulus control or cognitive restructuring [10], to taxing foods/beverages high in added sugars [11]. However, the application of these methods does not seem to be effective enough in the long run [12–16].

These procedures assume that people: make conscious eating decisions; consider their long-term health as the goal of these decisions; and can take different information into account. However, research has shown that eating behaviour is strongly influenced by automatic and impulsive psychological processes [6, 17], central in decision-making when cognitive resources are low [18]. The modern food environment, where unhealthy foods are widely available and accessible, constantly triggers these impulsive processes, making it less likely that decisions will be based on nutritional information and long-term health goals [19]. Given so, much research in recent years has led to the development and evaluation of impulse-focused interventions [4, 19–22]. One of the most relevant factors proposed in this regard is inhibitory control [23].

Inhibitory control is a cognitive ability, within executive functions, to override an impulse or stop an initiated action when it is inappropriate [24]. This ability seems to be crucial for understanding individual differences in eating behaviour, so much so that some studies indicate that the effect of the impulsive system on eating behaviour relies on inhibitory control [17, 21, 23, 25]. A growing body of evidence suggests that individuals with EW have deficits in inhibitory control that are associated with difficulty resisting highly palatable foods [26–29]. For this reason, the current neuroscientific approach proposes inhibitory control training as a possible effective complementary intervention to TAU. In fact, inhibitory control training using food imagery in Go/NoGo paradigms has shown effects on the reduction of reward value and intake of hypercaloric foods [22].

On the other hand, multiple brain regions related to the control of eating behaviors have been identified, highlighting among them the dorsolateral prefrontal cortex (DLPFC) since, in addition to being related to eating behaviour [30], it is associated with inhibitory control [31]. Some studies have found an association between increased activity in DLPFC, self-regulation of food intake and weight [32]. Also, people with obesity showed hypoactivated left DLPFC in response to food imagery [33]. Thus, non-invasive neuromodulation applied to the DLPFC becomes another interesting line of intervention to improve the eating behaviour of people with EW [34].

While inhibitory control training has been widely studied [4, 35–38], so far, only one randomised clinical trial has investigated the efficacy of multisession of repetitive transcranial magnetic stimulation (rTMS) in people with obesity. This study found that four sessions administered over two weeks on the left DLPFC decreased food intake and facilitated weight loss [39].

A type of rTMS that present promising advantages is intermittent theta burst stimulation (iTBS), as it allows a reduction in session time which is very advantageous from a cost-benefit point of view [40]. Importantly, theta rhythms facilitate long-term potentiation [41], so that iTBS induces faster and longer-lasting effects on synaptic plasticity. Nevertheless, there is no evidence of iTBS studies in people with EW. However, two different iTBS of DLPFC studies in people with eating behaviour problems have shown promising results. The first study demonstrated that following 18 sessions of iTBS of the left DLPFC, binge eating episodes ceased entirely in two women [42]. The second study, conducted in 22 women with disordered eating regulation, showed that single stimulation of the left DLPFC significantly reduced the desire for thinness and body dissatisfaction, risk factors for eating disorders [43].

In short, cognitive training and neurostimulation are promising interventions, but their combined effects and the impact of multiple sessions have yet to be thoroughly studied [44]. Specifically, the efficacy of inhibitory control

training could be improved by its joint application with neurostimulation [45]. Nevertheless, this hypothesis has not yet been studied, nor have the brain, cognitive and behavioural changes that may occur following these interventions. The protocol of this trial was designed to overcome these limitations. The main objective is to determine the effects of neuromodulation with iTBS in DLPFC as an add-on to the TAU, alone and in combination with inhibitory control training, to generate brain, behavioural, emotional, cognitive and biological changes in people with EW. The active stimulation will be compared to its sham version. The specific aims of the study are: (i) To determine the effectiveness of iTBS of the DLPFC as an add-on to the TAU for the treatment of EW (improvements in Body Mass Index, food assessment and intake, exercise, cognitive skills, anthropometric and biological measures); (ii) 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); (iii) To characterize the brain mechanisms of action involved in the interventions (iTBS, and iTBS combined with inhibitory control training) using fMRI; (iv) 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); (v) To conduct an economic evaluation of the cost-effectiveness and cost-utility of interventions for people with EW and to analyse the budgetary impact of their implementation on the public health system.

We hypothesize that inhibitory control training using the food Go/NoGo task and iTBS of the left DLPFC will be more effective to treat people with EW that iTBS alone and shamiTBS (always as an add-on to TAU). The interventions are expected to reduce Body Mass Index (BMI), cravings, and unhealthy food valuation, while changing brain connectivity and improving eating and exercise habits, inhibitory control, and anthropometric and cognitive measures. It is also expected to show benefits in the economic balance of cost-effectiveness and cost-utility.

