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Genetic Influences on the Response to Neuromodulation in Craving Behaviors

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GENETIC INFLUENCES ON THE RESPONSE TO NEUROMODULATION IN CRAVING BEHAVIORS

by

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The members of the Honors Thesis Committee appointed

to examine the thesis of Carly Haring

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ABSTRACT

Genetic Influences on the Response to Neuromodulation in Craving Behaviors

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Obesity and eating disorders are highly prevalent in the United States. People who suffer from obesity and/or eating disorders face serious health consequences and even death. Current treatments are not effective as recovery rates are low, so there is a dire need for an effective treatment for obesity and eating disorders. There have been studies investigating the use of transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) of the dorsolateral prefrontal cortex (DLPFC) as a means of treatment for these people. While findings show promise, there is much variability. The goal of this study is to further prior work by evaluating the ability of tDCS and TMS to modulate food cravings and impulsivity. Additionally, genetic factors will be analyzed for their use in predicting neuromodulation efficacy. For this study, we recruited a total of 30 participants who were assigned to either the tDCS group (n=15) or the TMS group (n=15). Each participant came in for a total of three visits where they completed a series of questionnaires, underwent sham or active neuromodulation, completed a food preference task, impulsivity task, and had blood drawn. Preliminary results demonstrate that tDCS and TMS can reduce wanting to eat in general. The reduction in wanting to eat may be through modifications of feelings of lack of control. More specifically, neuromodulation can selectively decrease the appeal of high calorie foods through activation of the dorsolateral prefrontal cortex. Further, analyzing genetic factors can help predict who will respond best to neuromodulation.

Keywords: Neuromodulation, Cravings, Eating Disorders, TMS, tDCS, SNP

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Genetic Influences on the Response to Neuromodulation in Craving Behaviors

1. Introduction

1.1 Eating Disorders

"Eating disorders" (ED) is a broad term that is used to categorize a group of mental health disorders that cause people problems with their thoughts about food and eating behaviors (MedlinePlus, 2021). Sadly, anyone can develop an eating disorder, and women are twice as likely to have one in their lifetime (Economics, 2020). In the United States, roughly nine percent of the population will have an ED in their lifetime, equal to about 28.8 million people (Economics, 2020). Clearly, ED affects a lot of people, and sadly, ED is the second most deadly category of mental illness, with about 26% of people with ED attempting suicide (Arcelus et al., 2011). There are a variety of eating disorders, and each one is characterized by different sets of symptoms and outcomes.

Three common types of ED are anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED). AN is a serious illness marked by the extreme fear of gaining weight. People with AN restrict their calorie intake and may also exhibit purging behaviors following eating. Excessive exercising and distorted body image are other common characteristics of AN (Anxiety & Depression Association of America [ADAA], n.d.). The outcomes for people with AN tend to be the worst compared to other ED. A 2002 study found that under fifty percent of patients that survive AN recover. In this study, the mortality rate for AN patients was five percent. One-third of the group showed improvement, while twenty percent remained chronically ill (Steinhausen).

Bulimia nervosa and binge-eating disorder are other very serious ED. BN is also characterized by a fear of weight gain despite the patients usually being at a typical weight. People with BN exhibit episodes of binge eating followed by purging. They may also excessively exercise or fast (MedlinePlus, 2021). A 2009 study on the outcomes for people with BN found that about 45% of patients showed a full recovery, while 27% improved considerably and 23% remained chronically ill. Out of the 4,309 patients in the study, there were 14 deaths (Steinhausen & Weber). Binge-eating disorder is a highly prevalent ED. People with BED exhibit episodes of binge eating where they continue to eat even when they are full and feel uncomfortable. While people with BED do not purge, they have feelings of guilt, shame, and distress. Obesity and weight gain are common outcomes of BED (MedlinePlus, 2021). Obesity can lead to a series of other serious health problems. The mortality rate for BED is 1.5% (Fichter & Quadflieg, 2016).

