

**INFRA-SLOW TRAINING FOR FOOD CRAVING IN OVERWEIGHT AND OBESE INDIVIDUALS- AN EXPLORATORY STUDY**

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**SUMMARY**

Dysfunctional neural activity in the cortical reward system network is implicated in food craving. Altering this pathological state using techniques of non-invasive neuromodulation may be a therapeutic option. To date, no published studies have used Infraslow neurofeedback (ISF) in the treatment of food craving among overweight and obese individuals. The aim of this study is to use ISF to target the Posterior Cingulate Cortex (PCC) as part of the default mode network (DMN) in overweight (body mass index ≥ 25) or obese (body mass index≥ 30) individuals with symptoms of food-addiction (Yale Food Addiction Scale score of ≥3) to investigate the effects on brain activity, food craving and wellbeing.

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**1.0. BACKGROUND**

In New Zealand, obesity affects almost 31% of the population [1]. Obesity contributes up to 8% of health costs and 10% of deaths worldwide [2]. In New Zealand, the World Health Organisation estimated that, yearly, between 2 and 7% of total health care expenditure is spent on obesity related disease [3]. Efforts to curb the obesity epidemic, such as public health strategies encouraging a change in eating habits and increasing physical activity, have not had significant wide-spread success [4]. Individualised treatments, such as behavioural and nutritional counselling also rarely result in long-term decreases in weight [5]. Bariatric surgery is one approach that has seen success but this is costly and can be risky to the individual [6, 7]. Therefore approaches that target the underlying drive to over eat and enable an individual to exist in an obesogenic environment without over consumption would be beneficial.

The regulation of food intake is a complex process which depends on a combination of both internal (i.e. homeostatic mechanism, cognitive state) and external factors (i.e., environmental cues, social context). Modular brain networks involved in the integration of these signals include the default mode network (DMN) and salience network (SN) [8]. The DMN consists of the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex, medial temporal lobe and inferior parietal cortices. Activity in the DMN reflects the brain’s baseline state such as when an individual is self-reflecting and disengaging from the external environment. The SN includes the anterior cingulate cortex (ACC) and insula. It has been postulated that the SN plays an important role in mediating relevance of internal and external stimuli [8]. Specifically, the core function of SN is to assess a particular salient event (i.e. visual food cue) and initiate a suitable control signal (pleasure signals) to guide behaviour (food consumption) [8]. In regards to eating behaviour, it can be conceptualised within this framework that: a) the urge to eat including pleasure signals and reward seeking behaviour is a bottom-up strategy; b) SN supresses DMN to facilitate attention when food is present and c) SN and DMN are anti-correlated.

Functional neuroimaging studies have shown that overfeeding resulted in increased DMN activity in lean but not obese individuals [9, 10]. These results suggest the possibility of a shift in balance between the DMN and SN in response to changes in energy balance among lean but not obese individuals. The maladaptive or inflexibility of the DMN towards alterations in energy dynamics could be a reason for the heightened craving for food among some obese individuals. In this study, wanting or craving for food is defined as the intense persistent desire to eat. The Yale Food Addiction Scale (YFAS) is a well validated tool used to identify individuals who display signs of food addiction similar to the Diagnostic and Statistical Manual of Mental Disorder V (DSM-V) for substance addiction and YFAS score of more than three will be used as an inclusion criteria [11].

 Results from our non-invasive neuromodulation pilot study suggest that transcranial pink noise stimulation (tPNS) of the ACC significantly inhibits desire to eat transiently [12]. This provides support for a more extensive investigation of non-invasive neuromodulation techniques in increasing the duration of any effects seen as a result of tPNS. Neurofeedback (NF) or EEG-biofeedback involves training the subject to modulate brain activity via operant conditioning through the use of EEG recordings or functional fMRI [13]. During an NF session, individuals learn to self-regulate and reinforce brain activity patterns by receiving continuous real-time feedback[13]. Studies have provided evidence that alpha/theta neurofeedback training can decrease strong food craving transiently in obese individuals and in non-clinical individuals with overeating [14, 15, 16]. Priming NF training with neuromodulation techniques (tRNS, tDCS) has been found to make the effects more pronounced [17].

The brain’s modular networks communicate in rich club or core (Figure 1) at different infra-slow frequencies between 0.01-0.1 Hz [18, 19]. In addition, different infra-slow frequencies integrate information from different resting state networks (i.e. 0.02 Hz in parts of the anterior cingulate cortex, 0.08 Hz in the precuneus) [20]. Given that the PCC incorporates information from other brain networks predominantly at 0.1 Hz, neurofeedback training of the PCC between 0.01-0.1 Hz may facilitate suppression of the of SN and consequently attention to food. Infra-slow neurofeedback (ISF) is a recent development in neurofeedback training focusing on modulating slow wave activity (<0.1 Hz) [21]. This neurobehavioural training is often applied in a clinical context, particularly in children with hyperactivity or deficit disorder and individuals suffering from epilepsy with positive outcomes. It has been reported that training using infra-slow band resulted in a significant reduction of behavioural disruptions, an improved ability to sustain attention during class and a reduction or elimination of psychotropic medication among children with Emotional Disorder and Pervasive Developmental Disorder [21]. To our knowledge, there are no ISF protocols that have been applied in the treatment of food craving. For that reason, we aim to develop an ISF protocol to modulate the DMN in overweight or obese individuals with heightened food cravings.