Methods

Experimental desing, setting, and dates

The study is a double-blinded, randomized, controlled trial with three parallel groups that will be based at the Mind, Brain, and Behavior Research Center (CIMCYC) at the University of Granada (Granada, Spain). A part of the interaction will be on site, and the other part will be online through the services contracted by the University of Granada on the platforms GoogleMeet (videoconference during the presentation and evaluation sessions), LimeSurvey and Millisecond Test Library (submission of the answers to the evaluation instruments administered during the assessment sessions). In addition, as part of the intervention, the participants will receive messages on their mobile phones. The study was registered at www.clinicalTrials.gov number NCT06668077 on February 2025, and follows the SPIRIT reporting guidelines [46]. All items from the World Health Organization Trial Registration Data Set are summarised in Table 1, according to the SPIRIT reporting guidelines. Data collection started in November 2024 and will be completed by December 31, 2026. There will be no financial compensation for participation in the study.

Sample size calculation

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 was 141 (47 participants per group).

Recruitment, participants, eligibility criteria, data collection, management, and analysis

Participant recruitment will be carried out through social and mass media, the website of the project (trainep.ugr.es), posters and Granada University communication channels. People between 18 and 60 years old will be candidates to participate in the study, with proficiency in the Spanish language and a range of BMI between 25 and 39.9 kg/m2. Participants must have at least two electronic devices available (one tablet, computer or smartphone to attend the online meetings and perform the online assessments).

All candidates will be screened for medical and psychological disorders and excluded if they have: (i) traumatic, metabolic or endocrine disorders; (ii) cardiovascular or any other disorder that prevent physical exercise; (iii) psychopathological disorders or presence of severe symptoms with suicidal ideation in the Depression Anxiety and Stress Scale-21 (DASS-21) [47]; (iv) eating disorders in Questionnaire on Eating and Weight Patterns-5 (QEWP-5; [48]; (v) contraindication for performing functional magnetic resonance imaging (pregnancy, metal

Table 1 Items from the world health organization trial registration data set

Section/Item	Information
Primary Registry and Trial Identifying Number	ClinicalTrials.gov, NCT06668077
Date of registration in primary registry	11 Feb, 2025.
Secondary identifying numbers	PID2022-137524OB-I00, SICEIA-2024-000656
Source(s) of monetary or material suppor	The Spanish Ministry of Science, Innovation. The European Regional Development Fund Ministry of Universities Mind, Brain and Behavior Research Center (CIMCYC), University of Granada.
Primary Sponsor	Prof. Vilar-López, R. and Prof. Caracuel-Romero, A.
Secondary sponsor (s)	Bernat-Villena, A., Pérez-Comino, F.J., Becerra-Losada, M., and Algarra-López, L.S.
Contact for public queries	Prof. Alfonso Caracuel-Romero, acaracuel@ugr.es
Contact for scientific queries	Prof. Raquel Vilar-López, rvilar@ugr.es
Public title	InhibE study.
Scientific title	Intermittent theta burst stimulation (iTBS) and Inhibitory Control Training for Excess Weight Treatment: Study Protocol for a Randomized Controlled Trial (InhibE).
Countries of recruitment	Spain.
Health condition(s) or problem(s) studied	To study the efficacy of neuromodulation with iTBS as an add-on to the weight loss treatment as usual (TAU: diet and exercise), alone and in combination with inhibitory control training, for excess weight treatment.
Intervention(s)	1. Combined intervention: active stimulation of the DLPFC with iTBS and inhibitory control training 2. iTBS alone intervention: active stimulation of the DLPFC with iTBS 3. Control intervention: sham iTBS. All interventions include individualized diet and physical exercise guidelines.
Key inclusion and exclusion criteria	People between 18 and 60 years old with BMI between 25 and 39.9 kg/m2 and no contraindication for performing fMRI (pregnancy, metal implants, etc.) or iTBS.
Study type	Interventional Allocation: randomised Intervention model: parallel assignment Masking: double Primary purpose: treatment
Date of first enrolment	November 2024.
Target sample size	145.
Recruitment status	Recruiting.
Primary outcome(s)	Outcome Name: Weight Method of measurement: Body Mass Index Timepoint: pre-treatment, post-treatment and follow-up.
Key secondary outcomes	Changes in neuroimaging measures Timepoint: pre-treatment and post-treatment Changes in anthropometric measures Timepoint: pre-treatment, post-treatment and follow-up.
Ethics Review	Approved by Research Ethics Committees of Andalusia on September 26, 2024.
Completion Date	December 31, 2026.

