THE ROLE OF TRANSCRANIAL DIRECT CURRENT STIMULATION AND COGNITIVE TRAINING TO DECREASE FOOD-RELATED IMPULSIVITY BEHAVIOR IN INDIVIDUALS WITH OBESITY: A REVIEW AND PILOT STUDY

A THESIS

SUBMITTED TO THE FACULTY OF THE UNIVERSITY OF MINNESOTA

BY

MADELEINE RENE SALISBURY

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

SHALAMAR SIBLEY MD, MPH

MAY 2021

ACKNOWLEDGEMENTS

There are many people who have contributed to the development and completion of this project.

First, I would like to express my deepest gratitude to my advisor Shalamar Sibley MD, MPH. Her constant support and guidance through not only this study but my master's program. I cannot imagine a better advisor or mentor.

I would like to thank. Kelvin Lim MD, Charles Billington MD, and the staff at the Geriatric Research Education and Clinic Center for Behavioral Research at the Minneapolis Veteran's Association in their tireless effort for bringing this study to fruition.

I would like to give a special thanks to my committee members Thomas Murray PhD at the University of Minnesota and Carrie Earthman PhD, RD at the University of Delaware, for their willingness to serve on my committee and for their prompt responses in answering all of my questions.

I would like to thank the faculty at the Department of Food Science and Nutrition at the University of Minnesota for their teaching and support throughout my master's program.

Finally, I would like to thank my mom, Jessie, and my sister, Hannah, for their constant support. I could not be here today without them.

This thesis is dedicated to my dad who showed me what advocacy for others looks like and for encouraging me to pursue my dreams.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BES: Binge eating scale

BIS: Barratt impulsiveness scale

BMI: Body mass index

BMOD: Behavioral modification classes at the Minneapolis Veteran's Association

CESD-R: Center for Epidemiological Studies depression scale – revised

CPT: Conners' continuous performance task

CT: Cognitive training

DBS: Deep brain stimulation

DEBQ-R: Dutch eating behavior questionnaire restraint

DLPFC: Dorsolateral prefrontal cortex

DMS-IC-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision

ECT: Electroconvulsive therapy

EPM: Elevated plus maze test

FCI: Food craving inventory

FCT: Food challenge task

FCQ-State and FCQ-Trait: Food craving questionnaires state and trait

FES: Functional electrical stimulation

F3: Over the left DLPFC

F4: Over the right DLPFC

F7: Over the left temporal lobe

F8: Over the right temporal lobe

HDS: Hypercaloric diet plus sham

HDT: Hypercaloric diet plus tDCS

MD: Medical Doctor

MN-BEST: The Minnesota blast exposure screening tool

MST: Magnetic seizure therapy

NAc: Nucleus accumbens

NIH: National Institute of Health

OF: Open field test

PHQ-9: The patient health questionnaire

PFC: Prefrontal cortex

PSS: Physical sensation scale

RCI: Reals control interview

SCWT: Stroop colors and words test

SDS: Standard diet plus sham

SDT: Standard diet plus tDCS

SMT- Sensory motor cortex

SOC: Stockings of Cambridge

SRT: Simple reaction time

TD: Temporal discounting

tDCS: Transcranial direct current stimulation

TFEQ-R21: Three-factor eating questionnaire-R21

TMS: Transcranial magnetic stimulation

VAS: Visual analog scale

VNS: Vagus nerve stimulation

CHAPTER 1: A REVIEW OF PREFRONTAL CORTEX-DIRECTED TDCS AND COGNITIVE TRAINING FOR IMPULSIVITY IN OBESITY

Obesity is a multi-faceted disease, which includes physiological, behavioral, psychological, genetic, and environmental factors [1,2,6]. As of 2014, the Center for Disease Control had estimated that nearly 37.7% of American adults had obesity[2]. Obesity, defined as a body mass index (BMI) of 30 or greater, increases the risk of many other health conditions including sleep apnea, osteoarthritis, hypertension, hyperlipidemia, type II diabetes mellitus, heart diseases, and even mortality[2,3,4,5,6]. The brain plays an integral role in eating behaviors and weight management. As such, recent research has delved into further understanding the underlying neurobiology of obesity and the development of new treatments to address neurobiological barriers to successful weight loss.

In this review, we will briefly discuss how the brain's homeostatic and hedonic pathways interact and regulate food consumption. We will examine impulsivity and compulsivity traits and their relationship to hedonic reward pathway signaling and difficulties with behavior change, respectively, as potential contributing factors to overweight/obesity. We will then evaluate the role of the prefrontal cortex in the regulation of food consumption as a potential mitigator of food-related impulsivity characterized by the inability to regulate response to excess input from reward signaling pathways in susceptible individuals who have heightened food cue sensitivity. To a lesser degree, we will examine the potential role of compulsivity, related to an inability to break old habits, as a potential barrier to successful weight loss and the potential role of effecting change in the prefrontal cortex as a potential treatment for this issue. Building on this background of the prefrontal cortex as a potential regulator of impulsivity and mitigator of excess food intake, we will consider the potential therapeutic role of

electrical stimulation as an additional weight loss treatment modality. In particular, we will focus on transcranial direct current stimulation (tDCS), a non-invasive form of electrical neuromodulation, as a possible treatment to strengthen prefrontal cortex function because of the relative safety of tDCS compared to other forms of electrical neuromodulation. We will consider and discuss inconsistent literature findings with regards to the effectiveness of tDCS for affecting food behavior change and weight loss. Lastly, we will highlight tDCS coupled with other modalities as a potential way to enhance the effectiveness of this device-related obesity treatment approach. By exploring the role of tDCS when coupled with other targeted modalities to harness neuroplasticity we have the potential to develop a new treatment approach for obesity.

Food Intake: Roles of Homeostatic and Hedonic Pathways

Food intake is complex, regulated in part by the homeostatic and hedonic pathways within the brain[7]. Within the homeostatic pathway, the hypothalamus regulates energy balance by integrating fuel-related signals received from the periphery[8,9,14]. Peripheral fuel-regulated signals received and integrated by the hypothalamus include those from the gut, adipose tissue, liver, and pancreas[8]. In contrast, the hedonic pathways comprise a reward related-system which can be impacted by cognitive and emotional factors[2,11,12,13]. Key components of the hedonic system are limbic system structures including the nucleus accumbens (NAc), amygdala, and hippocampus which are important for emotional and behavioral functions[2,12,13]. Adjacent to and connected with the limbic regions are the paralimbic cortical areas of the brain which include regions

such as, the cingulate gyrus, orbitofrontal cortex, and temporal pole insula. These regions are responsive to environmental cues that offer rewards[20,73].

Impulsivity, Compulsivity and their Relation to Eating Behavior and Refractory Obesity:

Obesity is a disease manifested through a compilation of a variety of contributing factors. More specific obesity phenotypes are being defined. While obesity does not necessarily require impulsivity, impulsivity could be a contributing factor to the development and maintenance of obesity. Impulsivity is a psychological construct that has been linked with loss of control eating, and in some studies, with obesity. Impulsivity has been defined as a multi-dimensional tendency to act without thinking or planning sufficiently[2020]. Impulsivity may involve a rash and spontaneous reaction in response to stimuli without consideration of possible consequences, as well as a purposeful drive towards obtaining rewarding stimuli. Individuals with impulsive behaviors often choose immediate small rewards over delayed larger rewards[60]. Impulsive behaviors may occur as a result of a lack of self-control and an over-active hedonic pathway[20].

Though findings have been inconsistent with regards to defining the link between impulsivity and obesity, some investigators have found that individuals with obesity are more likely to experience impulsive behavior on validated psychological testing, such as higher impulsivity ranked on the BIS-11 for impulsivity and obesity on the Odds ratio and are thus more likely to have a higher caloric intake[79,101]. Individuals with obesity may have a heightened sensitivity to environmental food cues, and this coupled with

impulsivity could predispose them to obesity. Studies have found that obese individuals are more likely to pay attention to food-related images compared to lean individuals, as well as show attentional bias to pictures of high caloric foods[82].

Inhibitory control is important for overcoming impulsive behaviors[23]. Inadequate inhibitory control with regards to response to food cues in the environment may influence the development and maintenance of overweight and obesity[25]. Studies utilizing neuropsychological testing, with regards to inhibitory control for eating behaviors and weight control, have linked lack of impulse control with obesity[25]. Cognitive inhibition, the ability to overcome distracting stimuli, arises when individuals filter out distractions; some investigators have found that individuals with obesity are less efficient in completing cognitive tasks in the presence of food-related stimuli and can have difficulty with impulse control[25]. Evidence for greater cognitive interference, as measured by studies utilizing a food-related stop-signal task, has been found in studies of individuals with obesity compared to lean controls[26,27,101,102].

Similarly, delay discounting, the decline in the value assigned to a reward that occurs when receipt of that reward is delayed, has been examined in individuals with and without obesity who have highly impulsive behaviors, such as gambeling[103,104]. Although an individual's delayed gratification rate is typically stable over time and possibly a heritable trait, its expression has been shown to be influenced by higher cortical, cognitive processes, executive function processes[61]. In addition to the mitigation of impulsivity, executive function processes can play a role in mitigating compulsivity, as will be discussed below.

Compulsivity is another psychological trait that has been linked in some studies with obesity, though the link between compulsivity and obesity has been explored less than the link between impulsivity and obesity. Compulsive behaviors are those that are persistent, repetitive, often habitual, difficult to control and interfere with activities or decision-making[29]. Compulsivity may affect the ability to make and sustain healthy behavior changes effectively. Compulsive behaviors are difficult to change and interfere with an individual's ability to redirect. Intrusions, which are spontaneous and discrete impulses that are difficult to control and interfere with actions and behaviors, can contribute to greater compulsivity[29,46]. Cognitive, emotional, contextual, and physiological components can trigger spontaneous emotional thoughts[29]. These intrusive thoughts, although they can be initially rewarding, can interfere with an individual's ability to make appropriate decisions. The result is a behavior that may become entrenched. Food-related compulsivity may involve habitual overeating, perhaps situational overeating to relieve negative emotional state or overeating despite aversive consequences[30]. Individuals who have obesity with a compulsivity component may have more difficulty disengaging from food cues compared to others[112]. Castellanos, Charboneau, Dietrich, Park, Bradley, Mogg, and Cowan (2009) found that both individuals with obesity and lean individuals had elevated food attentiveness in the fasted state[82]. However, individuals with obesity had higher self-reported scores in regard to responsiveness to external food cues and disruption to control of eating behavior as compared with individuals who were lean in the fed state[82]. In the fasted state, both groups had an increased gaze duration at food images (as compared with non-food images), which the individuals with obesity maintained into the fed state[78]. In brief,

successful mitigation of excess limbic input may be an important obesity treatment target. In this next section, we will explore the prefrontal cortex an area of the brain which is integral to limbic gatekeeping [15,16,17,18]. We will more specifically focus on its role in relation to mitigating impulsivity as the link between food-related impulsivity and prefrontal cortex function has been explored more to date than its link with compulsivity. In particular, we will next focus on the activation of the dorsolateral prefrontal cortex (DLPFC) in behavioral regulation of impulsivity in individuals with obesity.

The Dorsolateral Prefrontal Cortex's Role in Mitigation of Impulsivity:

The DLPFC is integral in the mitigation of impulsive behaviors. The prefrontal cortex (PFC) is located within the frontal lobe of the brain. The DLPFC may take part in controlling eating behaviors although the exact mechanisms by which the DLPFC influences eating behaviors is still unclear[42]. Interestingly, individuals who have obesity have been found to have lower left DLPFC postprandial activation than lean individuals, and disrupting activity in the right DLPFC was found to result in a worsened delay discounting[42]. Research suggests that the DLPFC's role in eating regulation is important locally and through connectivity with other brain regions involved in reward and homeostasis[75]. The DLPFC is highly activated, as shown through functional magnetic resonance imaging (fMRI) postprandially when regulating food desire[54]. Hollman et. al (2012) found that the DLPFC is considered to be involved with self-control and cognitive reappraisal, which can reduce the desirability of food intake[73,74]. Studies in animals have

linked food expectancy and food reward to neurons within the DLPFC[52,53]. One study found that the DLPFC can be activated by taste[5050].

