Tittle: Inhibitory Control Training for the Treatment of Excess Weight: Behavioural, Cognitive and Anthropometric Changes (InhibeT). Study Protocol and Statistical Analysis Plan.

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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. We propose an intervention that seeks to target these issues. Thus, the present study aims to determine the effectiveness of combining inhibitory control training with usual treatment (diet and physical exercise) in treating people with excess weight (EW) to produce cognitive, behavioral and anthropometric changes. Participants will be randomly allocated to one of two groups: 1) an experimental group that would receive active inhibitory control training and (2) the active control group that will receive inhibitory placebo training. Both groups will receive individualized diet and physical exercise guidelines. Training requires to inhibit responding to certain foods presented during computerized tasks. Using a food Go/No-Go paradigm, individuals are asked to press a button when a Go cue is presented next to an image and to refrain from pressing a button when a No-Go cue (e.g., a bold frame) is presented. In the experimental group pictures of healthy and unhealthy foods are always paired with the Go and the No-Go signal, respectively and in the active control group healthy and unhealthy foods are paired 50% of the time with the Go and the No-Go signal. We hypothesize that the experimental intervention would be effective improving (i) Body Mass Index (BMI), (ii) food craving, (iii) anthropometric measures (waist circumference and waist-to-hip and waist-to-height ratios), (iv) eating and exercise behaviors (decreased caloric intake and increased frequency and time of physical activity), (v) emotional symptoms and emotional eating (depression, anxiety, emotional regulation, emotional eating, reward-related eating, non-homeostatic eating), and (vi) cognitive abilities (motor and cognitive inhibition, delay of gratification, impulsivity, working memory, cognitive flexibility and decision making).

STARTING HYPOTHESES AND GENERAL OBJECTIVE

HYPOTHESIS: Inhibitory control training with the food Go/NoGo paradigm will be effective in treating people with EW. Thus, the active intervention, compared to the placebo, will achieve: (i) decreased BMI, (ii) decreased craving, (iii) improved anthropometric measures (waist circumference and waist-to-hip and waist-to-height ratios), (iv) improved eating and exercise behaviors (decreased caloric intake increased frequency and time of physical activity), (v) improved emotional symptoms and emotional eating (depression, anxiety, emotional regulation, emotional eating, reward-related eating, non-homeostatic eating), (vi) improved cognitive abilities (motor and

cognitive inhibition, delay of gratification, impulsivity, working memory, cognitive flexibility and decision making).

GENERAL OBJECTIVE: To determine the effectiveness of inhibitory control training for the treatment of people with EW (improvements in BMI, craving, anthropometric measures, food and exercise behaviours, emotional symptoms and emotional eating, and cognitive measures).

2. METHODOLOGY

2.1. Design: Randomized controlled trial of parallel groups.

2.2. Participants:

Sample size and statistical power:

The sample size calculation was performed with the G*Power 3.1 tool (Faul et al., 2009). To do so, we relied on the only study to date that applied food Go/NoGo training (4 sessions in one week) on a median effect size for reducing BMI post-treatment (Cohen's d = 0.57; (Lawrence et al., 2015) and at 6-month follow-up (Cohen's d = 0.48; Lawrence et al., 2015). Thus, considering a median effect size for conducting ANOVAs (f= 0.25), the minimum recommended N to reach a power of 0.80, assuming an alpha level of 0.05 with two groups and three repeated measures, was 44 participants, 22 per group. Nevertheless, we adopt a conservative approach and decided to increase groups to 27 participants.

Participants

The participants (N=54) will be randomly allocated to two groups: (i) experimental group (active inhibitory control training); n=27 and (ii) active control group (inhibitory control placebo training); n=27).

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/m^2. Also, participants must have access to the internet, a computer and a smartphone. All candidates will be screened for medical and psychological disorders and excluded if they have: (i) traumatic, digestive, metabolic or systemic disorders that affect the central nervous system, autonomic or endocrine, (ii) 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) and (iv) severe eating disorders.

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 exercise instructions to all participants.

Cognitive intervention (experimental group):

For 2 weeks participants should train inhibitory control from Monday to Friday for 10 minutes. To do so, participants will be instructed to use Food Trainer App (FoodT) (Lawrence et al., 2015) with their phones. Images of food and non-food appear on the left, right or centre of the screen and participants must touch it (or not, depending on the cue) with their index finger as quickly as possible. If the image has a green border around it, participants must tap the image and win 1 point. But if the image has a red border around it, participants must inhibit the tapping response, or they will lose 1 point. Participants must respond as quickly and accurately as possible. Pictures of healthy and

unhealthy foods are always paired with the Go and the No-Go signal, respectively. Non-food images are paired 50% of the time with the Go and the No-Go signal

Placebo intervention

This group will proceed the same than the experimental group, but a placebo version of FoodT will be available for them. In this case, three separate categories of non-food items (stationery, flowers and clothing) would be Go signal (associated with green 100%), No-Go signal (associated with red 100%) and control (50% red 50% green) respectively.

