Study Document

Study Title: Role of Transcranial Direct Current Stimulation to Decrease Impulsivity and Compulsivity in Individuals with Obesity
Short Title: tDCS for Impulsivity and Compulsivity in Obesity
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PROTOCOL TITLE:

Role of Transcranial Direct Current Stimulation to Decrease Impulsivity and Compulsivity in Individuals with Obesity

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1. STUDY SUMMARY

Study Title	Role of Transcranial Direct Current Stimulation to Decrease Impulsivity and Compulsivity in Individuals with Obesity
Study Design	Double-blind, randomized, sham-controlled pilot clinical study
Primary Objective	**Primary Objective:** To determine if there is a treatment-related decrease in measures of impulsivity and compulsivity with tDCS compared to sham Hypothesis: tDCS treatment decreases impulsivity and compulsivity.
Secondary Objective(s)	**Secondary Objectives:** (1)To compare tDCS treatment-related change in weight loss compared to sham (randomized intervention) in individuals prior to undergoing their 16 week structured behavior modification weight loss program (usual care) in the Minneapolis VAMC's Move Mass Program Hypothesis: tDCS treatment leads to weight loss (2) To examine the history of brain injury (no TBI, single TBI, multiple TBI) in individuals with obesity as a possible factor in impulsive and compulsive eating. Hypothesis: TBI as a co-morbid condition may have some impact on eating behaviors.
Research Intervention(s)/Investigational Agents	tDCS (Starstim Noninvasive Wireless neurostimulator)
IND/IDE # (if applicable)	Class IIa device
Study Population	500 Veterans will be screened to enroll up to 50 Veterans. Subjects will be recruited from Minneapolis VAMC's Move Mass Behavior Modification Classes
Sample Size (number of participants)	20 (10 will undergo tDCS and 10 will undergo sham procedure). All will undergo Brain HQ task training to enhance executive function.
Study Duration for Individual Participants	About 3-4 months

2. Abstract

Objectives. Impulsivity and compulsivity are two psychological factors which contribute to addictive behaviors. Impulsivity is characterized by lack of foresight and planning, and excessive risk taking. Impulsivity is a characteristic of poor executive functioning, reflective of deficits in goal-oriented behavior and self-regulation. Impulsivity is common to a number of psychiatric conditions which contribute to high morbidity and mortality in Veterans such as substance abuse disorders, post-traumatic stress disorder, and traumatic brain injury (TBI). Impulsivity has been implicated in refractory obesity, in both bariatric and non-bariatric subjects (Sutin 2011, Filbey 2017, Gunstad 2017, Galioto 2016). Individuals with food impulsivity report out of control eating; they may report binging and/or cravings. Compulsivity, characterized by inability to break old habitual behaviors, may also play a role in refractory obesity. Transcranial direct current stimulation (tDCS) has been shown in other settings to reduce impulsivity. Coupled with brain training tasks to strengthen key circuitry involved in impulse control, the prefrontal cortex, tDCS has the potential to reduce impulsivity and compulsivity in individuals with obesity, with the potential for therapeutic application as a non-pharmacologic treatment for obesity in individuals with food impulsivity.

Research plan and methods. We plan to enroll up to 50 individuals and complete studies in 20 individuals involved with the Minneapolis VAMC's Move Mass weight management clinic. Participants, who report that they tend to have out-of-control eating at least once per week, will be randomized to either active or sham tDCS, two 13-minute sessions separated by 20 minutes, for five consecutive treatment days; both groups will undergo brain training tasks during the treatments. After they complete the sessions subjects will complete a 16-week long structured Move Mass Behavior Modification program (usual care). In addition to the brain training tasks during the stimulation periods, subjects will complete a food-impulsivity related questionnaire (the Binge Eating Scale [BES]) and other instruments at several timepoints during the study. The effect of the active vs. sham treatment to reduce measures of impulsivity and improve measures of executive function will be assessed over time. As a secondary aim we will evaluate treatment effect on weight loss and examine the possible relationship to TBI.