The SPIRIT reporting guidelines recommend that these items be included in trial protocols to provide a brief, structured overview of a trial

implants, etc.) or iTBS (tinnitus, dizziness, surgical interventions, trauma, diseases or drugs that affect the central nervous system); (vi) pharmacological or any other kind of treatment for losing weight at present; (vii) candidates for bariatric surgery; (viii) weight loss > 5% during the three months previous to the intervention.

Participants ($N = 141$) will be randomly allocated by computer-generated random codes 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) $n = 45$. Participants may leave the trial at any time if they wish, but in no case the intervention allocation will be modified. All participants will receive individualized diet and physical exercise guidelines.

The psychologist that conducts the assessments (screening, evaluation sessions, and follow-ups) will be blinded to the group allocation during the whole project. Further, all participants will be blind to their condition. Additionally, the people who perform the statistical analyses will be blind to the condition of the participants through the coding of the interventions. The psychologist who is responsible for conducting the interventions and the nurse who assists with the stimulation sessions will be the only individuals who are not blind and will generate

the allocation. Therefore, it is unnecessary for any other individual to undertake the process of unblinding.

The informed consent form (appendix 1) is the only document that contains non-anonymized information, it will be collected on paper and will be kept under lock and key. The database will not contain any information that could reveal the identity of the participants and will be built and stored on a computer without internet connection.

Outcome measures

The measures have been selected whenever possible based on ADOPT (Accumulating Data to Optimally Predict Obesity Treatment) [49]. The assessments will be conducted across three different sessions throughout the study: pretreatment, posttreatment and 3-month follow-up.

Main outcome measure

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). Changes in BMI will be used to determine the results of the whole intervention. It will be measured at pre-treatment (week 2), post-treatment (week 6) and follow-up (week 18) assessments by the project nurse at the CIMCYC.

Secondary outcomes

Changes in neuroimaging measures at pretreatment (week 2) and posttreatment (week 6) assessments

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 min in the resonance. 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 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.
b) **White matter integrity.** Participants will be asked to remain still for 10 min to obtain diffusion tensor imaging (DTI) which provides indirect measurements of the architecture and connectivity of white matter fibres.
c) **Functional task: food go/no-go paradigm** (based on [50]). The task consists of touching as quickly as possible the items marked with a green circle (Go signal) and not responding to those marked with a red circle (No-Go signal). 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. In this evaluation version, 50% of images are presented under "Go" condition and 50% are presented under "No-Go" condition. Brain activation to Go vs. No-Go stimuli and food vs. non-food stimuli will be compared.
d) **Functional task: food decision making** (based on 38). This task consists of three blocks (healthiness, palatability and decision making). Participants answer on a 5-point Likert scale how healthy (block 1) and palatable (block 2) they consider 50 different foods. In the third block, a choice is made between a reference food (selected by an algorithm from among the food items rated as neutral in blocks 1 and 2), and an alternative food. Therefore, these forced binary choices will create cognitive conflicts when the reference food is more palatable than the alternative food, the alternative food is healthier than the reference food, and vice versa. In the cognitive conflict studies, the choice of the healthier food is defined as a controlled choice and the choice of the tastier food is defined as an uncontrolled choice. Brain activation will be compared between the controlled and uncontrolled choice conditions.

Changes in anthropometric measures at pre-treatment (week 2), post-treatment (week 6) and follow-up (week 18)

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 centimetres. The height in centimetres will be measured with a measuring rod (SECA Tape Measure 206). The WHtR is determined by dividing the waist circumference by the height.
b) **Body composition**. TANITA Scale provides (i) Percentage of fat mass, (ii) Kilograms of Muscle Mass, (iii) Bone Mass, (iv) Percentage of water, and (v) Visceral Fat.

Predictive and mediating/moderating variables

Changes in eating and physical activity behaviours at pre-treatment (week 2), post-treatment (week 6) and follow-up (week 18)

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) [51] 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.

b) **Physical activity.** The International physical activity questionnaire (IPAQ) [52] asks about physical activity related to work, activity at home and free time. This way, IPAQ determines the degrees of physical activity based on the metabolic equivalents (MET) consumed during said activity.

c) **Physical activity level.** Two questions on physical activity level (PAL), (based on [53]) at work and at leisure time, for energy expenditure will be asked.