Stice et. al (2010) used fMRI in adolescent female high school students who ranged from lean to obese to determine the blood oxygenation dependent (BOLD) imaging level response to highly palatable foods and to determine if the response of the limbic system to perceived food was related to BMI[97]. Additionally, they researched to see if the Dopamine Receptor D_2 (DRD2) and D_4 (DRD4) polymorphisms could impact future weight gain. They concluded that the lacking the dopamine receptor polymorphisms DRD2 TaqIA A1 allele of the DRD4-7R allele was correlated with a higher BMI. Bruce et. al (2010) used fMRI in both healthy weight and obese children to determine both limbic system and PFC activation in response to food both pre- and post-meal[98]. They found that although both groups of children had limbic activation in response to food pre-meal, the children with obesity were hyper-responsive to the food stimuli and were unable to diminish the limbic system activation post-meal, as compared to their healthy weight counterparts[102]. These studies suggest there is greater cognitive control in the PFC and less modulation within the limbic system in relation to food consumption in individuals who are lean. However, in individuals with obesity, there is greater cognitive-behavioral control of the limbic system while the prefrontal cortex is less modulated[76]. Individuals who have obesity have been found to have down-regulated DLPFC neuronal activity post-prandially[41,42]. Research suggests that individuals with obesity have a weaker activation in the PFC when exposed to food cues, regardless of whether that is before or after consumption, and that the weaker activation is a predictor

of BMI[97,98]. Upon weight loss, heightened regulation of the DLPFC was observed in this study. Accumulating information regarding the connectivity between functions of the DLPFC and limbic regions and accumulating suggests a potential field of treatment for obesity through enhancing DLPFC function. Some studies have concluded that the strengthening of the prefrontal cortex can help reduce food consumption[23,24].

Neuromodulation: An Expanding Therapeutic Role to Include Obesity Management?

Traditionally individuals with obesity have been treated with lifestyle, pharmacological and surgical management, in a tiered fashion, based on obesity stage and presence of comorbidities[94]. Despite the addition of new pharmacological options over the last decade, there remains a significant gap in effective obesity management. Contraindications and potential medication interactions may limit pharmacotherapeutic options for many patients; over time medications may become less effective and weight regain is common once medications are stopped[95]. Over the last decade as our understanding of the underlying neurobiology of obesity has grown, new treatment targets and therapies have been under development. Among these is the potential for use of electrical neuromodulation for the treatment of obesity.

Neuromodulation, as defined by the International Neuromodulation Society, is any application acting directly upon nerves to cause alternation – or modulation – of nerve activity by delivering electrical or pharmaceutical agents directly to the target area[36]. Neurophysiological signals are initiated or influenced with the intention of

therapeutic effects that thereby altering the performance of the nervous system through neuromodulation[22]. Within the range of types of neuromodulatory approaches, pharmacotherapeutic weight loss agents could be included, however, they can have possible side effects including addiction and organ damage[96]. Weight reduction medications work in conjunction with a caloric reduction, requiring individuals who consume these medications to be able to maintain a caloric reduction. Additionally, a common issue with pharmacological weight loss agents is that there is some weight re-gain after a year on the medication and once the medication is stopped[95]. Common contraindications for weight reduction pharmacological agents include blood thinners, pregnancy, and allergies to the medication. Such neuromodulation is often not optimally effective. In contrast, there are several potential benefits to effective neuromodulation, especially electrical neuromodulation, which include its potential for targeted specificity, revisability, and programmability[45]. Electrical neuromodulation includes invasive stimulation and non-invasive stimulation. Invasive devices require implanting electrodes that can provide stimulation to the specific brain or other neutral regions, while non-invasive stimulation involves external electrodes without incisions[37]. Examples of electrical neuromodulation include deep brain stimulation (DBS), vagus nerve stimulation (VNS), functional electrical stimulation (FES), electroconvulsive therapy (ECT), magnetic seizure therapy (MST), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS)[22].

TMS and tDCS are both noninvasive. While TMS induces action potentials in the cortical tissues beneath the scalp through discrete magnetic pulses, tDCS applies a low-

intensity electrical current directly to the scalp[30,32,33,34]. While it does not generate action potentials in quiet neurons, tDCS causes polarity-dependent modulation within the brain, utilizing anodal and cathodal directed stimulation[33]. This modulation can aid in generating a suprathreshold action potential production within neurons already attempting to fire enhancing synaptic efficacy. By enhancing suprathreshold action potentials, tDCS can amplify neural firing performance. In quiet neurons, anodal tDCS has been shown to minimally enhance activity by creating a subthreshold membrane fluctuation, however, this weak effect by itself is not enough to create an action potential[34]. In contrast, if active neurons are beneath the anode region, tDCS can aid subthreshold action potential to generate a suprathreshold action potential leading to enhancing firing[34].

tDCS is delivered through a battery-operated stimulation device between two electrodes (anode and cathode). The application of tDCS – the direction of the current, amplitude, and time- impact the benefits received. For anode right/cathode left tDCS, the electricity flows from the anode on the right of the prefrontal cortex to the cathode on the left of the prefrontal cortex[32]. The placement of the electrodes and direction of the current (traveling in one direction) is important to the mechanism of tDCS, as it will allow it to depolarize the neuronal membrane of neurons attempting to fire and thus enhance the chance of a suprathreshold action potential leading to enhanced firing[34]. In general, areas beneath the anodal stimulation will have increased cortical excitation, while cathodal stimulation will decrease the excitability[33,38]. Therefore, tDCS can increase neuronal stimulation through depolarization of the membrane potential and modify neuronal

synaptic efficacy and amplify behavioral performances[32,33,38]. However, as noted above, tDCS cannot produce an action potential in quiet neurons. In contrast, TMS uses excitatory stimulation to induce action potentials in quiet neurons that would not have fired otherwise[81].

tDCS, compared to TMS, is easily portable, applicable, inexpensive, and safe with minimal to no risk[33,38]. tDCS is a more attractive therapeutic option than many other forms of electrical neuromodulation because of scalability and portability of the device. Studies are underway to evaluate it for home use in several therapeutic settings[106].

Because TMS is excitatory and tDCS is modulatory, TMS has a higher risk rate as compared with tDCS. The most serious adverse effect of TMS, although rare, is the risk of seizures[40]. Additionally, single pulses of TMS can create heat within the brain tissues which can create skin burns or irreparable damage to the brain tissues from the heat of the electrodes when the temperature gets out of control[40]. The coil used in TMS produces a strong magnetic field, and with large voltages can induce voltages in nearby wires and electronic devices, causing damage to the internal circuitry of electronic implants near the coil, leading to device malfunction[40]. Therefore, it is important to use safe procedures and monitor electrode conductivity when TMS is being administered. tDCS, although a more attractive form of neuromodulation for the reasons listed above, could be less effective than TMS.

Additionally, of importance in the research setting, because tDCS scalp sensation only lasts a few seconds, subjects can be blinded to whether they are receiving the stimulation or a sham treatment[44]. However, as tDCS produces a small amplitude of

current, one potential concern is that it is not effective enough. In the next section, we will examine the potential application of tDCS for effecting obesity-related behavior change in the sections that follow.

tDCS: Effect on Eating Behavior and Obesity:

While our literature review is specifically focused on human clinical research studies, we will first briefly discuss a couple of relevant animal studies for background leading to the human work. Each study discussed found no weight loss in between active and sham stimulation groups, however, they found a change in eating-related behaviors between groups. Ziomber et. al (2018) conducted a thirty-seven-day study with Wistar rats at twelve to thirteen weeks old[59]. The purpose of the study was to understand the impact that tDCS had on feeding behaviors, metabolites, and neurotransmitters in obese rats. Fifty-seven male Wistar rats were split into five groups; obese animals, non-exposed to tDCS (n=10), obese animals, subjected to sham tDCS (n=11), obese animals subjected to anodal tDCS on the right PFC (n=14), obese animals subjected to cathodal tDCS on the left PFC (n=11) and lean animals, non-exposed to tDCS (n=11). Electrodes were placed 3 mm right and 3 mm left of the sagittal fissure on the 30th day, the rats began stimulation twice daily for eight consecutive days for ten minutes each at 200 μA. Bodyweight, food intake, blood total cholesterol, triglycerides, serum leptin, serum ghrelin, and Dopamine D_1 and D_2 receptor levels were measured. This active stimulation treatment decreased weight gain, food intake, blood levels of leptin, increased serotonin levels, as well as increased D_2 dopamine receptors density in the PFC and decreased

density in the dorsal striatum, five hours following the stimulation session[62]. Ziomber et. al (2018) concluded that the change in the dopamine receptor density in the brain could imply the role of dopamine in the development and maintenance of obesity[59]. However, there was no weight loss observed within the active stimulation groups. This could be in part due to the lack of follow-up observations as the study concluded on the last day of stimulation. Secondly, Macedo et. al (2016) conducted a study with the aim of understanding food consumption in rats receiving anode right/cathode left tDCS[86]. Eighteen rats at sixty-days old were randomized into three groups: control, no stimulation (n=6), sham, receiving thirty seconds tDCS at 500 µA (n=6), and tDCS, receiving twenty minutes at 500 µA. Stimulation sessions occurred over eight consecutive days. Food intake, weight, naso-anal length (cm), Open field (OF) test, elevated plus maze (EPM) test, palatable food consumption test, collection of hypothalamus tissue for BDNF were collected and measured. The active stimulation group had both a decrease in food consumption post-fasting and an increase in time between meals[86]. Again, there was no weight loss noted in between the groups, which could be due to the lack of follow-up. de Oliveria et. al (2019) conducted an eight weeklong study on Wistar rats to better understand the effects of tDCS on anxiety-like and feeding behaviors in obese rats[87]. Forty male Wistar rats were split into four groups, with 10 rats per group. The groups were: standard diet plus sham treatment (SDS), standard diet plus tDCS treatment (SDT), Hypercaloric diet plus sham treatment (HDS), and Hypercaloric diet plus tDCS treatment (HDT). After 40- days on their allotted diet, the rats completed baseline testing followed by eight consecutive days of stimulation for twenty minutes at 0.5 mA daily and monitored for the remainder of the eight weeks. Most notably, none of the groups lost

weight over the 8 weeks period, although the groups on the hypercaloric diet did gain weight compared to their standard diet counterparts. The lack of weight loss in the first two studies could be due in part to the lack of follow-up post tDCS stimulation after twenty-four hours[5,86]. De Oliveria et. al (2019) noted that the lack of weight loss could be correlated with levels of stress in the rats from the stimulation and their altered consumption of palatable foods to compensate, which was not allotted for in the study[84]. Although animal studies are foundational in understanding the neurophysiology of tDCS, research must be done in the human population to understand the behavioral adaptations.

We conducted a literature review through the OVID MEDLINE database using a modified systematic approach with MeSH subject headings, including the presence of search terms in the title, abstract, and author information based on the following terms/concepts listed in table 1:

Table 1: MeSH terms in literature search in author keywords, title, and abstract

Obesity terms	tDCS terms	Behavioral Terms
1. Obesity	1. Transcranial Direct Current Stimulation 2. Cathodal Stimulation Transcranial Direct Current Stimulation 3. Cathodal Stimulation tDCS 4. Repetitive Transcranial Electrical Stimulation	1. Impulsive Behavior 2. Behavior, Impulsive 3. Impulsivity 4. Psychological Inhibition 5. Inhibition 6. Health Behavior 7. Attitude to Health 8. Health Risk 9. Behavioral Research

	5. Transcranial Alternating Current Stimulation 6. Transcranial Direct Current Stimulation 7. Transcranial Electrical Stimulation 8. tDCS 9. Anodal Stimulation tDCS 10. Electric Stimulation Therapy 11. Transcutaneous Electric Nerve Stimulation	10. Behavioral Sciences 11. Compulsive Eating 12. Compulsive Behavior 13. Addictive Behaviors 14. Food Addiction 15. Cravings 16. Food Cravings 17. Eating 18. Calorie Consumption

From the literature that we pulled in the search, inclusion criteria were that the study was a randomized control trial of tDCS with an aim to improve impulsivity (cognitive and/or motor) and/or loss of control eating behaviors with or without a component of craving. Literature was excluded if the participants had endocrine disorders, overt eating disorders, and any disease or injury to the brain and if the literature was not available in the English language or did not have the full text available.