Clinical relevance. Refractory obesity, like other conditions with an addictive component, is in part related to impulsivity and inability to change compulsive behavior. More effective treatments are needed for this condition which significantly impacts morbidity and mortality in Veterans and non-Veterans. Safer, more effective treatments, including non-pharmacologic treatments which make use of the brain's own neuroplasticity to enhance function and heal or strengthen regions involved in impulse control represents an exciting new therapy for impulse control in individuals with obesity.

3. Objectives and Specific Aims

a. Purpose: The primary purpose of this study is to determine if tDCS coupled with executive function training decreases impulsivity and compulsivity in individuals with obesity. As a secondary aim, we will evaluate whether tDCS when coupled with executive functions training enhances weight loss in individuals with obesity attempting to lose weight in a structured behavior-modification based program.

b. Our **specific aims** are as follows:

i. **Aim 1:** To determine if tDCS with executive function tasks vs. sham paired with executive function tasks reduces impulsivity and compulsivity in individuals who report out of control eating and are enrolled in a 16 week structured behavior modification-based weight loss program

ii. **Hypothesis** 1: tDCS treatment decreases impulsivity and compulsivity in individuals with obesity who are enrolled in a structured behavioral modification weight loss program.

iii. **Aim 2 (secondary):** To test whether tDCS treatment, paired with executive function tasks, enhances weight loss compared to sham paired with executive function tasks in individuals who report out of control eating and are enrolled in a 16-week structured behavior modification-based weight loss program

iv. **Hypothesis 2**: tDCS treatment with executive functions training enhances weight loss in individuals with obesity who are enrolled in a structured behavioral modification weight loss program.

v. Aim 3: To examine the history of brain injury (no TBI, single TBI, multiple TBI) in individuals with obesity as a possible factor in impulsive and compulsive eating.

vi. Hypothesis3: TBI as a co-morbid condition may have some impact on eating behaviors.

In addition to the hypotheses and aims above, we intend to confirm the findings of Galioto *et al*, and demonstrate that baseline executive function predicts weight loss success (Galioto 2016).

4. Background, Significance, and Preliminary Data

Impulsivity and compulsivity are two psychological factors which contribute to addictive behaviors. Impulsivity is characterized by lack of foresight and planning, and excessive risk taking. Impulsivity is a characteristic of poor executive functioning, reflective of deficits in goal-oriented behavior and self-regulation. Impulsivity is common to a number of psychiatric conditions which contribute to high morbidity and mortality in Veterans such as substance abuse disorders, post-traumatic stress disorder and TBI. Impulsivity has been implicated in refractory obesity, in both bariatric and non-bariatric subjects (Sutin 2011, Filbey 2017, Gunstad 2017, Galioto 2016). Individuals with food impulsivity report out of control eating; they may report

binging and/or cravings. Compulsivity, characterized by inability to break old habitual behaviors, may also play a role in refractory obesity.

In our own experience with a non-veteran population followed in the Adult Medical Weight Management Clinic at the University of Minnesota where the average BMI is around 40, 89% of patients self-reported some level of out of control eating and/or craving at intake assessment (manuscript in preparation by PI). With regards to the veteran population at the Minneapolis VA, a large percentage of patients also report cravings for particular foods, binging, or out of control eating. It is also of note that insight into the underlying neurobiology of food impulsivity and/or cravings can also inform understanding of other compulsive, addictive behaviors such as gambling, and drug addictions including alcohol and cocaine abuse. These disorders manifest out of common neurobiological soil, a lack of impulse control.

Neurobiology underlying food impulsivity/cravings, and impulsivity. Eating and appetite behaviors are the output of brain networks comprised of homeostatic, reward and executive function components. Homeostatic appetitive centers in the brain include the hypothalamus, including the paraventricular (PVN), Arcuate, lateral, and dorsomedial nuclei. Traditionally, the hypothalamus has been considered an important region for acute and chronic fuel storage sensing, the basis for its homeostatic component to weight regulation. Other important components, brain reward centers, include the central nucleus of the amygdala, the nucleus accumbens, and the nucleus tractus solitaries which respond to other cues such as palatability; these limbic areas may also be affected by other non-homeostatic inputs such as emotions. Brain reward centers are strongly involved in mediating impulsivity- and compulsivity-related behaviors such as addictions, especially when these areas are not able to be adequately regulated by areas involved in executive function such as the prefrontal cortex.