Changes in emotional symptoms and emotional eating at pre-treatment (week 2), post-treatment (week 6) and follow-up (week 18)

a) **Stress and anxiety. The depression anxiety stress scale-21**: (DASS-21) [47] is a dimensional, self-report scale that was designed to measure negative emotional states. The stress and anxiety scales will be used, that contain seven items each. Participants are asked to endorse how much the item applied to them over the past week, rated on a 4-point scale.

b) **Depression symptoms**. The Beck Depression Inventory (BDI-II) [54] is a 21-item self-report inventory that measures the severity of depression. It has also been used in numerous treatment outcome studies.

c) **Emotion regulation.** Emotion Regulation Questionnaire (ERQ) [55] 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.

d) **Emotional eating.** The Coping subscale of the Palatable Eating Motives Scale (PEMS) [56] assesses across 4 items the intentionality for eating palatable foods to face negative emotions.

e) **Reward-related eating**. The Reward-Based Eating Scale (RED) [57] is a 13-item scale that assesses worries about food, loss of control over intake, and lack of satiety.

f) **Non homeostatic eating**. The Dutch Eating Behaviour Questionnaire (DEBQ) [58, 59] assesses restrictive eating behaviour in relation to external cues and emotional states using 33 items.

Changes in cognitive measures at pre-treatment (week 2), post-treatment (week 6) and follow-up (week 18)

a) **Motor inhibition**. The Food-Specific Go/No-Go Task [60] will be used to measure motor inhibition. The task consists of touching a key on the keyboard as quickly as possible when a food picture appears on the screen (Go signal) and not touching it when the picture is something else (No-Go signal). The stimulus set consists of 30 full-color pictures of common high-calorie [8] and low-calorie [7] foods and common toys. The average reaction time for the high-calorie and low-calorie foods paired with the Go signal is measured. Commission errors for Go and No-go items will be calculated according to the type of pictures (high-calorie, low-calorie foods and toys).

b) **Cognitive inhibition.** The Food Stroop Task [61] 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 with which they name the appropriate colour is calculated; a longer latency is thought to represent greater interference from task-irrelevant information, i.e. the meaning of the word.

c) **Inhibition and activation systems**. The Punishment Sensitivity and Reward Sensitivity Questionnaire (PSRSQ) [62] has 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.

d) **Delay of gratification**. The questionnaire Food Delay Discounting (DD) [63] will be used to measure the sensitivity relative to immediate rewards versus higher value rewards delayed at different time intervals, using the k parameter.

e) **Self-reported impulsivity**. Impulsive behaviour scale (UPPS-P) [64, 65]. This scale evaluates five personality factors that can trigger impulsive behaviours: negative and positive urgency, lack of premeditation, lack of perseverance and sensation seeking.

f) **Working memory (WM)**. N-back Task [66]. In this task, participants see a series of visual stimuli and are asked for each stimulus whether it matches a stimulus 1, 2 or 3 trials earlier (depending on the block). The task requires a cascade of cognitive processes: it requires encoding and temporary storage of each stimulus n in the stimulus sequence in WM, and continuous updating of incoming stimuli. At the same time, irrelevant stimuli must be inhibited, and currently irrelevant stimuli must be removed from WM. Performance is assessed using

an 'efficiency score' which includes accuracy and reaction times.

g) **Cognitive flexibility.** The Modified Card Sorting Test (MCST) [67] 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 24 response cards in each. Each card measures 7 × 7 cm, and there are various geometric shapes in different colours and numbers.

h) **Decision making.** The Iowa Gambling Task (IGT) [68] assesses real-world decision-making in a lab setting. Participants are asked to maximize profit over 100 trials by selecting cards from four decks. Decks A and B are "disadvantageous" and risky, and decks C and D are "advantageous". Favourable task performance requires subjects to forgo potentially large immediate rewards in exchange for small long-term rewards in order to avoid larger losses.

Motivation to change assessed at Pre-treatment (week 2), post-treatment (week 6) and follow-up (week 18)

a) **Motivation to change**. The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES 00) [69] relates motivations to change adapted to excess weight. It has 18 items that score readiness to change in people with abusive food use.

Changes in adherence to diet and physical exercise at post-treatment (week 6) and follow-up (week 18)

a) **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).

b) **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).

Clinical variables assessed at pre-treatment (week 2)

a) **Stigma**. Participants will answer whether they have experienced weight stigma (Yes/No) [70] and a VAS scale from 0 to 100 where they can rate the degree to which they have experienced it.

b) **Previous weight-loss interventions**. Participants will respond if and which previous weight loss interventions they have tried.

Biological samples collection at pre-treatment (week 2), post-treatment (week 6) and follow-up (week 18)

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. For blood parameter determinations, 10 ml of blood shall be collected by venipuncture and centrifuged to separate the plasma from the rest and stored at -80 °C until analysis.

a) **Hormone levels.** Fasting blood tests will determine hormone levels (pg/ml) of estradiol, progesterone, cortisol, leptin, adiponectin, TSH, thyroxine, triiodothyronine, ghrelin, glucagon and GLP-1.

b) **Glucose and triglycerides levels**. Fasting blood tests will determine glucose and triglycerides levels (mg/dl).

c) **Insulin levels**. Fasting blood tests will determine concentration of insulin (U/ml).