Figure 1: Flow chart for literature search

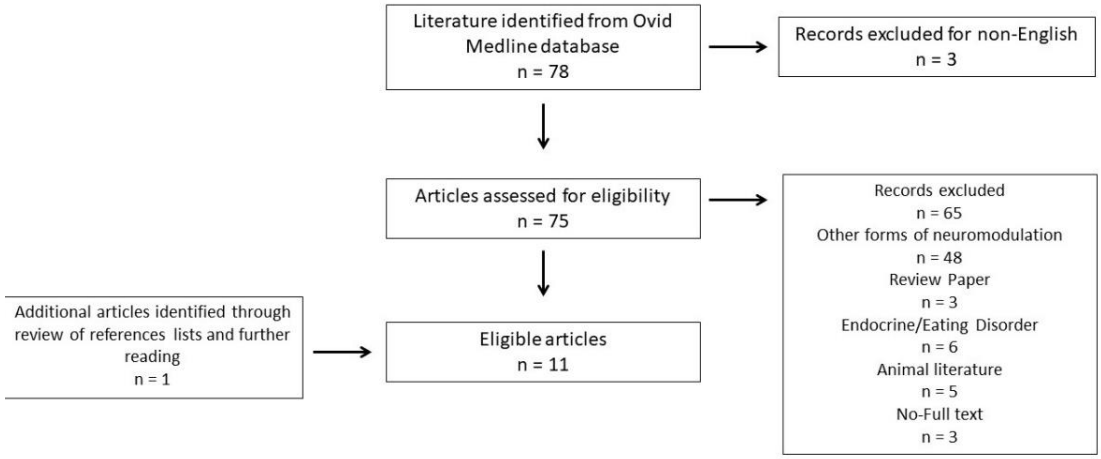


Table 2: Summary table of literature for tDCS, obesity and impulsivity.

Study	Participants / Number of Stimulation Sessions	tDCS Parameters	Paired	Duration of stimulation period in days (additional follow-up post-stimulation)	Outcome Measurements	Findings
Grundeis et. al (2017)	25 obese females, (age 14-43 years) (mean	Active anodal stimulation for 20 min at 2 mA with	none	3 weeks (0 days)	Primary: VAS, Food consumption	No difference in calorie consumption

	BMI 36.5 ± 4.1. 3 sessions	anode/cathode at AF7/F8. Cathodal stimulation for 20 min at 2 mA with cathode/anode at AF7/F8.				between groups.
Ray et. al (2017)	18 participants (mean age 22.7 ± 7.9) 10 female, (mean BMI 31.4 ± 9.1). Single Session.	Bilateral active tDCS for 20 min at 2mA anode/cathode at F4/F3. Sham stimulation for 1 min at 2 mA for first and last minute	none	2 days (0 days)	Primary: BIS-11, BMI, DEBQ-R, Food cravings test, in lab eating test	Active had reduced food cravings in females and preferred food calorie consumption in males compared to sham
Ray et. al (2020)	74 college students (age 18-41 years) 44 female, (mean	Bilateral active tDCS for 20 min at 2mA anode/cathode at F4/F3.	none	1 day (0 days)	Primary: Food Craving task, in lab eating test Secondary: Hunger Assessment, weight, BIS-11,	When told they received active, participants ate less than their counterpa

	BMI 31.8 ± 5.5). Single Session.	Sham Stimulation for 2 min			BMI, DEBQ-R, FCT	rts. No difference in calorie consumption intake between active and sham.
Stevens et. al (2020)	28 healthy participants (age 18-60 years), 19 females (mean BMI 34.0 ± 7.05). Single Session	Bilateral active tDCS for 20 min at 2mA anode/cathode at F4/F3. Control stimulation for 20 min at 2mA with anode/cathode at C3/C4.	none	2 day (0 days)	Primary: BMI, BIS-11, Palatable Eating movies scale, BES, short suggestibility scale, DEBQ-R, FCT, eating task Secondary: RCI, PSS	There was no difference in perceived food cravings or food consumption.
Ljubisavljevic et. al (2016)	27 college-age participants, (age 18 years or older), 8 females, (mean	Unilateral active tDCS for 20 min at 2 mA with anode at F4 and reference electrode at F3. Sham had 1 active	none	5 days (30 days)	Primary: FCQ-T, FCQ-S, FCI, CESD-R	Active decreased in self-reported cravings compared to sham

	BMI 25.6 ± 4.4). 5 sessions	followed 4 sham.				
Heinitz et. al (2017)	23 obese participants, 11 females (BMI 39.3 ± 8.42). 15 sessions.	Unilateral active tDCS for 40 min at 2 mA with anode at F3 and reference electrode at F4. Sham stimulation for 20 sec of stimulation at 2 mA	none	11 days inpatient, 4 weeks outpatient (0 days)	Primary: Vending machine paradigm for ad libitum food intake, Secondary: Bodyweight, Snack food taste tests (SFTTs), VAS, BES, TFEQ	No difference in weight change between groups. Active had decreased VAS hunger ratings compared to sham
Usanos et. al (2020)	38 females, (age 45-65 years) mean BMI 25-35. 8 sessions	Bilateral active stimulation for 20 min at 2 mA with anode/cathode at F3/F4.	Hypocaloric diet	2 weeks (2 weeks)	Primary: Weight, FCQ-T, FCQ-S, VAS Secondary: Go/no-go task, Food memory task	Active lost greater percent bodyweight compared to sham.
Gluck et. al (2015)	9 obese individuals (age 18-60	Study 1: Active cathodal stimulation at	Maintenance diet	Study 1: 8 days (0 days)	Primary: Weight log and recorded food log	Anodal stimulation resulted in lower

	years) (mean BMI 38 ± 7). 8 sessions	2 mA for 40 min with the cathode at F3 with the reference electrode on the left forearm Study 2: Active anodal stimulation for 40 min at 2 mA with anode at F3 and the reference electrode above the right eye.		Study 2: 8 days days (0 days)		calorie consumption compared to cathodal and sham.
Georgii et. al (2017)	42 healthy female participants (age 17-40 years) (mean BMI 22.6 ± 3.2). Single session.	Bilateral active stimulation for 20 min at 1 mA with anode/cathode at F3/F4. Followed by 1 week of sham stimulation for 15 sec at 1 mA.	Food Choice Task	14 days (7 days)	Primary: BIS-15, Hunger scale, computerized food-choice task, food cravings questionnaire-state, food intake test	Higher baseline non-planning impulsivity on the BIS-15 scale had a higher correlated calorie intake.

Kekic et. al (2014)	17 female participants (age 19-55 years) (mean BMI 23.8 ± 2.6). Single session.	Bilateral active tDCS for 20 min at 2mA anode/cathode at F4/F3.	Temporal discounting task	3 days (0 days).	Primary: FCT, FCQ-S, Free-eating task Secondary: TD task	No difference in perceived food cravings or food consumption.
Forcano et. al (2020)	18 participants (age 18-60 years) 12 females, (mean BMI 42.6 ± 4.9. 4 sessions	Bilateral stimulation for 20 min at 2 mA with anode/cathode at F3/F4/F7/FC5/FC6. Sham stimulation at for 3 sec	Cognitive tasks	11 days days (7 days)	Primary: Self-reported food intake log: SOC, Intra-Extra Dimensional Set shift, Spatial Span, SRT, Iowa gambling task, Stroop colors and words test, Symbol digits modality test, Conners' continuous performance test Secondary: eCB anandamide (AEA), 2-	Active had reduced calorie consumption compared to sham.

					arachindonoylglycerol (2-AG)	

We evaluated the literature based on parameters used such as the location of the electrodes, number of stimulation sessions, the direction of the current, and the addition of other modalities with potential for augmenting the treatment response. The location, duration, number of sessions, the intensity, and coupling with other modalities with a goal of enhancing targeted effectiveness are all important parameters in the application of effective tDCS[86,87]. Below, we will discuss the above studies within the context of these types of parameters.

Food Impulsivity - Brain Regions, Locations, and Number of Sessions for tDCS Application:

In a single session study, Stevens et. al (2020) conducted a randomized control trial that aimed to test the efficacy of tDCS to reduce food cravings and eating where the control and sham condition would be hard to distinguish, thereby preventing participants from guessing their treatment and a possible placebo effect[106]. Stevens et. al (2020) recruited 28 participants with a mean age of 21 years and a mean BMI of 34.0. Participants in the active stimulation received single session tDCS, anode-right/cathode-left (F3/F4) for 20 minutes at 2 mA, while the control group received stimulation over the sensorimotor cortex (SMC), anode-right/cathode-left (C3/C4) for 20 minutes at 2 mA. Participants' BMIs were obtained, and they were asked to complete psychological

questionnaires to assess eating behaviors, along with computerized food craving task and free eating task. Before leaving, participants completed a real vs. control interview where they were asked to guess whether they had been given 'real' or 'fake' stimulation. Investigators found no difference between the groups of food consumption and self-reported food cravings. Additionally, 71% of the participants were unable to guess real stimulation from control stimulation, thereby minimizing the placebo effect[110]. Though the researchers' study failed to find a significant effect of tDCS, there are several reasons why this might have occurred. Stevens et. al (2020) utilized a single session montage that was not paired with a trained executive function task to elicit food-related behaviors and as tDCS does not generate action potentials, rather enhances existing sub-threshold action potentials, this treatment may not have targeted food-related behaviors. Additionally, there was no follow-up time post-stimulation to determine if there were delayed effects from the stimulation.

Grundeis et. al (2017) conducted a multiple session study with three stimulation sessions utilizing a double-blind randomized control crossover trial in which the active treatment group received twenty minutes of anode/cathode stimulation at AF7/F8 at 2 mA and the cathodal group received twenty minutes of stimulation with the cathode/anode at AF7/F8 at 2 mA. The investigators aimed to determine if anode-right/cathode-left tDCS over the DLPFC would decrease food cravings and consumption as compared to anode-left/cathode-right tDCS and sham stimulation. A total of 25 females with obesity, mean BMI 36.5 and mean age 28.8 years, enrolled in the study. Electrodes were placed at AF7 and F8 and stimulation for both the anode-left/cathode-

right and cathode-left/anode-right lasted for 20 minutes at 2 mA, while sham stimulation only lasted for 30 seconds. They found no significant difference in food cravings or consumption between groups[91]. Ray et. al (2017) also conducted a double-blind randomized control study in relation to food cravings and consumption. They aimed to test the efficacy of right-anode/left-cathode tDCS to reduce food cravings and consumption in participants with obesity and to determine the degree to which the suppression of cravings and consumption was influenced by baseline differences. Eighteen participants were enrolled with a mean age of 22.7 years old and a mean BMI of 31.4. During the single active stimulation session, participants received tDCS anode-left/cathode-right (F4/F3) for 20 minutes at 2 mA, while during the single sham stimulation, participants only received stimulation for the first and last minute. Investigators found that when baseline BIS attentional scores were included as a covariate, perceived food cravings were significantly reduced in the active group compared to the sham ($p<0.05$) in females, with no difference in males. However, total food consumption decreased in males when BIS no-planning scores were included as a covariate ($p=0.0014$). Ray et. al (2017) concluded that a single session of tDCS over the DLPFC did appear to reduce appetite and food cravings for individuals with obesity[60]. However, in a study employing deception though otherwise similar study to the Ray et. al (2017) study because of the identical tDCS parameters, Ray et. al (2020) found that with the single session tDCS over the DLPFC, participants had a significant decrease in food consumption when they were told they were receiving active tDCS stimulation ($p=0.006$), whether or not they received sham stimulation or active stimulation and had no significant change in cravings when participants were informed that they received

sham stimulation, regardless of whether or not they received active or sham stimulation[90]. Therefore, the difference in findings comparing the three studies suggest single session tDCS may not elicit behavioral change and that careful study blinding is essential. Additionally, baseline traits such as impulsivity, need to be taken into account in single session tDCS studies. However, these studies were short proof-of-concept studies; none of them involved multiple sessions or had a longitudinal follow-up component, nor did they measure other outcomes of biological relevance. Single session studies have shown inconsistent results and on whole did not show a consistent effect of DLPFC-directed tDCS on appetite or food behavior control; multiple session studies would be needed to further evaluate the potential of this modality.

In a multi-session tDCS study directed over the left DLPFC (F3), Ljubisavljevic et. al (2016) aimed to determine if longer-term reductions in food cravings in healthy adults could be achieved and if results would differ between normal and overweight participants. A total of 27 participants with a mean age of 21.3 and mean BMI of 25.6 completed the study. The active stimulation participants (n = 13) received 5 sessions in consecutive days of stimulation for 20 minutes at 2 MA with the anode at F4 and the cathode over the left forehead. Sham stimulation participants received one day of active stimulation, followed by 4 sessions of sham stimulation, which was identical but only lasted for 30 seconds. Participants completed craving questionnaires, along with the Center for Epidemiological Studies depression scale – revised (CESD-R) at each visit and 30 days post-stimulation. Participants in the active stimulation group reported decreased self-perceived craving ($p<0.05$) immediately post-stimulation when compared to the

sham but this effect did not persist[92]. Over the 30-day follow-up period there was no significant treatment-related effect on food cravings between the groups, nor did baseline characteristics of BMI or gender predict the follow-up BMI. While suggestive that that multi-session tDCS may have an immediate impact on behavioral change, much work is needed to optimize the stimulation parameters in order to elicit long-lasting changes.