Inadequate "Gate-keeping": Executive function and Obesity. Areas of the brain involved in directing goal-oriented behavior, such as the prefrontal cortex, provide an important counter-balance to the activity of the brain reward centers, not only with regards to the impulse control involved in drug addictions but also with weight regulation. Executive function predicts weight loss success in structured medical weight loss programs (Galioto 2016). Ultimately it is the integrative interaction between and among the homeostatic, reward, and "gate-keeping" regions that determines appetite perception and response to it. There is no effective treatment for impulsivity. The ideal treatment would provide enhancement of function in areas of the brain which govern impulse control and may provide an important, under-appreciated target for obesity treatment.

One common factor to both obesity and executive dysfunction is traumatic brain injury (TBI). Survivors recovering from TBI are at risk for obesity and overweight problems and health conditions, particularly during long-term recovery (Dreer et al., 2017). Dreer et al. (2017) showed increased prevalence rates of obesity immediately following and with increasing time since injury. Both TBI and obesity have negative consequences on frontal cortical structure and function. Obesity has been associated with atrophy in frontal lobes, with concomitant impaired performance on cognitive testing (Fotuhi & Lubinski, 2013). Cognitive dysfunction, in the domains of attention, impulsivity, and executive function, is a leading cause of disability following TBI (Rabinowitz & Levin, 2014; Wood & McHugh, 2013). Thus, the relationship between obesity and TBI, and their effects on impulsive behavior, are important to consider with regard to identifying factors related to unhealthy weight management and the design of treatment programs.

Cognitive training coupled with transcranial direct current stimulation for impulsivity.
1. Cognitive training for reducing impulsivity in healthy subjects. The go/no-go task has been utilized successfully to reduce chocolate eating in female undergraduates with chocolate craving (Houben/Jansen 2011) and beer consumption in heavy alcohol drinkers

(Houben/Nederkoom/Wiers/Jansen 2011) in very short-term studies. While there is evidence that cognitive training may provide potential treatment for impulsivity, with application to obesity management, there is concern that the results from very task-specific cognitive training may not generalize to other desirable behavior change. Unfortunately, cognitive training can be time consuming and in addition to lack of generalization, results of cognitive training may not persist.
2. tDCS: A tool for reduction of impulsivity and compulsivity. tDCS, even in a single session, has been found to reduce cravings and enhance cue response to negative stimuli in individuals with alcohol use disorder (Boggio 2008). Furthermore, a multiple treatment schedule of tDCS (twice daily for 5 days) was found to help reduce relapse over a 6-month period in subjects with alcohol use disorder (Klauss 2014). Some investigators have found decreased cravings, as measured by questionnaires, after 5 days of treatment and 30 days later (Ljubisavljevic 2016). In preliminary data from members of our team tDCS over the dorsolateral prefrontal cortex was shown to reduce risk-taking impulsivity (see Preliminary Data section below).
3. Cognitive training with tDCS: complementary therapy to strengthen circuitry deficits which underlie impulsivity and compulsivity, a tool for augmentation of neuroplasticity. Application of tDCS with relevant task-based cognitive training may enhance the function of pathways being stimulated by the task training (Bikson/Rahman 2013). Coupling of tDCS with a broader array of task training, rather than narrow domain-specific component of executive function, may allow for generalization of enhanced executive function and better long term therapeutic results for impulsivity-related disorders, including substance abuse and obesity.

Significance. If tDCS can be utilized to enhance plasticity in regions of the brain involved in impulsivity and compulsivity, then tDCS combined with cognitive training becomes a powerful non-pharmacologic tool for altering brain circuitry to improve impulsivity and compulsivity. This approach has the potential to be applied to a wide range of neurobiological disorders.

Preliminary data. Prior work by members of our group demonstrates that the application of tDCS does appear to improve impulse control when applied with tasks which engage regions of the brain involved in executive function. Lim and colleagues conducted a VA-based study in 30 individuals who underwent two 25-minute sessions (active tDCS vs. sham procedure coupled with performance of the Balloon Analogue Risk Task [BART]) for five days followed by sessions at one and two months. Subjects completed questionnaires and behavioral tasks measuring impulsivity (the Risk Task) before and after the intervention. After receiving active tDCS, subjects showed a significant 46% decrease in risky choice in the Risk Task from pre- to post-intervention, which persisted through the one and two-month follow-up sessions. The sham tDCS group showed no significant change in risky choice from pre- to post-intervention.