**Figure 1:** Rich club or core of the brain’s modular network

**1.1. OBJECTIVES**

**Among overweight or obese women with features of food-addiction (as defined by YFAS) individuals, the study aims to:**

1. Examine the effectiveness of ISF training targeted at the PCC in modulating the DMN. In order to verify whether there is a benefit of ISF in overweight and obesity, the study intents to:

a) Investigate the mechanistic principles of ISF (i.e., how ISF affects resting state activity, functional and effective connectivity),

b) Investigate the effectiveness of ISF band training (0-0.1 Hz) on food craving.

c) Explore beneficial effects of ISF on wellbeing.

**1.2. PRIMARY OUTCOME MEASURES**

Resting state activity (functional, effective connectivity, cross-frequency coupling), State/Trait Food Craving Questionnaire.

**1.3. SECONDARY OUTCOME MEASURES**

Perceived Stress Scale, World-Health Organization-five well-being index, Yale Food Addiction Scale, Symptom checklist-90-revised.

**2.0. RESEARCH DESIGN**

Briefly, potential participants recruited via advertisement will be screened at week-0 (W0). Those who are eligible (n=20) will be randomised to either i) real ISF training (n=10) or ii) sham ISF training (n=10). Participants will receive a total of 6 sessions of either real or sham ISF. An EEG will be performed at baseline, after 3 sessions and 6 sessions. Participants will be followed-up (EEG and questionnaires) 2-weeks (W5) and 4-weeks (W7) post treatment (**Table 1**).

**Table 1. Schedule of activities**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Week 0** | **Week 1** | **Week 2** | **Week 3** | **Week 5** | **Week 7** |
| **Activity** | **Screening** | **S1** **(Mon)** | **S2** **(Tues)** | **S3** **(Fri)** | **FU 1 (Mon)** | **S4 (Tues)** | **S5 (Fri)** | **S6 (Mon)** | **FU 2****(Thurs)** | **FU 3****(Mon)** | **FU 4****(Mon)** |
| Informed consent | x |  |  |  |  |  |  |  |  |  |  |
| Anthropometry | x |  |  |  |  |  |  |  |  |  |  |
| Adverse events |  | x | x | x | x | x | x | x | x | x | x |
| EEG (Mitsar 202) | x |  |  |  | x |  |  |  | x | x | x |
| Questionnaires  | x |  |  |  | x |  |  |  | x | x | x |
| ISF randomisation |  | x | x | x |  | x | x | x |  |  |  |

**2.1. Participants**

**Recruitment will be via advertisement in local newspapers and on notice boards with an invitation to participate in a potential therapeutic method to curb food craving.**

**Individuals who show an interest will be asked to attend a screening session at the clinic of the University Hospital of Otago, Dunedin. Initially, potential participants will be assessed to see if they meet the inclusion criteria. Participants who meet the inclusion criteria will be asked to sign the consent form and complete baseline questionnaires. An EEG will also be conducted at this clinic visit on those who qualify for the study.**

**Recruitment of participants will continue until the sample size of 20 is achieved.**

**Our previous pilot study investigating the effect of transcranial pink noise stimulation on food craving in obese women showed that 50% of obese participants meet the criteria. In addition, given that an attrition rate of 20% is expected based on our previous pilot study, it is estimated that around 44 women will be attending the first screening session.**

***2.1.1. Inclusion* criteria will include:**

1. Symptoms of food addiction (score ≥ 3 on the YFAS)

2. Women aged 18-60 years

2. Being right handed

3. Overweight or obese (BMI ≥ 25)

***2.1.2. Exclusion* criteria will include:**

1. Major weight gain or loss (> 5kgs) in the last 6 months

2. Certain medications

3. Recent significant head injuries. e.g. concussion where consciousness is lost or surgery

4. Psychiatric disorders with psychotic symptoms or manic symptoms

5. Other health problems-diabetes, cancer, heart disease, uncontrolled hypertension

6. Females who are or intend to become pregnant

7. History of epilepsy

8. Metal implants or implanted electronics (pacemaker)

9. Recurring headaches

10. Previous bariatric surgery

11. Previous diagnosis of an eating disorder

**2.2. Informed consent (Appendix A)**

The Participant Information Sheet and Informed Consent Form explaining the procedures of the study will be given and explained to potential participants. A signed Informed Consent Form will be obtained from each potential participant before screening them for participation in the study.