In another multi-session study, Gluck et. al (2015) completed a double-blind randomized control study with a within-subject crossover. In the first part of the study (study 1), participants completed a 9-day, inpatient trial. The first 5 days consisted of following a weight maintenance diet where the macronutrient goals were provided to participants[41]. At the end of the 5 days, patients were randomized and began tDCS stimulation which had been planned to be cathode at F3 with an anode reference electrode over the left forearm for 3 consecutive days. However, after 34 of the 36 participants had completed the montage, the study was halted as the investigators discovered the leads had been reversed. In the second phase of this study (study 2), 9 of the original participants returned to complete another 9-day inpatient stay with three additional tDCS sessions. In both studies, tDCS was delivered at 2 mA for 40 minutes. In study 2, the anode was placed over F3 and the reference electrode was placed over the right eye. Sham stimulation consisted of identical electrode placement but only lasted for 15 seconds. After active anodal stimulation, participants tended (at a trend level) to consume fewer calories per day ($p=0.07$) compared with the cathodal stimulation, however, there was no significant difference in total calorie consumption between the sham and active groups when expressed as a percent of allotted calories calculated for

maintenance diet ($p>0.20$). Weight change over the eight-day stimulation period did not significantly differ between any of the groups in either study ($p=0.30$). In a similar study design, Heinitz et. al (2017) conducted a study to discern if a repetitive tDCS over the DLPFC had an effect on ad-libitum food intake, weight change, and appetite changes long term[85]. Twenty-three participants, 11 females, with a mean BMI of 39.3 completed the study. Patients began the study with an 11-day inpatient stay. On days 8-10, participants received tDCS stimulation followed by ad libitum food consumption from a vending machine. Following their inpatient stay, participants continued with tDCS stimulation 3 times a week (on separate days) for 4 weeks. tDCS was for a total of 15 sessions anode-left at F3 with a reference cathode placed on the right supraorbital region. Active stimulation lasted for 40 minutes at 2 mA, while sham stimulation lasted for 10 seconds. Investigators found no difference in total calorie consumption between the groups during the inpatient stay or in weight change between groups during the 4-week outpatient period ($p>0.18$). However, the active stimulation had a decrease in perceived huger according to the VAS during the 4-week outpatient period compared to the sham group ($p=0.05$). In consideration of these two studies, we see that repetitive anodal tDCS over the DLPFC may elicit food-related behavioral changes. However, as Heinitz et. al (2017) noted, weight loss did not occur after 4 weeks of stimulation. It is possible that the particular repetitive tDCS protocol used here may not have been adequate to induce effective behavioral change, but the follow-up duration is not long enough to ensure adequate assessment of weight loss effect; several months of follow-up would have provided a better observation timeframe for a weight loss outcome.

In a multi-session study in which participants were followed out 4 weeks after stimulation, Usanos et. al (2020) utilized repetitive tDCS in combination with a four-week-long hypocaloric diet to determine if tDCS over the DLPFC could enhance weight loss. A total of 38 female participants underwent 8 sessions of tDCS over 2 weeks on alternate weekdays. Active stimulation was delivered anode-left/cathode-right over F3/F4 for 20 minutes at 2 mA. Sham stimulation parameters were identical but only lasted for 15 seconds. Both at baseline and the end of week 2, participants were exposed to food-related pictures as part of the Go/No-Go task (not during stimulation). At the beginning of week 2, all participants began a hypocaloric diet of 20 kcal/kg/day at 45-55% carbohydrates and 15-25% protein, which lasted for a total of 3 weeks. Bodyweight was collected weekly, and participants completed the FCT-Q and TFEQ weekly. Additionally, participants completed the neurocognitive task, GO/No-Go, 2-back test, and Dual task, at baseline and the end of week 2. At the end of the 4 weeks, the group that received active tDCS had a significantly greater reduction in bodyweight percentage than their sham tDCS counterparts ($p=0.02$)[89]. The active stimulation group significantly improve in the dual task compared to the sham group ($p=0.007$) which required inhibitory control. Thus, a study of longer duration utilizing cognitive training tasks may have enhanced effectiveness demonstrated favorable results. This suggests that repetitive tDCS in combination with cognitive training tasks may enhance behavioral changes, which can enhance weight loss. However, while statistical significance in between-groups response was demonstrated, within the confines of this study a biologically meaningful response was arguably not achieved.

Coupling tDCS with Cognitive Training

tDCS has been coupled with additional therapies in an effort to elicit a more focused, effective response. tDCS has been coupled with physical and cognitive training therapies. Studies coupling tDCS with cognitive training are underway. By coupling tDCS with standardized cognitive training focused on specific executive function domains, such as inhibition, selective-task-related synaptic coactivation may allow for amplification of the effectiveness of tDCS[66].

In a study utilizing a single-session stimulation vs. sham condition, which was coupled with a food choice task, Georgii et al. (2017) conducted a double-blind randomized control study with a within-subject crossover design with the aim of investigating whether tDCS stimulation coupled with the food choice task (FCT) modifies food choice, craving, and consumption as a function of trait impulsivity. 42 female participants with a mean of 22 years old and mean BMI of 22.6 completed each of the sessions of stimulation and sham tDCS conditions. Participants either began with a single session of sham stimulation and returned for a single session of active stimulation a week later or vice-versa. tDCS was delivered anode-right/cathode-left (F4/F3) for 20 minutes at 1 mA. Throughout the stimulation, participants were asked to complete FCQs, a VAS for the general liking of food, and a taste test for food, and calorie consumption was monitored. Additionally, an FCT was completed during stimulation. Before starting the FCT, participants were told that the most selected food group (high-calorie or low-calorie) from blocks (high-calorie/high-calorie, low-calorie/low-calorie, or high-calorie/low-calorie) would be available after the stimulation period for a taste test.

Participants were then asked to select between the food groups on the computer and their response was recorded as a measure of inhibition. Baseline and post-stimulation impulsivity were measured through the BIS-15. Georgii et al. (2017) found no significant difference in calorie consumption between the active and the sham group. However, higher impulsivity through the BIS-15 was correlated with higher calorie consumption during the taste test, regardless of group ($p=0.007$)[58]. The researchers concluded that the null effect of the tDCS could in part be due to the low amplitude (1mA) of the stimulation, and in part due to the concern that the impulsivity task was not able to induce a conflict between food palatability and consumption, arguing that both a higher amplitude and more specific task could elicit better results. Also of note, is that the study did not involve an effort to retrain participants towards making healthier food choices and did not seek to improve inhibition. Kekic et. al (2014) conducted a double-blind randomized control study with a within-subject crossover design that aimed to determine if single session sham-controlled tDCS following a temporal discounting task would temporarily reduce food cravings, transiently alter temporal discounting behaviors and if the effects of tDCS on food cravings would be modified by individual differences in decision-making abilities. 17 female participants with a mean age of 19-55 years old and a mean BMI of 23.8 completed the study. Upon arriving to the stimulation session, participants completed a battery of questionnaires to assess food cravings and eating behaviors, along with a temporal discounting task. In the active stimulation session, participants received tDCS anode-left/cathode-right (F4/F3) for 20 minutes at 2 mA. Then, the baseline measurements were repeated, and participants received sham tDCS anode-left/cathode-right (F4/F3) for 30 seconds. Kekic et. al (2014) found no significant

difference in food cravings or food consumption between groups, nor was there a significant difference in temporal discounting. However, participants with lower baseline k-values had for temporal discounting were more susceptible to anti-craving effects of tDCS ($p < 0.05$)[87]. These findings suggest that baseline characteristics, such as inhibition, can identify responders and non-responders concerning the effectiveness of tDCS. As tDCS can only enhance already existing action potentials, the lack of significant findings in this study underscores the importance of utilizing the cognitive task which best selects the appropriate neuronal population and coupling it during tDCS delivery, not before or after. Additionally, more sessions or different duration of stimulation may be necessary to see a treatment-related effect of tDCS.

In a more recent multiple stimulation DLPFC-directed study coupled with cognitive training directed at executive function enhancement in individuals with obesity, Forcano et. al (2020) aimed to test the efficacy of the intervention on food consumption and cognition, in addition to endocannabinoid levels and electroencephalogram changes in participants with obesity[88]. A total of 18 participants with a mean age of 43.2 and a mean BMI of 42.6 completed the study. Participants begin with a baseline visit during which cognitive tasks, BMI, dietary measures were obtained, and seven days later, they underwent stimulation for 4 consecutive days. Active tDCS was applied using 8 multichannel electrodes at AF3, AF4, F3, F4, F7, F8, FC5, and FC6 (in a montage determined via Neuroelectrics StimWeaver to provide DLPFC-directed stimulation for 20 minutes at 2 mA. During stimulation, participants completed cognitive training tasks bingo, platforms, pyramid card, four in a row, temporary-order and go/no-go tasks to

assess their sustained attention, processing speed, planning, flexibility, response inhibition, decision-making, and working memory. On day 12, the postintervention assessment, identical to baseline assessment, was collected and on day 18, a 4-day dietary assessment was collected. The investigators found that the active group had an increase in the number of accurate responses to the bingo test (testing for sustained attention) compared to the sham group (Cohen's d=0.38) post-treatment. Additionally, Forcano et al (2020) found that tDCS coupled with cognitive training in individuals with obesity lead to a decrease in food consumption as compared to the sham group (Cohen's d=0.85)[91]. This study design suggests that repetitive tDCS paired cognitive training may enhance executive function domains and reduce caloric intake. However, this small study with very short follow-up is preliminary and limited in its application to weight management as the participants were only followed for 7 days post-stimulation and a sustained calorie reduction is necessary for weight loss.

As tDCS is a low-risk device, there have been concerns that effectiveness may also be minimal. Indeed, many studies have yielded inconsistent or negative results. However, the benefits of tDCS are influenced by the parameters used - amplitude of current, the direction of the current, and the activation of neurons in the target-based area[56]. Future studies should pair cognitive tasks targeted at impulsive behaviors along with tDCS over the DLPFC to examine the role of tDCS in the treatment of food-related impulsivity. Much work is still needed to optimize the coupled task selection, which is crucial to effectiveness, as well as the other tDCS parameters. In summary, the small proof-of-concept studies which are promising, require longer and larger follow-ups to

understand the lasting effects of tDCS over the DLPFC paired with cognitive training impulsivity food-related behaviors and weight management in obesity. While there is much additional work to do with regards to understanding and optimizing the role of tDCS application for obesity-related food impulsivity, even less is understood regarding the potential role of trait level compulsivity with regards to changing to and sustaining healthy food-related behaviors and the potential role of tDCS application for this issue. This area represents another potential area for future weight management research.

Conclusion:

Some individuals with obesity may experience impulsive eating-related behaviors. For some obese individuals, trait-level compulsivity may be a limiting factor in successful adaption and maintenance of healthy weight loss promoting behaviors. DLPFC deficits may contribute to increases in food impulsivity and leading to the development and maintenance of obesity. tDCS is a non-significant risk form of neuromodulation that can enhance neuronal activity by creating a subthreshold membrane fluctuation when delivered from anode to cathode. There is mixed evidence for tDCS in the treatment of obesity by itself, however, some evidence suggests tDCS in combination with cognitive training during repetitive DLPFC-directed tDCS sessions could potentially be therapeutic for diseases with an impulse-control component, including, addictive behaviors and potentially obesity. However, much further research is needed to optimize this approach with careful attention to the following: the location, duration, number of sessions, the intensity of the tDCS delivered, and specific, standardized cognitive task coupled with tDCS. The potential role of tDCS for weight management has yet to be

determined. It is not yet clear if utilizing a standardized but broad array of tasks targeting multiple executive function domains will be the optimal approach in the weight loss setting, or if targeting specific domains such as the inhibition domain, in particular, will be the best strategy for the selection of optimal cognitive tasks to be coupled with tDCS when utilized in the weight management setting.