Various components factor into people developing ED. Potential factors include genetics, environment/cultural pressure, peer pressure, emotional health, age, gender, and more (National Alliance on Mental Illness [NAMI], n.d.). Since eating disorders are a category of mental illness, it is essential to investigate what is happening in the brain. A common theme when looking into ED and the brain is an imbalance in reward processing and an impaired self-regulation capacity (Kaye et al., 2009; Van den Eynde & Treasure, 2009). Neuroimaging studies in 2012 identified the dorsolateral prefrontal cortex (DLPFC) as a critical area of the brain involved with many of the impaired functions of people with behavioral addictions which includes ED (Goudriaan et al., 2012).

With such a wide assortment of factors playing a role in the development of ED, it can often be challenging to treat people effectively. Several types of treatment options do

exist, however. According to NAMI, the most common treatment methods are psychotherapy, medicine for comorbid mental illnesses, and nutritional counseling (n.d.). Sadly, overall recovery rates still tend to be under 50%, and eating disorders lead to roughly 10,200 deaths yearly in the United States (Economics, 2020). Given all this, eating disorders are highly prevalent, and treatment is not very effective, so developing new treatment methods is greatly needed.

1.2 Non-Invasive Neuromodulation

Non-invasive neuromodulation is currently being investigated as a potential means of treatment for ED. In particular, two types of non-invasive neuromodulation show promising effects: transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). Both of these can manipulate cortical excitability, which could help counteract some of the ED symptoms (Kekic et al., 2007). The mechanisms behind the two differ, and it is unclear which one will work better for each individual.

tDCS works by applying a low and constant electrical current through electrodes placed on the scalp. This current does not create action potentials, but it can make them more or less likely depending on the placement of the anode and cathode. The anode is believed to excite the neurons, while the cathode is inhibitory. The benefits of using tDCS include its ease of use, low cost, safety, and portability (Lapenta et al., 2018). rTMS, on the other hand, uses a coil to generate a magnetic field that can penetrate the skull and induce an electric current that creates action potentials in the brain (Dunlop et al., 2016). Both methods have been shown to have several promising findings for treating ED; however, there have been numerous adverse and inconsistent outcomes (Luigjes et

al., 2019). More research is needed before neuromodulation can be an approved treatment for ED.

1.3 Dorsolateral Prefrontal Cortex

The DLPFC may contribute to eating disorders and obesity in several ways. One commonly known function of the DLPFC is inhibitory control, which is highly associated with impulsivity levels. Furthermore, impulsiveness is linked with overconsumption (Sedgmond et al., 2019). Overeating is one of the traits associated with BED, BN, and obesity. Hare et al. demonstrated that the DLPFC is involved in making controlled and healthy choices (2009). Sedgmond et al. investigated this concept by testing whether DLPFC activity is linked with the degree of success of dieting and long-term weight maintenance. They found that more activity in the DLPFC is associated with greater long-term dieting success and weight maintenance. Their findings also suggested the mechanism is due to better impulse control in the participants with greater DLPFC activity (2019). Additional studies have been conducted to investigate the use of neuromodulation on the DLPFC while measuring factors related to food cravings and impulsivity.

One of the earliest studies using neuromodulation to modulate food cravings was conducted by Fregni et al. In this study, researchers applied tDCS to the DLPFC of human participants and saw decreased food consumption following active stimulation sessions (2008). Given the findings of this study, other researchers wanted to investigate if the type of food would impact the results. A study conducted by Goldman et al. applied tDCS to the DLPFC in a very similar fashion. What they found confirmed that stimulating the DLPFC decreases food cravings, but furthermore, they found that food

craving ratings were reduced more for sweet foods and carbohydrates following active stimulation (2011). Perhaps the cravings could be more closely related to caloric contents of food items. To understand the role impulsivity plays in food behaviors, other studies have been conducted to compare food behavior and impulsivity modifications using tDCS. Kekic et al. found that highly impulsive participants were less susceptible to tDCS than the less impulsive participants (2014). Contrarily, Ray et al. found that tDCS significantly reduced food cravings in impulsive women (2017). Studies using tDCS to modulate food cravings and impulsivity appear promising, but the findings are inconsistent.