d) **Inflammatory parameters**. Fasting blood tests will determine concentration of IL-6 (pg/ml), CRP (mg/L) and TNF-alpha (pg/ml).

e) **Satiety markers**. Fasting blood tests will determine PYY [3–36] levels (pg/ml).

f) **Genetic analyses**. Genetic analyses will be performed by sequencing candidate genes. Genome-wide association analysis is proposed to identify new genes and variants associated with PD such as ZFP36, GAD2 on chromosome 10p12, Neuromedin β with whole exome sequencing and methylation analysis. The buffy coat deposited between plasma and red blood cells by centrifugation shall be used.

g) **Oral microbiota**. Saliva sample tests will determine oral microbiota (microbial taxa). It will be collected using two swabs (right cheek and left cheek) that will be stored at -80°C.

h) **Gut microbiota**. Participants will collect faecal samples and 1.5 g of the top layer will be stored in tubes at -80°C. Testing of faecal samples will determine gut microbiota composition (microbial taxa).

i) **Proteomics analysis**. Proteomics analyses will determine concentration of proteins (mg/mL). Blood samples will be collected in plastic bottles, centrifuged, and stored at -80°C.

Descriptive and screening measures (pre-treatment week 2)

a) **Sociodemographic questionnaire** (age, education, sex, socioeconomic variables) and clinical variables to consider exclusion and inclusion criteria.
b) **Depression symptoms**. Participants with a score above 29 in the Beck Depression Inventory (BDI-II), indicating severe symptoms, will be excluded.
c) **Anxiety**. Participants with anxiety scores greater than 8 on the Anxiety subscale of the DASS-21, indicating severe symptoms, will be excluded.
d) **Eating disorders**. Questionnaire on Eating and Weight Patterns-5 (QEWP-5) [48] will be used to exclude people with binge eating problems and bulimia. The questionnaire is adapted to DSM-5 criteria.
e) **Binge eating**. The Binge Eating Scale (BES) [71] will be used to ensure people with binge eating problems is excluded.
f) **fMRI and rTMS security questionnaire**. The safety questionnaires for each of the techniques approved by the research centre to gather information from the subject shall be used.

Measures to calculate cost effectiveness, cost utility, and budget impact analysis. Administered pre-treatment (week 2), post-treatment (week 6) and follow-up (week 18)

a) **Quality of life**. SF-36 Quality of Life 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 [72].
b) **Economic Evaluation**. 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**. The Food Cravings Questionnaire (FCQ-t-r) [73] 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**. The Health Resources Questionnaire enables the measurement of the healthcare resources utilised by participants, including primary care visits, urgent care, hospital admissions, and medication consumption.
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 3 min 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 min 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.

Procedure and interventions

The information meeting, psychological evaluations, nutrition and exercise sessions will be online. Otherwise, biological and fMRI evaluations, as well as neurocognitive interventions, will be on site. The participation will be conducted in small groups of 5–6 people. Eligible participants will attend an information session where they will receive written and verbal information about the project and will be asked for their informed consent for evaluations, interventions and collection and use of participant data and biological specimens. Participants will then be randomly assigned to groups and assigning them a code to guarantee their anonymity. The three groups of the study will complete all the assessments. In addition, all groups will receive the same TAU, which include diet and exercise sessions where they will receive individualised diet and exercise guidelines. What will differentiate the groups will be, therefore, the treatment (iTBS applied to left DLPFC combined with inhibitory control training vs. iTBS applied to left DLPFC vs. sham iTBS applied to vertex). All procedures will be conducted by psychologists, except the biological samples collection, nutrition and physical exercise plans, which will be conducted by a nurse, Ph.D. nutritionist and a Ph.D physical exercise professional, respectively. Upon conclusion of the study, should the combined treatment prove efficacious, groups 2 and 3 will be offered it. All participants will receive an individualized report with some results and the group they belonged to at the end of the follow-up.

The whole 18-week-procedure consists of the following (See Fig. 1):

1. Informative session (week 1, session 1): This group session aims to guarantee that all participants comprehend the rationale behind the intervention, they will be informed of the objectives, the rationale for the project, and the research procedure.