CHAPTER 2: A PREFRONTAL CORTEX-DIRECTED TDCS AND COGNITIVE TRAINING FOR IMPULSIVITY IN OBESITY: A PILOT STUDY

Background:

Obesity is a multifaceted disease that can be caused by an imbalance of energy intake and energy expenditure, and includes physiological, behavioral, psychological, genetic, and environmental factors1[1,2,6]. Obesity is defined by a body mass index (BMI) greater than or equal to 30 and increases the risk of metabolic diseases, cardiovascular diseases, and mortality[2,3,4,5,6]. Although not necessary to obesity, at a trait level impulsivity may be a factor in the development and maintenance of obesity in some individuals. Impulsivity is a psychological trait characterized by the lack of foresight, planning, and excessive risk-taking and can reflect poor executive function[20]. Inhibitory control is necessary for overcoming or managing impulsive behaviors and inadequate inhibitory control in relation to environmental food cues can enhance the development and maintenance of obesity[23,25].

The prefrontal cortex (PFC), also known as the gatekeeper of risk and reward thoughts and behaviors, plays an important role in executive function, including self-control and the ability to plan and understand the consequences of actions. Dysregulation of the prefrontal cortex can lead to addictive behaviors such as gambling and drug addictions, and possibly the development and maintenance obesity[109]. Hollman et. al (2020) found that the dorsolateral prefrontal cortex (DLPFC) is considered to be involved with self-control and cognitive reappraisal of food, the ability to reduce the desirability of food consumption[54]. Individuals with obesity may have a less modulated PFC[76]. Transcranial Direct Current stimulation (tDCS) could play an important role in

modulating the DLPFC to enhance executive function, mitigate impulsivity and potentially treat obesity.

tDCS is a non-invasive neuromodulation technique that can enhance sub-threshold action potentials and enhance neuronal efficacy. However, as a non-excitatory device, tDCS is unable to generate an action potential by itsef[34]. Previous research has found a therapeutic effect of tDCS in treatment of addictive behaviors, such as alcoholism. Boggio et. al (2008) found that tDCS reduced alcoholism relapse[17]. Additionally, tDCS has been used in some food-related behavior studies, such as cravings, calorie consumption and weight management with mixed results. In a randomized control trial, Ray et. al (2017) conducted single session tDCS over the DLPFC and found no difference in food consumption between groups[60]. In another study with repetitive tDCS sessions, Usanos et. al (2020) found that participants who received tDCS over the DLPFC had a greater percent bodyweight reduction compared to their sham counterparts[89]. Yet when Heinitz et. al (2017) conducted a repetitive tDCS trial, no changes in weight were seen between groups after four weeks[85]. This could be in part because of tDCS's modulatory nature; there has been mixed literature on its effectiveness in behavioral modification and weight management. However, as tDCS is a newer modality, there could be variability in its effectiveness of tDCS from parameters utilized for treatment. Moreover, it is possible that coupling tDCS with a cognitive training task may enhance the effectiveness of tDCS by amplification of synaptic coactivation.

Therefore, given the potential of tDCS as a treatment for impulsive eating behavior, the primary aim of this study was to investigate if tDCS over the DLPFC paired

with cognitive training could enhance executive function, and in particular, reduce impulsivity in participants with obesity. As a secondary aim, we aimed to determine if tDCS over the DLPFC paired with cognitive training could enhance weight loss in participants with obesity enrolled in a structured weight loss program.

Methods:

Participants:

Out of the 72 participants from the Minneapolis VAMC recruited for the study. Eligibility criteria included obesity (BMI > 30), age of 18 years or older, ability to understand English and consent to the study and procedures, and for females of child-bearing age to be willing to use a reliable form of birth control. Participants were excluded if they had a history of seizures, severe or moderate head injury, head surgery, a 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 the head (not including the mouth), implanted medical devices, pregnancy, active substance abuse, psychological or medical disorders requiring inpatient treatment, presence of a known metabolic or hormonal disorder that affects weight. Participants with a history of hypothyroidism are acceptable if the treatment is on treatment and maintains normal TSH and FT4 levels within the previous 3 months before treatment and has been on a stable dosage of l-thyroxine for 3 months as prescribed. Thirty-two of the participants screened were eligible for the study and enrolled. Three

participants withdrew before their first stimulation session and 22 participants completed all 8 visits. Due to the need for virtual visits during the COVID-19 pandemic, only 17 participants total finished their visits in-person which was required for on-site weight measurement and NIH Examiner completion. For the virtual visits, weight collection occurred over the phone the day of the visit, and scale type was collected, or weights were pulled from the participants; chart from their most recent medical visit. Weights pulled from participants charts were excluded if they were not within ±14 days of the study visit. Additionally, 1 of the 17 participants who completed the NIH Examiner measurements was unwilling to complete their Binge Eating Scale (BES) at visit 8.

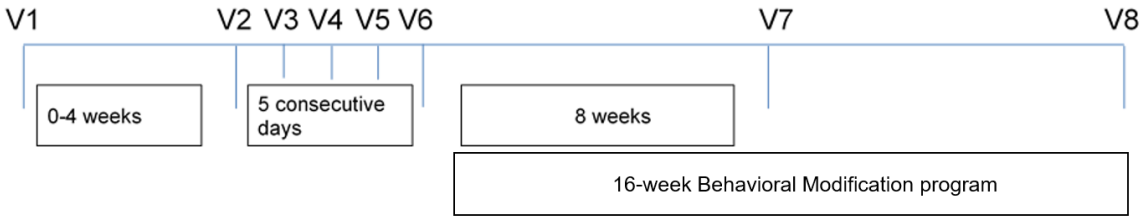
Participants were allowed in the study if on medications that could impact weight but were required to be on a stable dose for three months prior to beginning the study. Changes to medications during study participation were not recommended, but if necessary, adjustments were noted and reviewed. Table 3 summarizes the medications that could influence weight taken during the study duration.

Study Design:

The study protocol is depicted in figure 1. A baseline visit consisted of a medical doctor (MD) screening/interview, and BES, Minnesota Blast Exposure Screening Tool (MN-BEST), Patient Health Questionnaire (PHQ-9), and the National Institute of Health (NIH) Examiner battery were conducted. Within 1-4 weeks, participants were randomized into treatment groups and began stimulation. Visits 2-6 were completed on

consecutive days where participants received tDCS in combination with BrainHQ. After the consecutive stimulation sessions, participants then began a 16 week Move Mass Behavior Modification (BMOD) program through the Minneapolis VAMC. Visit 7 occurred at week 8 (halfway through the behavior modification program) and visit 8 occurred at week 16. Visit 7 consisted of measuring weight, BES, and the NIH Examiner. In addition, on visit 8, both PHQ-9 and a short blinding questionnaire were assessed.

Figure 2: Study protocol design and timeline



MN-BEST:

The MN-BEST is a self-reported interview tool. The three most significant blast exposure events are recorded in addition to the frequency and duration of the post-concussive symptomatology. Additionally, the three most significant head injuries for the participant will be recorded to determine the presence of a traumatic brain injury.

PHQ-9:

The PHQ-9 was conducted to determine the presence of the nine Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DMS-IV-TR) criteria

for depression. The scores ranged from 0-27 with a higher score being consistent with more depressive symptoms.

BES:

The BES is a 16-item questionnaire that assessed the presence of binge eating behaviors. The questions were conducted as a group of statements about behavior, thoughts, and emotional states. Higher scores are consistent with more binging behavior.

NIH Examiner:

A computerized battery of neuropsychological, experimental tests to assess four domains of executive function.

a) The Dot Counting test (working memory):

   The Dot Counting test assesses working memory. Participants were asked to count and remember the number of blue circles in a display of other shapes. There were six trials in which the number of shapes displayed in each trial increased from two to seven. Participants were asked to recall, in order, the total number of blue circles on each display, and the correct responses were recorded.

b) The Flanker test (impulsivity):

   The Flanker test assesses impulse control. Participants were asked to make rapid decisions about the direction of a central stimulus when the surrounding items are congruent, pointed in the same direction, or incongruent, pointed in the opposite direction. Lower scores are related to poor impulse control. A

summary score that takes into account the correctness of response and speed of response may be computed. A reaction time that relates more specifically to motor impulsivity may also be evaluated, both for the trials total and for the congruent and incongruent trials specifically.

c) Set Shifting (cognitive flexibility)

The Set Shifting task assesses cognitive flexibility which relates to compulsivity as a trait. Participants were asked to match a stimulus on the screen to either of the two stimuli in the corner of the screen on one of two types of characteristics (color or shape). The matching characteristics alternate in a pseudorandom fashion. Lower scores relate to greater behavioral compulsivity.

d) The Unstructured Task (executive planning)

The Unstructured Task assesses executive planning. Participants are asked to complete several simple puzzles, with different assignments (high and low value) within six minutes. Participants must plan which order of puzzles to complete to obtain as many points as possible. Higher scores are associated with higher planning skills.

BrainHQ:

An interactive computer software package where participants work through a series of structured exercises designed to stimulate neuroplasticity. BrainHQ was conducted as a trained task concurrently with tDCS. BrainHQ contains exercises challenging cognitive skills including attention, processing speed, and working memory.

tDCS:

tDCS was delivered using the Ngeuroelectrics Starstim system, a wireless multichannel transcranial current stimulator. Carbon rubber core electrodes were soaked in saline solution (25 cm^2) and placed in a neoprene headcap marked with locations based on the 10-10 EEG system. Using a montage directed at enhancing the neuroplasticity of the left DLPFC, the anode placed over F4 over the left DLPFC, and the cathode placed at F3 over the right DLPFC. The current was delivered at 2mA for 13-minutes, followed by a 20-minute stimulation break and another 13-minute stimulation. For sham stimulation, the procedure was identical to active stimulation except for the current only flowed for the initial 30 seconds.

Statistical Analysis:

Data analyses were performed using RStudio software. Descriptive statistics were conducted on groups at baseline. Differences between groups were assessed. Paired t-tests were used to assess within-group measures while independent t-tests were assessed between-group measures.

Results:

Table 3 shows the baseline anthropometric characteristics of the 22 participants enrolled in the study.

Table 3: Baseline characteristics of 22 participants enrolled in the study.

Variable Mean (SD) Median (Range)	Active (n = 11)	Sham (n = 11)	p-value

Age	57 y/o (11.78) 58 (37 to 72)	60.64 (11.90) 66 (35 to 71)	0.52
Sex (M/F)	8/3	8/3	0.67
Weight	276.19 (56.69) 278 (182.4 to 368.8)	252.49 (37.60) 256.6 (188.4 to 315.2)	0.73
BMI	39.84 (5.31) 38.77 (30.82 to 47.99)	37.46 (4.43) 35.31 (32.34 to 44.85)	0.65
Diabetes (%)	5 (45.45)	4 (36.36)	1.0
HbA1c (pts with DM)	7.18 (0.965) 7.1 (6.1 to 8.7)	7.53 (1.70) 7.4 (5.9 to 9.3)	0.71
Smoke (%)	4 (36.36)	1 (9.09)	0.14
Hypothyroidism (%)	0 (0)	0 (0)	0.63
Total PHQ	8.36 (2.98) 8 (3 to 13)	5.64 (5.20) 4 (0 to 14)	0.15
Total BES	21 (9.50) 20 (10 to 33)	16 (6.28) 16 (4 to 7)	0.16

Due to the COVID-19 pandemic, this pilot study was shortened and only 17 participants were able to complete the NIH Examiner at visits 7 and 8. Table 5 shows the baseline anthropometric characteristics and NIH Examiner results of the 17 participants.