Other studies have been using rTMS to investigate the same questions. A study by Uher et al. found that rTMS applied to the DLPFC can inhibit the development of food cravings. However, this did not translate into decreased food consumption following stimulation (2005). A study applying rTMS to the DLPFC on participants with bulimic-type eating disorders found reduced self-reported food cravings and fewer binge-eating episodes over a 24-hour follow-up period (Van den Eynde et al., 2010). When looking more at impulsivity, Liu et al. demonstrated that rTMS of the DLPFC can reduce impulsivity and cue-induced cravings in patients with methamphetamine use disorder (2022). Because impulsivity and cue-induced cravings are also involved in eating disorders and obesity, this study might indicate that rTMS could also help this patient population.

These findings suggest NIBS could be a method of modulating food cravings and impulsivity. However, results seem to be inconsistent between studies. This inconsistency should not be a big surprise due to variations in methodology between studies for both

tDCS and rTMS. This leads to the development of new questions. Which NIBS technique is better – tDCS or rTMS? Are different categories of food, such as high versus low calorie content, affected differently by NIBS? How exactly does NIBS modulate food cravings - is it related to impulsivity or feelings of control? Can genetic factors help predict the effectiveness of NIBS? Additional follow-up studies will be needed to address many of these remaining questions.

1.4 Genetic Factors

Investigating genetic markers, including single nucleotide polymorphisms (SNPs), could help explain some of the variation between individuals' responsiveness to NIBS and food craving behaviors. Looking specifically at genes that have been associated with factors that influence cortical plasticity could help predict individuals' responsiveness to NIBS. Genes related to addictive behavior, impulsivity, or mental illness could provide insight into which people at higher risk of developing eating disorders.

SNP rs6265 on the brain-derived neurotrophic factor (BDNF) gene may be associated with differences in cortical plasticity following neuromodulation (Witte et al., 2012). The BDNF protein normally has the amino acid valine which is coded by guanine. However, some people have adenosine in this location which results in the amino acid methionine (Fratelli et al., 2021). When this occurs, there is a decrease in secretion of BDNF which has been associated with major depressive disorder and increased suicidality (Kim et al., 2007). Furthermore, it appears that BDNF levels are linked to visual food cue reactivity which corresponds with food cravings and obesity (Bumb et al., 2021). Findings do appear mixed between studies though, so investigating the

relationship between BDNF levels with food cravings before and after stimulation could help identify if BDNF can be used to predict people at risk of experiencing elevated food cravings and if NIBS can be an effective treatment for the patient.

SNP rs9939609 within the first intron of the FTO Alpha-Ketoglutarate Dependent Dioxygenase protein coding gene are associated with obesity. FTO is expressed in the hypothalamus which is involved in regulation of food intake (Abdella et al., 2019). An association has been identified between the A allele of the FTO gene and increased fat intake and food cravings (Sonestedt et al., 2009). This puts people with the A allele at higher risk for obesity. This relationship can be explored further in this study by investigating relationships between the FTO gene and responses to food craving questionnaires or tasks.

Additional SNPs may also be of interest to predict patients that may struggle with food cravings and overconsumption. SNP rs16969968 within the CHRNA5 gene is related to addiction. The A allele, as opposed to G, has been demonstrated to be a risk factor for developing drug addictions due to modifications in the reward processing (Besson et al., 2019). SNP rs6295 within the HTR1A gene is related to depression and impulsivity. Subjects with two G alleles demonstrate higher levels of impulsivity (Benko et al., 2010) along with depression and anxiety (Mekli et al., 2011). Due to the relationship between impulsivity and eating disorders, this gene could indicate susceptibility to developing eating disorders.

SNP rs4680 within the COMT gene is involved in the breakdown of dopamine and is related to anxiety and memory. People with the G allele have higher COMT enzymatic levels than people with the A allele. This means that people with two A alleles

may build up dopamine in the brain making them more susceptible to anxiety and stress. Contrarily, people with two G alleles clear dopamine quickly and may be more resilient to stress and anxiety (Xcode Life, n.d.). Because dopamine levels are strongly linked to addiction and mental disorders, it is likely that this SNP could help us identify people at risk of developing eating disorders.