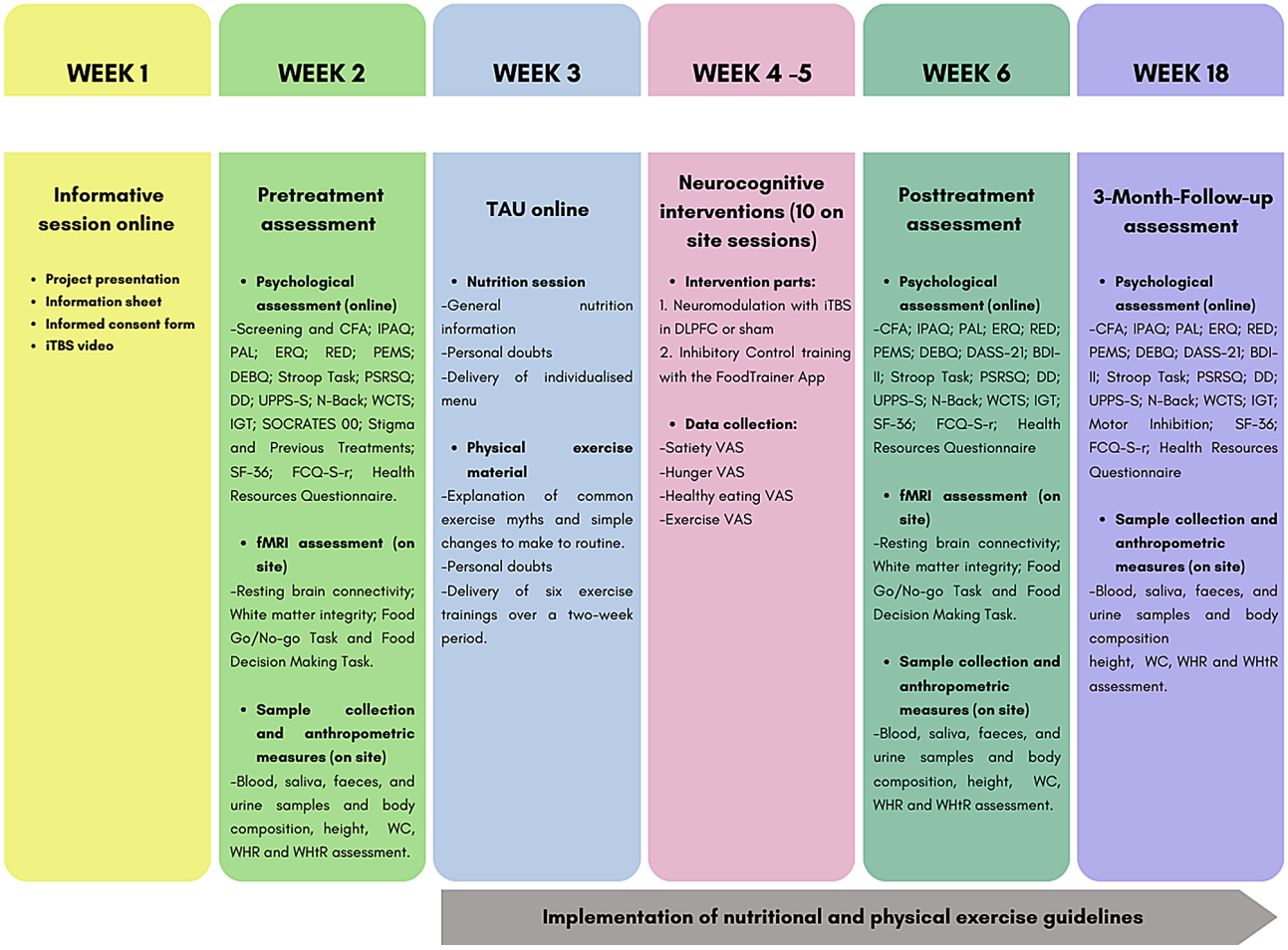

Fig. 1 Procedure

Furthermore, they will be requested to provide written informed consent.

2. Pretreatment assessment (week 2, session 2, 3 and 4): Session 2 will be conducted online and will take about two hours. All participants will complete the screening instruments (DASS-21, BDI-II, QEWP-5, the socio-demographic, and MRI and rTMS safety questionnaires). In this baseline assessment, participants will also complete the psychological assessment (CFA; IPAQ; ERQ; RED; PEMS; DEBQ; Stroop Task; PSRSQ; DD; UPPS-S; N-Back; WCTS; IGT; SOCRATES 00; Stigma and Previous Treatments; SF-36; FCQ-S-r; Health Resources Questionnaire). In session 3, all participants will undergo an individual fMRI session which will last 90 min (Resting brain connectivity; White matter integrity; Food Go/No-go Task and Food Decision Making Task). In session 4, participants will attend the CIMCYC, during where the nurse will collect blood, saliva, faeces, and urine samples. Additionally, the nurse will measure body composition with the TANITA scale and measure the height, WC, WHR and WHtR of the participants. This session will last 20 min.
3. TAU (week 3, session 5 and 6): Participants will receive information on healthy nutrition habits (with a Ph.D in nutrition) and physical exercise (with a Ph.D in Sports Science) in online sessions, and also through videos and written material designed by the professionals. In addition, they will receive individualised guidelines on nutrition and six physical exercise trainings along the two weeks of intervention. Both professionals will be constantly in touch through WhatsApp groups to solve doubts or modifications during the whole participation. The final material provided to participants will include further nutritional and exercise guidelines, enabling them to devise their own menus and incorporate more sophisticated exercises into their routine.
4. Neurocognitive intervention sessions (week 4 and 5, sessions 7 to 16): These interventions will be conducted over a period of two weeks, with five one-on-one sessions scheduled per week, the duration will be 10–20 min. The stimulation parameters are

based on the protocols for the application of iTBS in individuals with food intake problems, as outlined by Barone and cols [43], and in accordance with international safety recommendations [74]. The procedure is as follows: Sessions have two parts for group 1 and only the first part for groups 2 and 3:

- Part 1: Neuromodulation with iTBS (DLPFC or sham) (3 min). The complete iTBS process includes 3 min of stimulation and preparation time (10 min). More specifically, it consists of:

  A. The stimulation area will be identified by T1-sequence structural neuroimaging images using *Brainsight software* for the placement of the stimulation coil. In the active stimulation group, this will be the left DLPFC area (x -37, y 27, z 44), which corresponds to the F3 position in the EEG 10–20 system based on [75]. In the control group, the stimulation site will be the vertex (x 0, y -34, z 78), which has no cognitive effects after stimulation but coincides with sensory effects [76].
  B. iTBS stimulation will be conducted with *the Megastim Rapid 2 magnetic stimulator* for a duration of three minutes. The stimulation parameters will be as follows: 50 Hz frequency, 3 pulses; 10 bursts; an eight-second cycle duration; 20 cycles; a 5 Hz burst rate; and a total of 600 pulses. The stimulation intensity will be maintained at 30% of the maximum stimulator output.

- Part 2: The combined intervention group (group 1) will also receive inhibitory control training with the FoodTrainer App [4]. The App is similar to the Food Go/No-Go task described above. In this case, it is performed with the mobile phone by touching the image with the finger to the Go signal and not responding to the No-Go signal. The training differs from the evaluation so that all healthy food pictures are paired with the "Go" signal and the unhealthy ones with the "No-go" signal. The non-food pictures are still paired 50/50 with "Go" and "No-go" signals.

Immediately after each neurocognitive session, participants will answer, on a VAS scale of 0 to 100, how satiated they are, as well as how hungry they feel and how much they are implementing exercise and nutrition guidelines. Every day, before and after the stimulation, participants are asked if they have experienced any atypical sensations or discomfort that may be related to the trial, and this is recorded in the database. The nurse in charge of the project must supervise all sessions in order to be able to intervene in case of unintended effects of the trial.

5. Posttreatment assessment (week 6, session 17, 18 and 19). Participants will repeat the whole initial evaluation in session 17 (CFA; IPAQ; ERQ; RED; PEMS; DEBQ; DASS-21; BDI-II; Stroop Task; PSRSQ; DD; UPPS-S; N-Back; WCTS; IGT; SF-36; FCQ-S-r; Health Resources Questionnaire). The fMRI will be the 18 session and biological and anthropometric measures will be collected in session 19, following the same procedure than in week 2.
6. 3-Month-Follow-up assessment (week 18, session 20 and 21): Three months after the final intervention session, participants will be contacted for the purpose of repeating the psychological assessments in session 20 (CFA; IPAQ; ERQ; RED; PEMS; DEBQ; DASS-21; BDI-II; Stroop Task; PSRSQ; DD; UPPS-S; N-Back; WCTS; IGT; Motor Inhibition; SF-36; FCQ-S-r; Health Resources Questionnaire), in addition to biological and anthropometric assessments (session 21).

Compliance and adherence

Different strategies are implemented to improve adherence to intervention protocols throughout the participation. WhatsApp messages are used to send alerts and important reminders, such as cautions for fMRI or iTBS or appointment reminders. It is intended that the information session will be conducted in a group setting where participants will watch a video of what an iTBS session looks like. This will help allay any concerns about this type of technology. On the initial day of iTBS, the researcher provides a comprehensive explanation of the machine's functionality. To optimise the time dedicated to this explanation, the first session is slightly longer. Regarding inhibitory control training, if any participant has problems perceiving colours, the Food Trainer app allows him/her to substitute this variable for another pattern (continuous vs. discontinuous line). If a participant misses a session, it will be scheduled for the following Monday. In the Posttreatment assessment participants will have the chance to share their opinions by completing a debriefing questionnaire that will provide insight into possible compliance and adherence problems. At the end of the follow-up, an individualized report will be given with some of the results.

Statistical methods

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 [77], 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 [78]. 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 [79] and Spanish standards [80]. 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 [81]. 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. The missing data will be imputed according to the participant's last recorded values.