Table 4: Baseline characteristics of 17 participants who completed in-person visits (NIH Examiner completers)

Variable Mean (SD) Median (Range)	Active (n = 8)	Sham (n = 9)	p-value
Age	56.5 (13.22) 58 (37-722)	58.78 (12.44) 64 (35 to 69)	0.72
Sex (M/F)	7/1	6/3	0.34

Weight	294.38 (50.46) 309.5 (212.8 to 368.8)	247.49 (39.75) 253.6 (188.4 to 315.2)	**0.049**
BMI	41.72 (4.57) 42.67 (34.34 to 47.99)	37.09 (3.93) 35.31 (32.34 to 44.04)	**0.040**
Diabetes (%)	4 (50.0)	3 (33.33)	0.52
HbA1c (pts with DM)	6.8 (0.53) 6.9 (6.1 to 7.3)	8.35 (1.34) 8.35 (7.4 to 9.3)	**0.093**
Smoke (%)	2 (25.0)	0 (0)	0.12
Hypothyroidism (%)	0 (0)	0 (0)	0.62
Total PHQ	9 (3.07) 9.5 (3 to 13)	5.44 (4.80) 4 (1 to 14)	**0.093**
Total BES	20.38 (10.13) 18 (10 to 33)	16.22 (6.98) 18 (4 to 27)	0.34
Flanker Summary Score	8.36 (0.54) 8.52 (7.37-8.69)	8.23 (0.53) 8.30 (7.06-8.99)	0.62
Flanker Reaction Time	0.93 (0.19) 0.88 (0.76-1.33)	0.97 (0.23) 0.95 (0.69-1.47)	0.70
Dot Counting Score	15.63 (4.24) 14.5 (10-24)	15.89 (3.89) 16 (11-23)	0.90
Set Shifting Score	7.56 (1.06) 7.65 (5.84-9.33)	7.66 (0.67) 7.63 (6.75-9.10)	0.82
Unstructured Task Score	352.25 (76.21) 332.5 (275-505)	307.56 (93.7) 300 (140-451)	0.30

Although there were no between-group differences in weight or BMI for the 22 completers, there were significant between-group differences in baseline weight ($p = 0.049$) and BMI ($p = 0.040$) in the NIH completers. Additionally, there was a baseline (trend-level) difference in PHQ-9 in the NIH completer groups ($p = 0.093$). However, the active tDCS with cognitive training (tDCS+CT) group had a lower HbA1c score

compared to their sham counterparts at baseline ($p = 0.093$); the sham had worse glycemic control at baseline which might predispose to greater weight loss.

Table 5 summarizes the medications taken by participants throughout the study. No significant changes in medications were seen within groups throughout the study.

Table 5: Baseline and follow-up medications in all NIH completers

	Active (n = 8)		Sham (n = 9)	
Medication	Baseline	Follow-up	Baseline	Follow-up
Empagliflozin (%)	Baseline	Follow-Up	Baseline	Follow-Up
HCTZ (%)	1 (9.09)	1 (9.09)	1 (9.09)	1 (9.09)
Liraglutide (%)	1 (9.09)	1 (9.09)	2 (18.18)	2 (18.18)
Metformin (%)	0 (0)	0 (0)	1 (9.09)	1 (9.09)
Metoprolol (%)	2 (18.18)	2 (18.18)	3 (27.27)	3 (27.27)
Semaglutide (%)	2 (18.18)	2 (18.18)	3 (27.27)	3 (27.27)
Topiramate (%)	0 (0)	0 (0)	1 (9.09)	1 (9.09)

tDCS was tolerated well. Some subjects noted tingling sensation during sessions, both active and sham. Participant blinding was assessed at the end of the study and was determined to be successful; 66% of the sham group participants believed they had received active stimulation, while 25% of the active group thought they received active stimulation. Conversely, 11% of the sham participants believed they received sham stimulation while 38% of active participants believed they received sham stimulation. The remaining participants were unsure of what stimulation they had received.

In their study, Galioto et. al (2016) found that a slower Flanker response time was associated with better impulse control, or inhibition, and subsequent weight loss[108]. For this reason, we chose to focus on the Flanker reaction time rather than the Flanker

summary score. We found that over the course of the study, the total mean Flanker reaction time score improved in the active tDCS+CT group at visit 7, before tapering off at visit 8. For that reason, we chose to focus on visit 7 for the NIH Flanker. Table 6 shows the within and between-group comparisons from baseline to visit 8 in the NIH Flanker reaction time.

Table 6: Primary Aim: NIH Examiner Flanker reaction time throughout the study duration.

	Active Group (n=8)			Sham Group (n=9)			Compare	
	Baseline	Results	Paired t-test	Baseline	Results	Paired t-test	Independent t-test	
Variable	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value	p-value	95% CI
Flanker Reaction Time Vis 6	0.93 (0.19)	0.875 (0.18)	0.22	0.97 (0.23)	0.82 (0.099)	0.087	0.48	-0.098 to 0.20
Flanker Reaction Time Vis 7	0.93 (0.19)	0.91 (0.14)	0.79	0.97 (0.23)	0.81 (0.062)	0.057	**0.075**	-0.011 to 0.21
Flanker Reaction Time Vis 8	0.93 (0.19)	0.84 (0.087)	0.11	0.97 (0.23)	0.83 (0.11)	0.07	0.56	-0.13 to 0.23

Table 7 summarizes the effect of the intervention on the NIH Examiner within and between groups at visit 8 compared to the baseline visit 1 for the 17 NIH completers.

No significant changes were seen in the total Dot counting score, total Set Shifting score, or total Unstructured task score between groups.

Table 7: Additional NIH Examiner at baseline visit 1 compared to visit 8 between and within groups.

	Active Group (n=8)			Sham Group (n=9)			Compare	
	Baseline	Results	Paired t-test	Baseline	Results	Paired t-test	Independent t-test	
Variable	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value	p-value	95% CI
Dot Counting Score Vis 8	15.63 (4.24)	18.5 (5.32)	0.11	15.89 (3.89)	16.22 (5.85)	0.86	0.31	-2.59 to 7.68
Set Shifting Score Vis 8	7.56 (1.06)	8.02 (0.66)	0.08	7.66 (0.67)	8.09 (0.82)	0.12	0.94	-0.69 to 0.75
Unstructured Task Score Vis 8	352.25 (76.21)	416.5 (117.6)	0.07	307.56 (93.7)	340.56 (130.3)	0.37	0.51	-67.12 to 129.62

tDCS treatment did not lead to weight change during the study. There were no significant differences between groups in the number of BMOD classes attended.

Discussion:

The primary objective of this study was to determine if there is a treatment-related decrease in measures impulsivity in individuals with obesity receiving tDCS treatment in combination with cognitive training compared to sham treatment. The NIH Flanker reaction time was our aim one measurement. We found no differences at visit 8 in total

mean flanker reaction time, but at visit 7, a treatment-related effect can be seen with the active tDCS+CT group having a slower total mean reaction time compared to their sham counterparts (p=0.075). Galioto et. al (2016) found that a slower Flanker response time was associated with better impulse control, or inhibition, and subsequent weight loss[108]. Regarding the other NIH Examiner components, no differences were seen in Dot counting, Unstructured planning, or Set Shifting throughout the study.

The secondary objective of this study was to determine if there is a treatment-related change in weight loss with tDCS treatment in combination with cognitive training compared to sham treatment. As mentioned before, despite finding a tDCS-related effect on Flanker reaction time maximizing at about 2 months after stimulation, our findings did not show the link between this NIH Examiner measurement and subsequent weight loss that Galioto had demonstrated; we did not see a treatment-related effect for weight loss. However, randomization was not optimal in our small study; there were trend-level differences in baseline weight, BMI, and trend-level PHQ-9 with the sham group tending to have lower values ($p = 0.049$ for weight at baseline, $p = 0.040$ for BMI at baseline, and $p = 0.093$ [trend-level significance] for PHQ-9 at baseline) among the NIH Examiner completers. Additionally, among those with diabetes, HbA1c level at baseline trended higher for those in the sham group compared to the active among the NIH Examiner completers ($p = 0.093$). These baseline differences may have contributed to the lack of treatment related weight loss in those who completed the NIH Examiner (those who had in-person weights and were able to complete all study activities), as the baseline differences arguably would have been more likely to have led to less weight loss in the

active group. The potential for such baseline differences needs careful consideration in future studies. Future studies utilizing larger sample sizes should allow for better randomization, leading to more congruent baseline characteristics between groups.

Though we had hoped to complete studies in 20 participants, due to the COVID-19 pandemic, we were unable to collect complete primary data in only 17 individuals. Despite the lack of demonstration of weight loss with tDCS paired with cognitive training in these individuals, the results of this study suggest that tDCS paired with cognitive training may enhance executive function, specifically motor inhibition peaking around two months post-stimulation and then returning to baseline. Much work is needed to optimize treatment parameters. A trained task more specific to impulsivity, food-related impulsivity, in particular, may elicit a better response and subsequent weight loss than we found with the use of BrainHQ. Other possibilities for future optimization include the changes to tDCS parameters: location, duration, number of sessions, and/or intensity of the stimulation. Further research is needed to better understand the ideal parameters of tDCS in this setting.

Conclusion:

The primary aim of the study was to determine if tDCS in combination with cognitive training decreased impulsivity in individuals with obesity compared to sham treatment. Future work is needed regarding the tDCS parameters and trained tasks best suited to elicit these changes; future research should be conducted in a larger sample population. However, this small pilot study does suggest that tDCS over the DLPFC in combination with cognitive training may enhance motor inhibition in individuals with

obesity and thus may hold potential promise as a new modality for weight loss management.

References:

1. Hurt, R. T., Frazier, T. H., McClave, S. A., & Kaplan, L. M. (2011). Obesity epidemic. Journal of Parenteral and Enteral Nutrition, 35(5), 4S-13S. doi:10.1177/0148607111415110
2. Flegal, K., Kruszon-Moran, D., Carroll, M., Fryar, C., & Ogden, C. (2016). Trends in Obesity Among Adults in the United States, 2005 to 2014. JAMA, 315(21), 2284-2291.
3. Lee, P., & Dixon, J. (2017). Food for Thought: Reward Mechanisms and Hedonic Overeating in Obesity. Current Obesity Reports, 6(4), 353-361.
4. Allison, D., & Pi-Sunyer, F. (1995) Obesity treatment: examining the premises. Endocr Pract - Am Assoc Clin Endocrinol, 1(5):353-364.
5. Pi-Sunyer, F. (1996). A review of long-term studies evaluating the efficacy of weight loss in ameliorating disorders associated with obesity. Clinical Therapeutics, 18(6), 1006-1035.
6. Ogden, C., & National Center for Health Statistics. (2010). Obesity and Socioeconomic Status in Adults : United States, 2005-2008.
7. Nederkoorn, C., Braet, C., Van Eijs, Y., Tanghe, A., & Jansen, A. (2006). Why obese children cannot resist food: The role of impulsivity. Eating Behaviors, 7(4), 315-322.
8. Lutter, M., & Nestler, E. (2009). Homeostatic and Hedonic Signals Interact in the Regulation of Food Intake1-3. The Journal of Nutrition, 139(3), 629-32.
9. Apovian, C. M., Aronne, L. J., Bessesen, D. H., McDonnell, M. E., Murad, M. H., Pagotto, U., Ryan, H. D., & Still, C. D., (2015). Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism, 100(2), 342-362.

10. Sfera, A., Osorio, C., Inderias, L., Parker, V., Price, A., & Cummings, M. (2017). The Obesity-Impulsivity Axis: Potential Metabolic Interventions in Chronic Psychiatric Patients. Frontiers In Psychiatry, 8, 20. doi:10.3389/fpsyt.2017.00020
11. Coll, A., Farooqi, I., & O'Rahilly, S. (2007). The Hormonal Control of Food Intake. Cell, 129(2), 251-262. doi:10.1016/j.cell.2007.04.001
12. Lowe, M., & Butryn, M. (2007). Hedonic hunger: A new dimension of appetite? Physiology & Behavior, 91(4), 432-439. doi:10.1016/j.physbeh.2007.04.006
13. Berthoud, H. (2011). Metabolic and hedonic drives in the neural control of appetite: Who is the boss? Current Opinion in Neurobiology, 21(6), 888-896. doi:10.1002/bmb.20244.DNA
14. Volkow, N., Wang, G., & Baler, R. (2011). Reward, dopamine and the control of food intake: Implications for obesity. Trends in Cognitive Sciences, 15(1), 37-46. doi:10.1016/j.tics.2010.11.001.Reward
15. Min, B. (2010). A thalamic reticular networking model of consciousness. Theoretical Biology & Medical Modelling, 7(1), 10. doi:10.1186/1742-4682-7-10
16. Barraclough, D. J., Conroy, M. L., & Lee, D. (2004). Prefrontal cortex and decision making in a mixed-strategy game. Nature Neuroscience, 7(4), 404-40410. doi:10.1038/nn1209
17. Fecteau, S. H., Pascual-Leone, A. S., Fregni, F., Zald, D., Liguori, P., Boggio, P., & Théoret, H. (2007). Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. Journal of Neuroscience, 27(23), 6212-6218. doi:10.1523/JNEUROSCI.0314-07.2007
18. Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., & Robbins, T. (2002). Decision-making processes following damage to the prefrontal cortex. Brain, 125, 624-639.