2.4. Outcome measures:

1. Main outcome measure

a.) Change in BMI. Weight for BMI calculation (kg/m2) will be obtained with a pharmacy scale.

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 Food Craving

a) 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)

2.2 Anthropometric measures:

To take these measurements at home, participants should ask someone for help and follow our instructions:

a) Waist circumference (WC): The WC will be calculated with participants standing, heels together and trunk upright, by placing a tape measure around the waist, just above the navel, to measure the waist circumference in centimetres.

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

b) Waist-to-hip ratio (WHR): This will be calculated with participants standing with heels together and trunk upright. To measure the hip circumference, the tape measure is placed at the maximum prominence of the buttocks. The WHR is determined by dividing the waist circumference (in cm) by the hip circumference (in cm).

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

c) 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.

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).

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, 201; BDI-II). 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).

2.5 Changes in cognitive measures

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 (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 (Kirby et al., 1999).

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 adaptation by Verdejo-García et al., 2010). This scale evaluates five personality factors that can trigger impulsive behaviours: negative and positive urgency, lack of premeditation, lack of perseverance and sensation seeking.

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)

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).

3. PROCEDURE

The whole study will be delivered online. 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. Both groups of the study (experimental and active control groups) will complete all the evaluations, as well as the follow-up (see below). What will differentiate the groups will be, therefore, the treatment: active vs. placebo inhibitory control training. If the intervention is effective, the placebo group will be offered to use

active FoodT app (without the assessment components) after the end of the 3-month follow-up.

All sessions will be developed in groups of 4-6 people. There will be at least 5 groups of intervention sessions (27 participants) and 5 groups for the placebo condition (27 participants). The program will comprise 6 weeks including two assessments (pre- and post-treatment), two FoodT training weeks, as well as the information and nutrition and exercise sessions. Also, a follow-up will be conducted 3 months after treatment (see below). Assessment sessions will last about 2 hours while inhibitory control will be trained for 10 minutes per day.

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; week 2):** All participants will complete 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, FCQ-S-r, 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.

3. **Nutrition and exercise sessions (session 3; 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 participants will be able to consult any doubts to both professionals through WhatsApp groups.

4. **Training sessions (sessions 4 to 14, weeks 4 and 5)**: A daily reminder will be sent by WhatsApp to the participants' phone to train from Monday to Friday during 10 minutes for two weeks. The FoodT app will partbe used to pair high-calorie meals with the no-go cue. Images can appear on the left, right or center of the screen, and should be tapped or not depending on whether the image has a green or red circle around them. Participants earn points for correct tapping responses and lose points for incorrect tapping responses and must respond as quickly and accurately as possible.

5. **Post-treatment assessment (session 15; week 6):** To evaluate the effectiveness of the interventions, BMI and the following instruments will be administered to obtain the main and secondary outcomes: FCQ-T/S-r, 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.

6. **Follow-up (session 16; week 18):** Follow-up at 3 months after the intervention will include the following measures: FCQ-T/S-r, WCST, Food Go/NoGo, IGT, Stroop, Food DD, N-Back, FCQ-S-r, CFA, IPAQ, DASS-21, BDI-II, PEMS, RED, DEBQ, PSRSQ, ERQ, UPPS-P, SF-36 and a questionnaire about used health resources. Anthropometric measures will be repeated as well. Every month after the end of the treatment, participants will be contacted by email and mobile message to maintain adherence.

4. DATA ANALYSIS PLAN

Once the preliminary analyses for the detection of possible errors in the recording of the data have been carried out, exploratory and descriptive analyses will be performed to investigate the distribution of variables and the presence of outlier. The inferential statistics applied will be in accordance with the characteristics of the data obtained (distribution of the data, qualitative/quantitative nature of the data, etc.) and with the hypotheses put forward in the study.

Models of repeated measures mixed models will be performed (2 groups X 3 moments) using BMI, craving, anthropometric measures, eating and exercise behaviors, emotional symptoms measures, eating emotional measures and cognitive abilities as dependent variables. The independent variables will be the type of treatment: inhibitory control training vs. placebo inhibitory control training. Effect sizes will be calculated for between-group and within-group comparisons. Both Intention to Treat (efficiency) and per protocol (effectiveness) analysis will be conducted. Appropriate corrections to control for multiple comparisons will always be considered.