Subjects may withdraw at any time without giving a reason or may be withdrawn by the investigators if significant adverse effects occur or they are unable to adhere to the protocol.

**2.3. Randomisation and Blinding**

***Randomisation***

**To ensure that sample size is balanced across the sham and real ISF groups over time, block randomisation will be applied. Given the small sample size, a block size of 4 will be used. Therefore, 20 individuals will be randomised into 2 treatment groups in sizes of 4.**

**A researcher from the group who has no direct contact with the participants will conduct the randomisation process using the program on randomization.com. This tool is a valid randomisation program utilised by clinical trial researchers.**

***Blinding***

This exploratory study will be a double blind trial. Different researchers will be conducting the EEG assessments/craving status to those carrying out the treatments. All researchers who have contact with participants will be blinded to treatment allocation to minimise possible bias. All patients will be blinded to treatment assignment.

**2.4. Procedures**

***2.4.1. Screening***

All potential participants will be asked to complete the Yale Food Addiction Scale as well as provide height and weight. Eligible participants will then be asked to provide demographic information (i.e., age, ethnicity). Height and weight for eligible participants will be measured to calculate BMI. Participants who are unable to be weighed will provide self-report estimates. Eligible participants will also be administered the State and Trait Food Craving Questionnaire, Perceived Stress Scale, World-Health Organization-five well-being index, and the Symptom Checklist-90-Revised Scale. Eligible participants will also undergo a resting state EEG recording.

***2.4.2. EEG***

*EEG data collection*

EEGs will be obtained in a way previously described by the investigators [22, 23]. Data will be resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2-44 Hz and subsequently transposed into Eureka! Software [24], plotted and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or ECG artifact will be removed from the stream of the EEG. Average cross-spectral matrices will be computed for bands delta (2-3.5 Hz), theta (4-7.5 Hz), alpha1 (8-10 Hz), alpha2 (10.5-12.5Hz), beta1 (13-18 Hz), beta2 (18.5-21 Hz), beta3 (21.5-30 Hz) and gamma (30.5-45 Hz).

*Source localisation*

Based on the scalp-recorded electric potential distribution, the standardised low resolution brain electromagnetic tomography (sLORETA) software will be used to compute the cortical three-dimensional distribution of current density as previously described by the investigators [22, 23].

The tomography LORETA has received considerable validation from studies combining LORETA with other more established localization methods, such as functional Magnetic Resonance Imaging (fMRI) [25, 26], structural MRI [27], Positron Emission Tomography (PET)[28-30]. Further LORETA validation has been based on accepting as ground truth the localization findings obtained from invasive, implanted depth electrodes, in which case there are several studies in epilepsy [31, 32] and cognitive ERPs [33].

***2.4.3. Questionnaires (Appendix B)***

a) *Yale Food Addiction Scale (YFAS).* A questionnaire used to identify individuals who display signs of food addiction similar to the Diagnostic and Statistical Manual of Mental Disorder V (DSM-V) for substance addiction and YFAS score of more than three will be used as an inclusion criteria [11].

b) *State/Trait Food Cravings Questionnaires.* A 36-item questionnaire assessing temporal and situational states of food craving [34].

c) *Perceived Stress Scale.* A 10-item scale assessing the perception of stress during the last month [35].

d) *World Health Organization-five well-being index (WHO-5).* A 5-item scale assessing aspects of wellbeing within the last 2 weeks [36].

e) *Symptom Checklist-90-Revised (SCL-90-R).* A 90-item questionnaire used to assess psychopathology, The SCL-90-R consists nine primary symptoms dimension: somatisation, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism [37].

***2.4.4. Infraslow frequency training***

Participants will complete a total of 6 ISF sessions. The ISF will be administered with 3 sessions during the first week, 2 sessions in the second week and 1 session in the third week. ISF training will be 10 minutes for the first session and 20 minutes for the subsequent 5 sessions.

Infraslow slORETA neurofeedback will be implemented with a 24 channel DC coupled amplifier produced by Brainmaster Inc.

ISF will be administered with the participant sitting in a comfortable chair with their eyes opened. After careful skin preparation, the appropriate Comby EEG cap (AGg/AgCl) will be placed on the participant’s head with reference electrodes at the mastoids. The impedances of the active electrodes will be kept below 5k Ω. Before the training period, participants will be instructed to relax and listen to the sound being played. A distinct tone will be used for ISF reinforcement at the PCC. Reward threshold will be adjusted in real time at above 90%. For sham ISF, the simulation protocol by Brainmaster Inc will be administered.

Before the first ISF session, a simple explanation will be given to participants. They will be informed that research has shown that the brain of individuals with a BMI of more than 25 functions a little differently from normal weight individuals and that we are trying to train their brain to normalise. The sound they hear during neurofeedback reflects whether they are doing well.