4. Study Endpoints

Primary Endpoint: decrease in impulsivity and compulsivity (as measured by change in NIH Examiner Score) with active tDCS compared to sham

Secondary Endpoint: change in weight over the study period

5. Study Intervention(s)/Investigational Agent(s)

a. Description: tDCS and discussion of device handling. We will use the Neuroelectrics Starstim system, a wireless multichannel transcranial current stimulator. Periods of tDCS stimulation of 13 minutes will be twice a day, separated by 20 minutes (Monte-Silva et al., 2013), for five consecutive days (10 total tDCS stimulation sessions). Active tDCS: A 2-mA current will be administered via two circular carbon rubber core electrodes in saline-soaked surface sponges (25 cm^2), placed in a neoprene headcap with marked locations based on the 10-10 EEG system. The anodal stimulating electrode will be at location F4, over right dorsolateral prefrontal cortex (DLPFC) and cathodal electrode at location F3, over left DLPFC. Sham tDCS: For sham stimulation, the electrodes will be placed at the same positions as for active stimulation (F3 and F4), but current will be ramped down immediately after the initial 30 s ramp up period. Thus, participants will feel the initial itching sensation associated with tDCS but will receive no active current for the rest of the stimulation period. This method of sham stimulation has been shown to be reliable (Gandiga, Hummel, & Cohen, 2006). The Starstim software supports the measurement of electrode impedance. Before each training session, the impedance of the electrodes will be checked and verified to be ≤10 KOhm. During a training session, the impedance is measured every second and if found to be > 20 KOhm stimulation will be terminated for safety. The current and impedance will be recorded for every session.

b. IND/IDE: The FDA has classified this as a NSR device (an FDA letter for use of this same device in another study by members of our research team for a similar purpose and protocol is included with our IRB packet for this current application)

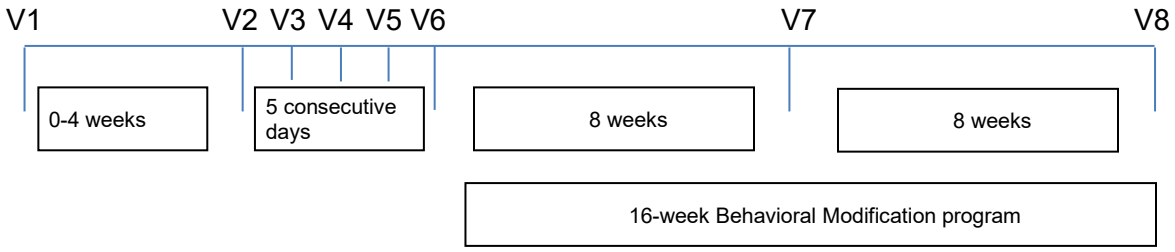
6. Study Methods, Procedures, and Statistical Plan

Study Design:

For this single-site pilot study our statistical approach will be similar to prior work done by members of our team previously, a double-blind, randomized controlled design with participants randomized to either active or sham tDCS. For this study Veterans will be referred as potential candidates because they have obesity and self-report that they tend to have at least one occasion of out-of-control eating per week on average. Participants will be trained on the Brain HQ, an interactive computer software package in which subjects work through a series of structured exercises designed to stimulate neuroplasticity. Participants will be randomly assigned to receive either active tDCS or sham stimulation with their training during one hour session each day(13 minutes of stimulation , 20 minute stimulation break, followed by 13 more minutes of stimulation) over five days. A 2 mA current will be applied with two 25 cm^2 saline soaked electrode sponges with anode at F4 (right) and cathode at F3 (left) concurrent with the Brain HQ. To evaluate generalization, an untrained NIH Examiner Battery sub-set testing 4 modalities of executive function will be performed before and after the five days of training. Subjects will then go through the Move Mass Behavior Modification after completing the five days of treatment. (This 16-week structured behavior modification program of bi-weekly sessions is usual care for these participants.) Participants will return for the trained and untrained testing at V7 (halfway through the behavior modification course) and V8 (final study visit to occur after the behavior modification course) follow-up sessions without stimulation. For the trained Brain HQ tasks, growth curve analysis (GCA) examining individual variation of the