19. Mcclure, S., Laibson, D., Loewenstein, G., & Cohen, J. (2004). Separate neural systems value immediate and delayed monetary rewards. Science (New York, N.Y.), 306(5695), 503-507. doi:10.1021/es0717414
20. Jasinska, A., Yasuda, M., Burant, C., Gregor, N., Khatri, S., Sweet, M., & Falk, E. (2012). Impulsivity and inhibitory control deficits are associated with unhealthy eating in young adults. Appetite, 59(3), 738-747. doi:10.1016/j.appet.2012.08.001.Impulsivity
21. Dawe, S., & Loxton, N. (2004). The role of impulsivity in the development of substance use and eating disorders. Neuroscience and Biobehavioral Reviews, 28(3), 343-351. doi:https://doi-org.ezp1.lib.umn.edu/10.1016/j.neubiorev.2004.03.007
22. Neuromodulation. (2009). Retrieved from https://ebookcentral.proquest.com
23. Verbruggen, F., & Logan, G. (2009). Models of response inhibition in the stop-signal and stop-change paradigms. Neuroscience and Biobehavioral Reviews, 33(5), 647-661. doi:10.1016/j.neubiorev.2008.08.014.Models
24. Houben, K., & Jansen, A. (2011). Training inhibitory control. A recipe for resisting sweet temptations. Appetite, 56(2), 345-349. doi:10.1016/j.appet.2010.12.017
25. Bartholdy, S., Dalton, B., O'Daly, O., Campbell, I., & Schmidt, U. (2016). A systematic review of the relationship between eating, weight and inhibitory control using the stop signal task. Neuroscience And Biobehavioral Reviews, 64, 35-62. doi:10.1016/j.neubiorev.2016.02.010
26. Guerrieri, R., Nederkoorn, C., Schrooten, M., Martijn, C., & Jansen, A. (2009). Inducing impulsivity leads high and low restrained eaters into overeating, whereas current dieters stick to their diet. Appetite, 53(1), 93-100. doi:10.1016/j.appet.2009.05.013
27. Guerrieri R, Nederkoorn C, Jansen A. (2007). The interaction between impulsivity and a varied food environment: Its influence on food intake and overweight. *International Journal of Obesity*, *32*(4), 708-714. doi:10.1038/sj.ijo.0803770

28. Nederkoorn, C., Smulders, F., Havermans, R., Roefs, A., & Jansen, A. (2006). Impulsivity in obese women. Appetite, 47(2), 253-256.. doi:10.1016/j.appet.2006.05.008
29. Houben, K., & Jansen, A. (2019). When food becomes an obsession: Overweight is related to food-related obsessive-compulsive behavior. Journal of Health Psychology, 24(8), 1145-1152. doi:10.1177/1359105316687632
30. Moore, Catherine F. Sabino, Valentina. Koob, George F. Cottone, Pietro. (2019). Chapter 3 - dissecting compulsive eating behavior into three elements. Compulsive eating behavior and food addiction: Emerging pathological constructs (pp. 41) Academic Press. doi:doi.org/10.1016/B978-0-12-816207-1.00003-2
31. Naish, K. R., Vedelago, L., Mackillop, J., & Amlung, M. (2018). Effects of neuromodulation on cognitive performance in individuals exhibiting addictive behaviour: A systematic review protocol. Systematic Reviews, 7(1), 1-6. doi:10.1186/s13643-018-0749-y
32. Fertonani, A., & Miniussi, C. (2017). Transcranial Electrical Stimulation: What We Know and Do Not Know About Mechanisms. The Neuroscientist, 23(2), 109-123. doi:10.1177/1073858416631966
33. Boggio, P., Sultani, N., Fecteau, S., Merabet, L., Mecca, T., Pascual-Leone, A., Basaglia, A., & Fregni, F. (2008). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled study. Drug and Alcohol Dependence, 92(1-3), 55-60. doi:10.1016/j.drugalcdep.2007.06.011
34. Philip, N. S., Nelson, B. G., Frohlich, F., Lim, K. O., Widge, A. S., & Carpenter, L. L. (2017). Low-intensity transcranial current stimulation in psychiatry. American Journal of Psychiatry, 174(7), 628-639. doi:10.1176/appi.ajp.2017.16090996
35. Goldman, R., Borckardt, J., Frohman, H., O'neil, P. M., Madan, A., Campbell, L., K., Budak, A., & George, M. (2011). Prefrontal cortex transcranial direct current stimulation

(tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. Appetite, 56(3), 741-746. doi:10.1016/j.appet.2011.02.013

36. International neuromodulation society. (2017). Retrieved from https://www.neuromodulation.com/brief-history-neuromodulation
37. Gebodh N., Esmaeilpour Z., Adair D., Schestattsky P., Fregni F., Bikson M. (2019). Classification, history and technology. Transcranial direct current stimulation among technologies for low-intensity transcranial electrical stimulation. Springer, Cham. doi:https://doi-org.ezp3.lib.umn.edu/10.1007/978-3-319-95948-1
38. Saleem, G., Crasta, J., Slomine, B., Cantarero, G., & Suskauer, S. (2019). Transcranial Direct Current Stimulation in Pediatric Motor Disorders: A Systematic Review and Meta-analysis. Archives of Physical Medicine and Rehabilitation, 100(4), 724-738.. doi:10.1016/j.apmr.2018.10.011
39. U.S. Food & Drug Administration. FDA takes action to ensure regulation of electroconvulsive therapy devices and TMS therapy system. https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm629012.htm. Published 2018. Accessed January 17, 2020.
40. Rossi, S., Hallett, Rossini, Pascual-Leone, & The Safety of Tms Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical Neurophysiology, 120(12), 2008-2039. doi:10.1016/j.clinph.2009.08.016.Rossi
41. Gluck, M.E., Alonso-Alonso, M., Piaggi, P., Weise, C.M., Jumpertz-von Schwartzenberg, R., Reinhardt, M., Wassermann, E.M., Venti, C.A., Votruba, S. B., & Krakoff, J. (2015). Neuromodulation targeted to the prefrontal cortex induces changes in

energy intake and weight loss in obesity. Obesity (Silver Spring, Md.), 23(11), 2149–2156. doi:10.1002/oby.21313

42. Le, D.S.N.T., Pannacciulli, N., Chen, K., Salbe, Arline D., Hill, J.O., Wing, Rena R., & Krakoff, Jonathan. (2007). Less activation in the left dorsolateral prefrontal cortex in the reanalysis of the response to a meal in obese than in lean women and its association with successful weight loss.(Original Research Communications)(Author abstract)(Clinical report). American Journal of Clinical Nutrition, 86(3), 573-579. doi: 10.1093/ajcn/84.4/725
43. Stoeckel, L.E., Birch, L.L., Heatherton, T., Mann, T., Hunter, C., Czajkowski, S., Onken, L., Berger, P.K., & Savage C.R. (2017). Psychological and neural contributions to appetite self-regulation. *Obesity*, *25*(Suppl 1), S17-S25.
44. Gandiga, P., Hummel, F., & Cohen, L. (2006). Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. Clinical Neurophysiology, 117(4), 845-850. doi:10.1016/j.clinph.2005.12.003
45. Kumar, K., & Rizvi, S. (2014). Historical and Present State of Neuromodulation in Chronic Pain. Current Pain and Headache Reports, 18(1), 1-7. doi:10.1007/s11916-013-0387-y
46. Guerrieri, R., Nederkoorn, C., Stankiewicz, K., Alberts, H., Geschwind, N., Martijn, C., & Jansen, A. (2007). The influence of trait and induced state impulsivity on food intake in normal-weight healthy women. Appetite, 49(1), 66-73.
47. Clark, D. (2005). Intrusive thoughts in clinical disorders : Theory, research, and treatment. New York: Guilford Press.
48. May, J., Andrade, J., Kavanagh, D., & Hetherington, J. (2012). Elaborated Intrusion Theory: A Cognitive-Emotional Theory of Food Craving. Current Obesity Reports, 1(2), 114-121.

49. Cook, R.L., O'Dwyer, N.J., Donges, C.E. Parker, H.M., Cheng, H.E., Steinbeck, K.S., Cox, E.P., Franklin, J.L., Garg, M.L., Rooney, K.B., O'Connor, H.T. (2017). Relationship between Obesity and Cognitive Function in Young Women: The Food, Mood and Mind Study. *Journal of Obesity, 2017*(2017), 11.doi:10.1155/2017/5923862
50. Gropper, S., & Smith, J. (2013). Advanced nutrition and human metabolism (6th ed.). Belmont, CA: Wadsworth/Cengage Learning.
51. Kringelbach, M. L., de Araujo, I. E. T., & Rolls, E. T. (2004). Taste-related activity in the human dorsolateral prefrontal cortex doi:https://doi.org/10.1016/j.neuroimage.2003.09.063
52. Tremblay, L., & Schultz, W. (1999). Relative reward preference in primate orbitofrontal cortex. Nature, 398(6729), 704-708
53. Watanabe, M. (1996). Reward expectancy in primate prefrental neurons. Nature, 382(6592), 629-632.
54. Hollmann, M., Hellrung, L., Pleger, B., Schlögl, H., Kabisch, S., Stumvoll, M., Villringer, A., & Horstmann, A. (2011). Neural correlates of the volitional regulation of the desire for food. *International Journal of Obesity, 36*(5), 648-655. doi:10.1038/ijo.2011.125
55. Jacoby, N., & Ahissar, M. (2013). Chapter 5 - what does it take to show that a cognitive training preocedure is useful?: A critical evaluation. Progress is brain research (pp. 121-140) ELSEVIER. doi:https://doi.org/10.1016/B978-0-444-63327-9.00004-7
56. Oldrati, V., Colombo, B., & Antonietti, A. (2018). Combination of a short cognitive training and tDCS to enhance visuospatial skills: A comparison between online and offline neuromodulation. Brain Research, 1678, 32-39. doi:10.1016/j.brainres.2017.10.002

57. Ray, M., Sylvester, M., Osborn, L., Helms, J., Turan, B., Burgess, E., & Boggiano, M. (2017). The critical role of cognitive-based trait differences in transcranial direct current stimulation (tDCS) suppression of food craving and eating in frank obesity. Appetite, 116, 568-574.. doi:10.1016/j.appet.2017.05.046

58. Georgii, C., Goldhofer, P., Meule, A., Richard, A., & Blechert, J. (2017). Food craving, food choice and consumption: The role of impulsivity and sham-controlled tDCS stimulation of the right dlPFC. Physiology & behavior, 177, 20–26. doi:10.1016/j.physbeh.2017.04.004

59. Ziomber, A., Rokita, E., Kaszuba-Zwoinska, J., Romańska, I., Michaluk, J., & Antkiewicz-Michaluk, L. (2018). Repeated Transcranial Direct Current Stimulation Induces Behavioral, Metabolic and Neurochemical Effects in Rats on High-Calorie Diet. Frontiers in behavioral neuroscience, 11, 262. doi:10.3389/fnbeh.2017.00262

60. Manuel, A. L., Murray, N., & Piguet, O. (2019). Transcranial direct current stimulation (tDCS) over vmPFC modulates interactions between reward and emotion in delay discounting. Scientific reports, 9(1), 18735. doi:10.1038/s41598-019-55157-z

61. Anokhin, A. P., Grant, J. D., Mulligan, R. C., & Heath, A. C. (2015). The genetics of impulsivity: evidence for the heritability of delay discounting. Biological psychiatry, 77(10), 887-894.

62. Lempert, K. M., & Phelps, E. A. (2016). The malleability of intertemporal choice. Trends in Cognitive Sciences, 20(1), 64-74.

63. Bechara, A., Damasio, H., & Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. Cerebral cortex, 10(3), 295-307.

64. Johnson, P. M., & Kenny, P. J. (2010). Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nature neuroscience, 13(5), 635–641. doi:10.1038/nn.2519

65. Baik J. H. (2013). Dopamine signaling in food addiction: role of dopamine D2 receptors. BMB reports, 46(11), 519–526. doi:10.5483/bmbrep.2013.46.11.207

66. Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry, 17(1), 37–53. doi:10.1177/1073858410386614

67. Tanaka, S.C., Doya, K., Okada, G., Ueda, K., Okamoto, Y., & Yamawaki, S. (2004). Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. *Nature Neuroscience*, *7*(8), 887-88793.. doi:10.1007/978-4-431-55402-8_22

68. Meng, Z., Liu, C., Yu, C., & Ma, Y. (2014). Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates smoking behavior. Journal of Psychiatric Research, 54, 19-25.