2. Hypotheses and Predictions

This study aims to quantify the ability of NIBS to alter food preferences and reduce impulsivity. Because of the strong link between DLPFC activity and food cravings it is hypothesized that both NIBS techniques, rTMS and tDCS, will alter food preference from high-caloric to low-caloric (high-nutritional) value in a food preference test. Additionally, it is expected that measures of impulsivity will decrease following NIBS, which can be reflected in a Go/No-Go task. This study also aims to examine the use of genetic markers to predict who is most susceptible to developing eating disorders and who may respond to the neuromodulation techniques. An improved recovery prognosis may be accomplished by accurately being able to predict the response and utilization of neuromodulation as a treatment for patients.

3. Methods

3.1 Participants

Thirty participants were recruited from the University of South Dakota campus, Vermillion, Yankton, and Sioux Falls via the posting of fliers. Digital fliers were also posted on the Functional Imaging Core website and Facebook page. Interested participants were contacted via phone or email and asked screening questions before

scheduling visits. Qualified participants were randomly assigned to a stimulation group, either rTMS or tDCS. Each group contained 15 participants.

3.2 Apparatus and Materials

3.2.1 Surveys and Questionnaires. A series of questionnaires were used in this study to measure demographics, psychological state, and eating behaviors. The demographic survey contained questions about current medications, diet and exercise, content and timing of meals over the last 24 hours, and general health measures. The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) provided information regarding the participant's substance use. Two psychological assessments were used to evaluate depression and anxiety scores. They were the Beck Anxiety (BAI) and Depression (BDI) Inventories (Hewitt & Norton, 1993; Beck et al., 1996). Evaluation of eating disorder criteria was accomplished by using the Eating Disorder Examination Questionnaire (EDE-Q) and the Eating Attitudes Test (EAT-26) (Mond et al., 2006; Garner et al., 1982). The Food Craving Trait and State Questionnaires (FCQ-T and FCQ-S) and the Three Factor Eating Questionnaire (TFEQ-R) were used to determine craving behavior and food value (Nijs et al., 2007; Stunkard & Messick, 1985).

3.2.2 Neuromodulation Techniques. During the participants' visits, active and sham tDCS or TMS was used to stimulate the left DLPFC (L-DLPFC). All stimulation sessions were 20 minutes in length. During the active tDCS sessions, participants received 3mA stimulation over the F3 position based on the 10/20 EEG system. Sintered Ag/AgCl ring electrodes were used to ensure maximum stimulation. During the sham tDCS sessions, electrodes and their positioning were identical; however, the current was only applied for

30 seconds. In past studies, this method has been reliable for blinding participants in the tDCS trials while not inducing effects on the brain's excitability (Borckardt et al., 2012).

During the active rTMS stimulation sessions, the stimulus intensity was set to 110% of the participant's motor threshold. The coil was held over the L-DLPFC using neuro-navigation software to ensure the accuracy of the stimulation location (Brainsight, Rogue Research, Canada). The stimulation consisted of 20 trains of 5 seconds with 55 seconds of inter-train intervals. The trains were administered with a frequency of 10 Hz. During the sham rTMS sessions, the location, intensity, and frequency are the same; however, the coil is turned away from the scalp. This method provides a similar experience for the participant without actually stimulating the brain.

3.2.3 Tasks. The Food Preference task was used to examine craving behaviors. The participants performed this task during all three sessions. During the Food Preference task, participants viewed various images on a computer screen. They were asked to rank them based on desirability, recognition, and familiarity. The images used for this task consisted of sweet versus salty, high versus low calorie, and whole versus processed and were selected from a database containing 896 photos (Blechert et al., 2019; Blechert et al., 2014). To help minimize age, ethnicity, culture, and dietary preference bias, images consisted of various colors, textures, and complexity. Additionally, non-food items were included to act as a control for generalized arousal from perceived palatability.

The Go/No-Go task was used to examine impulsivity, although the results will not be discussed in this paper. This task was performed during all three sessions. During the Go/No-Go task, participants were shown stimuli on a computer screen. The stimuli consisted of the numbers 1-9, which were presented sequentially, one at a time, and in a

pseudo-random order. Participants were instructed to respond to the number ‘7’ when it is the third digit following the number ‘3’ (i.e., 3, x, x, 7, where x is any digit other than ‘3’ and ‘7’). The participants were also instructed to withhold a response during any other sequence of numbers. The Go stimuli were presented 70% of the time, and the No-Go the additional 30%. To ensure participant understanding, there was a short training session. The reaction times to the Go stimuli and response accuracy were measured during the task.