growth rates over time will be done (across the 5 days of tDCS sessions and the subsequent follow-ups) to examine for change in individual and group trajectories over time. For the untrained NIH Examiner tasks, GCA will be used to evaluate for individual and group effects in executive function in the four domains of the NIH Examiner Battery from pre- to post-treatment and through follow-up sessions. We will also compare pre- and post- treatment results in the cravings and binging questionnaires within and between groups.

Figure 1: Study Visit Schedule



Study Subjects:
Potential subjects identified at the Minneapolis VAMC's MOVE Mass Medical Weight Management Clinic where Drs. Sibley and Billington attend will be recruited into this 18-week clinical intervention using tDCS. The MOVE Mass Clinic at Minneapolis has a long history, having been established more than 30 years ago and having served as a prototype for the MOVE National Program. Flyers and/or posters will be posted throughout the Minneapolis VA facility and study staff will also present the study to other VA staff during team meetings and via emails to clinicians regarding recruitment. Letters may also be sent out to potential research patients.
Inclusion criteria:
Obese (BMI>30)
Adults, ages 18 years or older
Able to understand English, self-consent and follow study-related procedures
Willing to use a reliable form of birth control if they are of females of child-bearing potential
Exclusion criteria:
History of any of the following: seizures, severe or moderate head injury, head surgery, significant neurological disorder(significance based on Principal Investigator's judgment), frequent severe headaches, history of scalp conditions such as eczema or seborrheic dermatitis, metal in head (other than in mouth) including shrapnel/surgical clips/welding fragments, implanted medical devices (including pumps and cardiac pacemakers), pregnancy, active substance abuse, psychological or medical disorders requiring inpatient treatment, presence of a known metabolic or hormonal disorder (such as Cushing's) which affects weight. History of hypothyroidism is acceptable if subject is on treatment with normal TSH and FT4 on most recent check within the last 3 months and has been on stable dosage of l-thyroxine for at least 3 months, taking it as prescribed.

Subjects will be allowed to participate in the study if they are on obesity medications. It is recommended that patients do not adjust obesity medications once they have enrolled in the study, but if they need to stop or adjust medications due side effects, it will be documented on a medication review form that will be collected at each visit.

Study Procedures:

Five hundred individuals will be screened with the goal of consenting 50 patients and 20 patients completing the study. The study consists of 8 study visits including 4 testing days, one before (V2) and one on the day of the fifth session of tDCS (V6) followed by the structured 16-week long behavior modification class, and test visit half way through the 16-week class (V7) (2 months into the behavior modification class), and a final test visit 2 months later (+/- 2 weeks) (V8). At consent/screening visit (V1), baseline serum biochemistries, a general physical (including weight measurement) pregnancy test, impulsivity questionnaire (Binge Eating Scale [BES], depression screening (PHQ-9 [https://patient.info/doctor/patient-health-questionnaire-phq-9]), Minnesota Blast Exposure Screening Tool (MN-BEST), and executive function-related testing (NIH Examiner and Brain HQ) will be performed; these can be completed at V2 if those were not completed after consent on V1. These tests; other than the pregnancy, biochemistries, and PHQ-9; are repeated at V6-V8. While subjects are undergoing the 5 days of tDCS treatments (V2-V6) they will undergo Brain HQ testing during the treatment sessions. PHQ-9 is repeated at the final visit.