69. Wang, Y., Shen, Y., Cao, X., Shan, C., Pan, J., He, H., Ma, Y., & Yuan, T. F. (2016). Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates cue-induced craving for heroin. Journal of psychiatric research, 79, 1-3.

70. Klauss, J., Penido Pinheiro, L. C., Silva Merlo, B. L., Correia Santos, G. D. A., Fregni, F., Nitsche, M. A., & Miyuki Nakamura-Palacios, E. (2014). A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. International Journal of Neuropsychopharmacology, 17(11), 1793-1803.

71. Lam, R. W., Chan, P., Wilkins-Ho, M., & Yatham, L. N. (2008). Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and metaanalysis. Canadian journal of psychiatry. Revue canadienne de psychiatrie, 53(9), 621–631. doi:10.1177/070674370805300909

72. Brunoni, A. R., Tortella, G., Benseñor, I. M., Lotufo, P. A., Carvalho, A. F., & Fregni, F. (2016). Cognitive effects of transcranial direct current stimulation in depression: Results

from the SELECT-TDCS trial and insights for further clinical trials. Journal of affective disorders, 202, 46–52. doi:10.1016/j.jad.2016.03.066

73. Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. Science (New York, N.Y.), 324(5927), 646–648. doi:10.1126/science.1168450
74. Kober, H., Mende-Siedlecki, P., Kross, E. F., Weber, J., Mischel, W., Hart, C. L., & Ochsner, K. N. (2010). Prefrontal-striatal pathway underlies cognitive regulation of craving. Proceedings of the National Academy of Sciences of the United States of America, 107(33), 14811–14816. doi:10.1073/pnas.1007779107
75. Horstmann, A., Busse, F. P., Mathar, D., Müller, K., Lepsien, J., Schlögl, H., Kabisch, S., Kratzsch, J., Neumann, J., Stumvoll, M., Villringer, A., & Pleger, B. (2011). Obesity-Related Differences between Women and Men in Brain Structure and Goal-Directed Behavior. Frontiers in human neuroscience, 5, 58. doi:10.3389/fnhum.2011.00058
76. Carnell, S., Gibson, C., Benson, L., Ochner, C. N., & Geliebter, A. (2012). Neuroimaging and obesity: current knowledge and future directions. Obesity reviews: an official journal of the International Association for the Study of Obesity, 13(1), 43–56. doi:10.1111/j.1467-789X.2011.00927.x
77. Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F.A., Nitsche, M.A., Mecca, T., Maceedo, E.C., Pascual-Leone, A., & Boggio, P.S. (2008). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite, 51(1), 34–41. doi:10.1016/j.appet.2007.09.016
78. Castellanos, E.H., Charboneau, E., Dietrich, M.S., Park, S., Bradley, B.P., Mogg, K., & Cowan, R.L. (2009). Obese adults have visual attention bias for food cue images: evidence for altered reward system function. International journal of obesity (2005), 33(9), 1063–1073. doi:10.1038/ijo.2009.138

79. Carters, M.A., Rieger, E., & Bell, J. (2015). Reduced Inhibition of Return to Food Images in Obese Individuals. PloS one, 10(9), e0137821. doi:10.1371/journal.pone.0137821

80. Martin, D.M., Liu, R., Alonzo, A., Green, M., & Loo, C.K. (2014). Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. Experimental brain research, 232(10), 3345-3351.

81. Nitsche, M., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of Physiology, 527 Pt 3, 633-9.

82. Bastani, A., & Jaberzadeh, S. (2014). Within-session repeated a-tDCS: the effects of repetition rate and inter-stimulus interval on corticospinal excitability and motor performance. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, *125*(9), 1809–1818. https://doi.org/10.1016/j.clinph.2014.01.010

83. Chew, T., Ho, K. A., & Loo, C. K. (2015). Inter- and Intra-individual Variability in Response to Transcranial Direct Current Stimulation (tDCS) at Varying Current Intensities. *Brain stimulation*, *8*(6), 1130–1137. https://doi.org/10.1016/j.brs.2015.07.031

84. De Oliveira, C., De Freitas, J., Macedo, I., Scarabelot, V., Ströher, R., Santos, D., Souza, A., Fregni, F., Caumo, W., & Torres, I. (2019). Transcranial direct current stimulation (tDCS) modulates biometric and inflammatory parameters and anxiety-like behavior in obese rats. Neuropeptides, 73, 1-10.

85. Heinitz, S., Reinhardt, M., Piaggi, P., Weise, C., Diaz, E., Stinson, E., Venti, C., Votruba, S., Wassermann, E., Alonso-Alsonso, M., Krakoff, J., Gluck, M. (2017). Neuromodulation directed at the prefrontal cortex of subjects with obesity reduces snack food intake and hunger in a randomized trial. The American Journal of Clinical Nutrition, 106(6), 1347-1357.

86. Macedo, I., De Oliveira, C., Vercelino, R., Souza, A., Laste, G., Medeiros, L., Scarabelot, V.L., Nunes, E.A., Kuo, J., Fregni, F., Caumo, I.L.S., Torres, I. (2016). Repeated transcranial direct current stimulation reduces food craving in Wistar rats. Appetite, 103(C), 29-37.

87. Kekic, M., Mcclelland, J., Campbell, I., Nestler, S., Rubia, K., David, A., & Schmidt, U. (2014). The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with frequent food cravings. Appetite, 78, 55-62.

88. Forcano, L., Castellano, M., Cuenca-Royo, A., Goday-Arno, A., Pastor, A., Langohr, K., Castaner, O., Pérez-Vega, K. A., Serra, C., Ruffini, G., Alonso-Alonso, M., Soria-Frisch, A., & Torre, R. (2020). Prefrontal Cortex Neuromodulation Enhances Frontal Asymmetry and Reduces Caloric Intake in Patients with Morbid Obesity. Obesity, 28(4), 696-705.

89. Usanos, C., Valenzuela, P.L., De La Villa, P., Navarro, S.M., Melo Aroeira, A., Usanos, I., Martínez Cancio, L., Cuesta Villa, L., Shah, H., Magerowski, M. & Alonso-Alonso, Miguel. (2019). Neuromodulation of the prefrontal cortex facilitates diet-induced weight loss in midlife women: A randomized, proof-of-concept clinical trial. International Journal of Obesity (2005), 44(3), 568-578. https://doi-org.ezp2.lib.umn.edu/10.1038/s41366-019-0486-x

90. Ray, M., Sylvester, M., Helton, A., Pittman, B., Wagstaff, L., Mcrae, T., Turan, B., Frontaine, K., Amthor, F., & Boggiano, M. (2019). The effect of expectation on transcranial direct current stimulation (tDCS) to suppress food craving and eating in individuals with overweight and obesity. Appetite, 136, 1-7. https://doi-org.ezp1.lib.umn.edu/10.1016/j.appet.2018.12.044

91. Grundeis, F., Brand, C., Kumar, S., Rullmann, M., Mehnert, J., & Pleger, B. (2017). Non-invasive Prefrontal/Frontal Brain Stimulation Is Not Effective in Modulating Food Reappraisal Abilities or Calorie Consumption in Obese Females. *Frontiers in neuroscience*, *11*, 334. https://doi.org/10.3389/fnins.2017.00334

92. Ljubisavljevic, M., Maxood, K., Bjekic, J., Oommen, J., & Nagelkerke, N. (2016). Long-Term Effects of Repeated Prefrontal Cortex Transcranial Direct Current Stimulation (tDCS) on Food Craving in Normal and Overweight Young Adults. *Brain stimulation*, *9*(6), 826–833. https://doi.org/10.1016/j.brs.2016.07.002

93. Kushner, R. (2018). Weight Loss Strategies for Treatment of Obesity: Lifestyle Management and Pharmacotherapy. Progress in Cardiovascular Diseases, 61(2), 246-252.

94. Samaranayake, N. R., Ong, K. L., Leung, R. Y., & Cheung, B. M. (2012). Management of obesity in the National Health and Nutrition Examination Survey (NHANES), 2007–2008. *Annals of epidemiology*, *22*(5), 349-353.

95. Gadde, K. M., Martin, C. K., Berthoud, H. R., & Heymsfield, S. B. (2018). Obesity: Pathophysiology and Management. *Journal of the American College of Cardiology*, *71*(1), 69–84. https://doi.org/10.1016/j.jacc.2017.11.011

96. Hur, J., Iordan, A. D., Dolcos, F., & Berenbaum, H. (2017). Emotional influences on perception and working memory. *Cognition and Emotion*, *31*(6), 1294-1302.

97. Stice, E., Yokum, S., Bohon, C., Marti, N., & Smolen, A. (2010). Reward circuitry responsivity to food predicts future increases in body mass: moderating effects of DRD2 and DRD4. *Neuroimage*, *50*(4), 1618-1625.

98. Bruce, A. S., Holsen, L. M., Chambers, R. J., Martin, L. E., Brooks, W. M., Zarcone, J. R., ... & Savage, C. R. (2010). Obese children show hyperactivation to food pictures in brain networks linked to motivation, reward and cognitive control. *International journal of obesity*, *34*(10), 1494-1500.

99. Fassini, P., Das, S., Magerowski, G., Marchini, J., Da Silva Junior, W., Da Silva, I., de Souza Riberio Salguerio, R., Machado, C.D., Marques Miguel Suen, V., Alonso-Alonso, M. (2020). Noninvasive neuromodulation of the prefrontal cortex in young women with obesity: A randomized clinical trial. International Journal of Obesity (2005), 44(6), 1279-1290.

100. Bénard, M., Camilleri, G. M., Etilé, F., Méjean, C., Bellisle, F., Reach, G., Hercberg, S., & Péneau, S. (2017). Association between Impulsivity and Weight Status in a General Population. *Nutrients*, *9*(3), 217. https://doi.org/10.3390/nu9030217

101. Nederkoorn, C., Coelho, J. S., Guerrieri, R., Houben, K., & Jansen, A. (2012). Specificity of the failure to inhibit responses in overweight children. *Appetite*, *59*(2), 409–413. https://doi.org/10.1016/j.appet.2012.05.028

102. Mühlberg, C., Mathar, D., Villringer, A., Horstmann, A., & Neumann, J. (2016). Stopping at the sight of food - How gender and obesity impact on response inhibition. *Appetite*, *107*, 663–676. https://doi.org/10.1016/j.appet.2016.08.121

103. Jarmolowicz, D. P., Cherry, J. B., Reed, D. D., Bruce, J. M., Crespi, J. M., Lusk, J. L., & Bruce, A. S. (2014). Robust relation between temporal discounting rates and body mass. *Appetite*, *78*, 63–67. https://doi.org/10.1016/j.appet.2014.02.013

104. Amlung, M., Petker, T., Jackson, J., Balodis, I., & MacKillop, J. (2016). Steep discounting of delayed monetary and food rewards in obesity: a meta-analysis. *Psychological medicine*, *46*(11), 2423–2434. https://doi.org/10.1017/S0033291716000866

105. Van de Winckel, A., Carey, J. R., Bisson, T. A., Hauschildt, E. C., Streib, C. D., & Durfee, W. K. (2018). Home-based transcranial direct current stimulation plus tracking training therapy in people with stroke: an open-label feasibility study. *Journal of neuroengineering and rehabilitation*, *15*(1), 83. https://doi.org/10.1186/s12984-018-0427-2

106. Stevens, Carl E, Lausen, Marissa A, Wagstaff, Laura E, McRae, Tommy R, Pittman, Bethany R, Amthor, Franklin R, & Boggiano, Mary M. (2020). Effect of transcranial direct current stimulation (tDCS) on food craving and eating when using a control method that minimizes guessing of the real vs. control condition. Eating and Weight Disorders, Eating and weight disorders, 2020-08-03.

107. Jeon, S.Y., & Han, S. J. (2012). Improvement of the working memory and naming by transcranial direct current stimulation. Annals of rehabilitation medicine, 36(5), 585.

108. Galioto, R, Bond, D, Gunstad, J, Pera, V, Rathier, L, & Tremont, G. (2016). Executive functions predict weight loss in a medically supervised weight loss programme. Obesity Science & Practice, 2(4), 334-340.

109. Goldstein, Rita Z, & Volkow, Nora D. (2002). Drug Addiction and Its Underlying Neurobiological Basis: Neuroimaging Evidence for the Involvement of the Frontal Cortex. The American Journal of Psychiatry, 159(10), 1642-1652.

110.