Expected results

The combined intervention is expected to yield superior outcomes compared to neuromodulation alone. Furthermore, any of both interventions is anticipated to demonstrate greater efficacy than sham iTBS in several key areas. These include reductions in BMI, attenuation of cravings, modifications in brain connectivity and activation during rest and tasks involving food stimuli, and enhancements in anthropometric measures and eating and exercise behaviors. Additionally, the intervention is anticipated to decrease waist circumference and waist-to-hip and waist-to-height ratios, improve eating and exercise behaviors through reduced caloric intake and increased physical activity, and ameliorate emotional symptoms and eating patterns, such as depression, anxiety, emotional regulation, emotional eating, and reward-related eating. Cognitive abilities, including motor and cognitive inhibition, delay of gratification, impulsivity, working memory, cognitive flexibility, and decision-making, are also expected to improve. Furthermore, changes in biological parameters, such as plasma and microbiota, and advantages in cost-effectiveness and cost-utility based on economic evaluations, are expected outcomes of the combined intervention.

The results of the clinical trial will be published in conferences and journals following open science guidelines.

Discussion

The objective of this double-blind, randomised, controlled trial with parallel groups is to evaluate the efficacy of neuromodulation with iTBS in the dorsolateral prefrontal cortex alone and in combination with inhibitory control training as an add-on to a Behavioral Weight Loss Intervention, in generating brain, behavioural, emotional, cognitive and biological changes in individuals with excess weight. The study presents a number of challenges, including recruiting 141 volunteers who are able to attend the CIMCYC several times, and examining mid-term (three months) outcomes for three different interventions. In order to facilitate the generation of evidence that can be readily compared with the efficacy

of other obesity interventions, the international ADOPT consensus has been applied in the selection of outcome measures.

Abbreviations

EW	Excess Weight
DLPFC	Dorsolateral prefrontal cortex
BMI	Body mass index
rTMS	repetitive transcranial magnetic stimulation
iTBS	intermittent Theta Burst Stimulation
ADOPT	Accumulating Data to Optimally Predict obesity Treatment
CIMCYC	Mind, Brain and Behavior Research Center
fMRI	functional Magnetic Resonance Imaging
DTI	Diffusion tensor imaging
CFA	Food frequency questionnaire
IPAQ	Questionnaire about Physical Activity
PAL	Physical Activity Level
VAS	Visual Analog Scale
WC	Waist circumference
WHR	Waist-to-hip ratio
WHtR	Waist-to-height
BDI-II	Beck Depression Inventory
ERQ	Emotion Regulation Questionnaire
PEMS	Coping subscale of the Palatable Eating Motives Scale
FCQ-T-r	Food Craving Questionnaire Trait-reduced
RED	Reward-Based Eating Scale
DEBQ	Dutch Eating Behavior Questionnaire
SOCRATES 00	Stages of Change Readiness and Treatment Eagerness Scale
UPPS-P	Impulsive Behavior Scale
PSRSQ	Punishment Sensitivity and Reward
DD	Delay Discounting
WM	Working memory
WCST	Wisconsin Card Sorting Test
IGT	Iowa Gambling Task
DASS-21	Anxiety and Stress Scale-21
QEWP-5	Questionnaire on Eating and Weight Patterns-5
BES	Binge Eating Scale
QALYs	Quality-adjusted life years
FEA	Area Specialist Physician
SPM12	Statistical Parametric Mapping
ICA	Independent component analysis
PPI	Psycho-physiological interaction
FA	Fractional anisotropy
ADC	Apparent diffusion coefficient
ICER	Incremental cost-effectiveness
ICUR	Incremental cost-utility ratios
SA	Sensitivity analyses
ITT	Intention to treat
PP	Per protocol

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40359-025-02556-9.

Supplementary Material 1

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Author contributions
A.B-V wrote the main manuscript text, all the authors reviewed the manuscript under the special supervision of R.V-L and A.C-R. L.S.A-L is expected to be in charge of the biological samples. F.J.P-C will be in charge of the intervention sessions. A.B-V and M.B-L will be in charge of the evaluations.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The protocol has been approved by the Research Ethics Committees of Andalusia (SICEIA-2024-000656). All participants provide informed consent before being enrolled in the study. A random ID generator will be applied to ensure pseudonymization of the research data. All personal data will be stored securely and separately from the research data. At the end of the trial, if the results show that the combined intervention is significantly more effective, participants in the stimulation alone and sham groups will be offered the opportunity to receive the combined intervention. Trial results will be disseminated at relevant conferences and published in peer-reviewed journals. Informed consent was obtained from all subjects involved in the study specifying that the protocol and results will be published anonymously. In the event of any damage to a participant due to the clinical trial, the liability insurance of the University of Granada will be covered post-trial care.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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