Study Visit Details:

Screening visit (Visit 1 [V1]):

Subjects will be recruited from the clinic where Drs. Billington and Sibley attend. Interested subjects will be screened for inclusion/exclusion criteria and review study details. Medical records will be reviewed for eligibility, and interested subjects will be consented if they are eligible. They will then undergo baseline blood draw (to include a comprehensive metabolic panel if not available within last 6 months, directed history and physical (including a weight measurement). If thyroid tests, (TSH alone or a TSH with a free T4), were not done and normal in the last 3 months for individuals taking thyroid hormone replacement, these will be done at baseline assessment. Baseline testing including the NIH Examiner Battery (which measures executive function domains), MN-BEST and BES (may either be done at the end of V1 or beginning of V2).

tDCS session visits (V2-6):

Subjects will go to the Minneapolis VAMC GRECC where they will undergo the tDCS sessions. Subjects will be randomly assigned to active vs. sham treatments which will occur on 5 sequential weekdays. The tDCS session will include a pre/post symptom rating questionnaire, 13 minutes of stimulation, a 20-minute stimulation break, followed by 13 more minutes of stimulation. Subjects will complete the Brain HQ test during stimulation and the stimulation break. The final stimulation visit, V6 will include NIH Examiner and their weight will be collected. These sessions will last around 1 hour to 1.5 hours each.

Visits post tDCS intervention (V7 and V8):

These visits will be identical to V1 with the exceptions that the history and physical, MN-BEST and blood draw will not be repeated; a weight measurement will be taken along with completion of the BES questionnaire, the Brain HQ and NIH Examiner. A short blinding questionnaire will be asked at V8 to assess the adequacy of tDCS blinding.

Table 1. Table of Assessments

Visit	Assessments	Stimulation	Duration	Compensation
Visit 1	HIPAA, Consent, NIH Examiner, BES, PHQ-9, Medication Review, MN-BEST, Blood Draw, Physical (Weight Measurement), Pregnancy Test (if applicable)	None	120 minutes	$30
Visit 2-5	tDCS, Pre/Post SRQ, Brain HQ, Medication Review	tDCS	60 minutes	$15
Visit 6	tDCS, Pre/Post SRQ, Brain HQ, NIH Examiner, Medication Review, Weight Measurement	tDCS	90 minutes	$22.50
Visit 7-8 (follow-ups)	NIH Examiner, Medication Review, Brain HQ, BES, Weight Measurement, Visit 8 only: PHQ-9, Blinding Questionnaire	None	120 minutes	$30
		Total:	11.5 hours	$ 172.50

tDCS Device: We will use the Neuroelectrics Starstim system, a wireless multichannel transcranial current stimulator. Periods of tDCS stimulation of 13 minutes will be twice a day, separated by 20 minutes, for five consecutive days (5 total tDCS stimulation sessions). Active tDCS: A 2-mA current will be administered via two circular carbon rubber core electrodes in saline-soaked surface sponges (25 cm^2), placed in a neoprene headcap with marked locations based on the 10-10 EEG system. The anodal stimulating electrode will be at location F4, over right dorsolateral prefrontal cortex (DLPFC) and cathodal electrode at location F3, over left DLPFC.This tDCS configuration has been shown to be effective for stimulating DLPFC. Sham tDCS: For sham stimulation, the electrodes will be placed at the same positions as for active stimulation (F3 and F4), but current will be ramped down immediately after the initial 30 s ramp up period. Thus, participants will feel the initial itching sensation associated with tDCS but will receive no active current for the rest of the stimulation period. This method of sham stimulation has been shown to be reliable (Gandiga, Hummel, & Cohen, 2006). The Starstim software supports the measurement of electrode impedance. Before each training session, the impedance of the electrodes will be checked and verified to be ≤10 KOhm. During a training

session, the impedance is measured every second and if found to be > 20 KOhm stimulation will be terminated for safety. The current and impedance will be recorded for every session.

Computerized cognitive training during the tDCS or sham sessions: We will utilize Brain HQ Cognitive Training software (www.brainhq.com).

Untrained tests (to evaluate for generalization at the beginning and end of the study):
As done by Galioto and predictive of weight loss success in individuals with obesity (Galioto 2016), we will utilize four components of the NIH EXAMINER battery, a validated computerized battery of experimental tests to assess four domains of executive function before and after the weight loss period.