**3.0. STATISTICAL ANALYSES**

**3.1.EEG**

sLORETA will be used to perform a voxel-by-voxel analysis (comprising 6239 voxels) for the different frequency bands of the current density distribution to identify potential differences in brain electrical activity between the two different treatment groups at baseline, after 5 sessions, 10 sessions, 15 sessions and 20 sessions. Nonparametric statistical analyses of functional sLORETA images (statistical nonparametric mapping: SnPM) will be performed for each contrast using sLORETA’s built-in voxel wise randomization tests (5000 permutations) and employing a log-F-ratio statistic for independent groups with a threshold P < 0.05. As explained by Nichols and Holmes, the statistical nonparametric mapping method does not rely on an assumption of a Gaussian distribution for the validity and corrects for all multiple comparisons (i.e. for the collection of test performed for all voxels and for all frequency bands) by employing a locally pooled (smoothed) variance estimate that outperforms the comparable statistical parametric mapping [29, 30].

In addition, resting state lagged linear connectivity will be calculated using the technique introduced by Pascual-Marqui, 2007 [38, 39]. The measures will be defined in the following frequency domain: delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12.5 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–45 Hz). Three region of interest (ROI)’s will be identified based on a previousstudy suggesting that brain activity in the pgACC and posterior cingulate cortex (PCC) may be anti-correlated with activity in the dACC [8].

3.2. State/Trait Questionnaire

Independent t-test will be used to examine differences between the sham and treatment groups for FCQ-S scores at baseline. Repeated measures analysis of variance (ANOVA) will be conducted with group (sham or real) as between subject variable, time as a repeated factor and the questionnaire scores as dependent variable.

Our previous pilot study using transcranial pink noise stimulation showed that among 16 women (8 in sham and 8 in real treatment), after the treatment period, the real treatment group had a 22% reduction (mean decrease of-1.11, 95% CI:-2.09, -0.14, p=0.029) on the intense desire to eat subscale compared to the sham group. Given that we hypothesized that ISF would be more efficient than transcranial pink noise stimulation, a sample of 10 in each group will be sufficient to show a significant difference on the scale.

**4.0. RISKS TO PARTICIPANT**

There are no known serious adverse events associated with ISF training except for a seldom-occurring headache. In this study participants will be asked to fill out an evaluation questionnaire on their experience of undergoing ISF after each session.

**Table 2.** Adverse reaction to ISF.

|  |  |  |  |
| --- | --- | --- | --- |
| Do you experience any of the following symptoms or side-effects? | Enter a value (1-4) in the space below (1, absent; 2, mild; 3, moderate; 4, severe) | If present: Is this related to ISF? (1, none; 2, remote; 3, possible; 4, probable; 5, definite) | Notes |
| HeadacheSleepinessTrouble concentratingAcute mood changeOthers (specify) |  |  |  |

Adverse events will be recorded from when each participant provides written consent until the final visit. All adverse events observed or reported will be recorded on the Case Report Form (CFR) specifying the verbatim description of the event, time of onset, time of resolution, severity, causality, duration, seriousness, treatment and resolution of each episode. All participants will be advised that they are to contact the PI or other research staff at any time if they feel unwell or have any concerns while they are in the study.

**5.0. DATA CONTROL**

A Case Report Form (CRF) will be used for the purposes of recording participant specific data. The CRFs will be completed in a timely fashion and will contain all study data. Any change (s) of information made on the CRF will be appropriately initialled and dated by the Principal Investigator or study personnel.

**6.0. COMMUNICATION OF RESULTS**

Results from the study may be written up for publication in peer-reviewed scientific journals, presented at scientific conferences and may form part of grant applications. All data will be de-identified.

**7.0. CONFIDENTIALITY**

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study. However, authorised regulatory officials and sponsor personnel will be allowed full access to the records. All materials collected shall be used solely in accordance with this protocol.

Only participant’s initials and unique participant study numbers will identify participants. However, participants’ full names may be made known to a regulatory agency or other authorised official if necessary.

**7.0. SIGNIFICANCE**

The use of ISF as a treatment for food-addicted obesity is novel. If the proposed technique is proven to be effective, the inclusion of ISF will be of clinical importance in advancing the current treatment for obesity. In New Zealand neurofeedback is currently widely used to treat adults and children with a variety of brain issues including brain injuries, anxiety, depression, ADHD and psychological trauma. Neurofeedback is a simple, non-invasive procedures (approximately 40 minutes per session) conducted using a portable device. Currently, to our knowledge, ours is the only group utilising this technique to study neural networks in obesity and the data that this study produce will be unique. In addition, once we have established the technique we believe that it will be easily applied to a number of research questions pertaining to the control of appetite and the abnormalities that exist in obesity.

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