Domains:

a. Working memory

The Dot Counting Test. Subjects will count and remember the number of blue circles in a display of other shapes. There are six trials in which the number of displays presented in each trial increases from two to seven. Participants are instructed to recall, in order, the total number of blue circles on each display and the correct responses are recorded.

b. Inhibition

The Flanker test. Subjects must make rapid decisions about the direction of central stimuli when surrounding items are congruent, pointed in the same direction or incongruent, pointed in the opposite direction. Lower scores on this domain are related to poor impulse control.

c. Set shifting

The Set Shifting task. A stimulus at the time of the screen must be matched to either of two stimuli in the corner of the screen on one of two types of characteristics (color and shape). The matching characteristic alternates in a pseudorandom fashion. Cognitive flexibility is evaluated with this task. Lower scores on this domain are related to greater behavioral compulsivity.

d. Planning

The Unstructured Task. A number of simple puzzles are completed, with differing point assignments (high and low value puzzles). Subjects must plan the order in which they do the puzzles to obtain as many points as possible in 6 minutes. Puzzles with various assigned point values in order to obtain as many points as they can in 6 minutes.

Other instruments:

a. PHQ-9

Mood will also be assessed at the beginning and end of the study.
The Patient Health Questionnaire. The PHQ-9 will be used to assess nine DMS-IV-TR criteria for depression. Scores range from 0 to 27 with higher scores being consistent with more depressive symptoms.

b. Binge Eating Scale (to be done at the same timepoints as the untrained cognitive testing)-
The BES is a 16-item questionnaire assessing the presence of binge eating behaviors. The questions are presented as groups of statements about behavior, thoughts, and emotional states. Individuals indicate which statement in each group best describes how they feel. Higher scores are consistent with more binging behavior.

c.Minnesota Blast Exposure Screening Tool (MN-BEST)

The MN-BEST is a semi-structured interview to collect self-reported information. Using the instrument, the three most significant blast exposure events will be recorded in addition to the frequency and duration of post concussive symptomatology. A similar appraisal will be made of

the three most significant impact head injuries for the person in their lifetime. This information will then be used to make determinations about the presence of TBI from the events.

d. Blinding Questionnaire

The blinding questionnaire is a short, 3 question assessment administered by research staff at the end of study participation. The purpose of the questionnaire to assess the adequacy of tDCS blinding.

Statistical Plan and Power Analysis

For this pilot study our statistical approach will be similar to prior work done by members of our team, a randomized controlled design with participants randomized to either active or sham tDCS.

Power Analysis. For Aim 1, the primary comparison will be difference in change before and after training on untrained impulsivity-related tests of executive functioning between active and sham tDCS. Lim and colleagues' preliminary data found an effect size of d=.97 between active and sham tDCS groups. Based on these results, the current pilot project is powered to detect an effect size of .97 with 80% power and an alpha = .05 (N = 20). Power to detect a medium effect size will be approximately .60. Thus, this study is well-powered to detect changes on the primary cognitive outcome variables.

For the secondary aim of weight loss, an ANOVA will be used with weight as the dependent variable and the grouping variable will be active vs. sham. We will be testing for a Group x Time interaction for weight.

7. Sharing of Results with Participants

Subjects will receive a copy of the laboratory screening done at study entry and asked to follow up with their primary care providers further to discussion of those results.

8. Study Duration

Individuals will be in the study for about 3-4 months each. We anticipate screening 500 subjects to enroll 50 for this protocol over 12-14 months. The duration anticipated to complete all study procedures and data analysis is expected to be 6 months after the last subject is enrolled; the study duration for the entire study is expected to be about 2 years.

9. Vulnerable Populations

☐ Children

☐ Pregnant women/Fetuses/Neonates

☐ Prisoners

☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders

☐ Non-English speakers

☐ Those unable to read (illiterate)

☐ Employees of the researcher

☐ Students of the researcher

☒ None of the above

Adults must have the capacity to self-consent to be in this study.

10. Recruitment Methods

a. Recruitment Process: Subjects will be approached in person by Co-investigators Sibley or Billington when they present for Move Mass appointments and will be directed to call the Study Coordinator for more study details and to set up their consent visit. Subjects may also self-identify after seeing posters or flyers posted in the Minneapolis VAMC facility and contact the investigator team. Subjects may also contact the study team after hearing about the study from other providers at the Minneapolis facility. Consenting will take place in a private setting at the Minneapolis VAMC. Subjects may take as long as needed to decide whether or not to participate once they have heard about the study-related details from the investigative team and study staff will emphasize the voluntary nature of participation and that whether or not a subject participates has no bearing on clinical care provided by the VAMC.

b. Source of Participants and identification of potential participants: Subjects will be recruited from the Minneapolis VAMC and surrounding CBOC's patient population via clinical contact with the study investigators, or by self-identification after seeing flyers/posters or after hearing about the study from their other providers at this facility. Subjects who expressing interest in the study and appearing to meet the eligibility criteria and agreeing to medical record review for the purposes of this study will then have their medical records reviewed to further assess study eligibility.

c. Payment:

Due to the commitment of time, and the potential for transportation costs and lost wages due to participating, subjects will be compensated for their study participation at a rate of $15 per hour. If a subject completes only part of a visit they will be compensated at a rate of $10 per hour, prorated for the time spent in that visit.

11. Withdrawal of Participants

a. Withdrawal Circumstances: Subjects are free to withdraw from the study at any time and they may be withdrawn by the study investigators if it is deemed that it would not be safe for them to continue with the study or if subjects are not following the study-related procedures which would compromise the scientific integrity of the study.

b. Withdrawal and Termination Procedures: If a subject wishes to withdraw or is asked to withdraw from the study the participant would be asked to participate in an early end-of-study visit (procedures to be followed would be those of V8) and the subject would be asked about continued data collection of clinical data (vitals and medications) to finish out the period of time they would have participated in the study. All data collected up to the period of withdrawal or termination and as arranged with the subject through partial withdrawal would continue to be used as per study-related purposes.

12. Risks to Participants

a. Foreseeable Risks:

Physical—tDCS is considered to be a safe brain stimulation modality which is rarely associated with adverse events and there is no evidence of serious side effects. Subjects will be discontinued from the study if they develop sores at the administration site or headaches which impair global functioning. Milder side effects that subjects could experience include itching at the site, nausea, milder headaches, and fatigue. Subjects may choose to discontinue stimulation at the session at any time they experience discomfort or side effects. We will be utilizing the standards which have been utilized previously for this modality; trained study staff will administer the treatment sessions.

Psychological—Questionnaires as well as the tDCS active vs. sham treatments are utilized during the visits; subjects could experience mental fatigue related to the testing.

Social—there is no anticipated social risk to participating.

Economic—Subjects could incur financial risks related to transportation and lost wages while participating; for this reason, study compensation is provided to help minimize this risk.

Legal-- there is no anticipated legal risk to participating

13. Potential Benefits to Participants and Society

Potential Benefits: There is not potential for direct benefit other than as related to a decrease in food impulsivity but there is no guarantee of direct benefit. Societal benefits could include providing better treatment for conditions related to impulsivity.

14. Data Management

Data Analysis Plan: For this pilot study participants will be randomized to either active or sham tDCS. For the trained task, growth curve analysis (GCA) examining individual variation of the growth rates over time will be done (across all 10 tDCS sessions and the subsequent follow-ups) to examine for change in individual trajectories over time. For the untrained task (NIH Examiner), GCA to evaluate for enhancement of executive function in the four domains from pre- to post-treatment as compared with the sham group will be analyzed. As a secondary aim we will evaluate weight loss response during and after the behavior modification program

and evaluate the effect of active vs. sham treatment on weight loss. Results from this study will inform larger follow up studies supported by external applications.

15. Data security

All PHI will be kept in a secure database behind the VA firewall. Any paper records will be stored in a locked file cabinet accessible to study staff only. Data from each subject will be assigned a unique study identifier with the key available only to study staff, stored in secure database behind the VA firewall. Patient identifiers may only be disclosed to the study's finding entities for reporting and record keeping purposes as required by law. Any data that may leave the Minneapolis VAMC will be de-identified.

16. Provisions to Monitor the Data to Ensure the Safety, privacy, and confidentiality of Participants

Data privacy and confidentiality protection are described above. The study will also have an external study monitor, Catherine Niewoehner, MD, whose roles may include reviewing the study protocol and recruitment procedures with study staff, monitoring tDCS device utilization, and following up with any subjects and the IRB regarding any adverse events which occur.

17. Discontinuation criteria

- Sores at the tDCS site
- Headaches that impair global functioning

18. References

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