3.3 Procedure

3.3.1 Screening. Interested participants were required to pass a screening performed via phone or email before coming in for their first session. It was important to ensure minimal risk to the participants, so if they met any of the exclusion criteria, they could not participate in the study. The exclusion criteria included: outside the ages of 18 to 40, pregnant or planning to become pregnant within the month, mastectomy/lymph node removal or otherwise unable to have blood drawn from the arm, history of seizures or brain injury, metal within the head, implanted neurostimulator device, presence of known psychological disorders, on blood thinners, on epilepsy medications, on sedatives, recreational drug use or more than three alcoholic beverages within 24 hours of participation.

3.3.2 Laboratory Sessions. Participants that passed the screening were then invited to attend a total of three sessions. Each session was about two hours and was conducted in the Baugh Neuro Lab within Lee Medicine Building. Ideally, the participants’ sessions were scheduled around the same time for all three sessions.

The first session started with the participant consenting to the procedure. After informed consent was obtained, the participant was asked to fill out the Qualtrics survey. While the Qualtrics demographics were checked, the participant filled out the ASSIST, BAI, BDI, State Craving, and appropriate neuromodulation screening form. After completing the surveys and questionnaires, participants were fitted with a 64-channel electrode cap used for taking electroencephalographic measurements. The tDCS electrodes were also connected to this cap for the participants assigned to the tDCS stimulation group. For the rTMS group, the areas where the tDCS electrodes were located were left vacant, and the stimulation device was calibrated. This was done using neuro-navigation software to map the abductor brevis site in the left motor cortex. Then, the motor threshold for the participant could be determined using the PEST procedure (Borckardt et al., 2006). Once the equipment was set up, the participant received 20 minutes of sham stimulation. Following the sham stimulation, the participant completed the Food Preference and Go/No-Go tasks while the electroencephalography (EEG) recorded the brain activity. The analysis of EEG recordings will not be included in this paper. After completing the tasks, the participant was asked to fill out the state food craving questionnaire again. Then, a blood sample was collected. The participants were free to leave after the blood draw for genetic analysis.

Sessions two and three were very similar to the first visit. After the participant signed the consent form, they filled out the state food craving questionnaire. Upon completion, the participant was hooked up to the electrode cap, and the appropriate neuromodulation device was set up. Next, the L-DLPFC was actively stimulated for 20 minutes. After stimulation, the participant completed the Food Preference and Go/No-Go

tasks. Again, they filled out the state food craving questionnaire and had blood drawn for genetic analysis. This paper will only include highlights from the genetic analysis. The blood draw marked the end of sessions two and three.

3.4 Analysis

Descriptive statistics such as the mean, median, standard deviation, 95% CI, frequencies, relative frequencies, etc., were used to summarize the outcome variables between/among groups. For continuous variables, series of 2x2x2 between-subject repeated-measures ANOVAs (rm-ANOVA) StimType (tDCS vs. TMS), Calorie (High vs. Low) and StimSession (Sham vs. Active) as factors were used to study treatment effects, with neurostimulation type the between-subject factor. To control the false positive rate, Bonferroni t-tests were used for pairwise comparisons. If data are not normally distributed, non-parametric statistical methods (Kruskal Wallis test) were used. Target genes were examined following global screening array using linear regression analyses to assess the influence on neuromodulation response. For all analyses, a p-value of ≤ 0.05 will be considered statistically significant.

4. Preliminary Results

4.1 Food Preference Task

During the food preference task, participants were answered questions related to images displayed on a screen. One of the questions asked with each image was, “How much do you want to eat right now?” Analysis revealed that the overall desire to eat was less following active neuromodulation than it was following sham stimulation ($p = 0.002$). This was true for both neuromodulation methods – TMS and tDCS, $F(1,19) = 12.73068$.

Figure 1. Desire to Eat

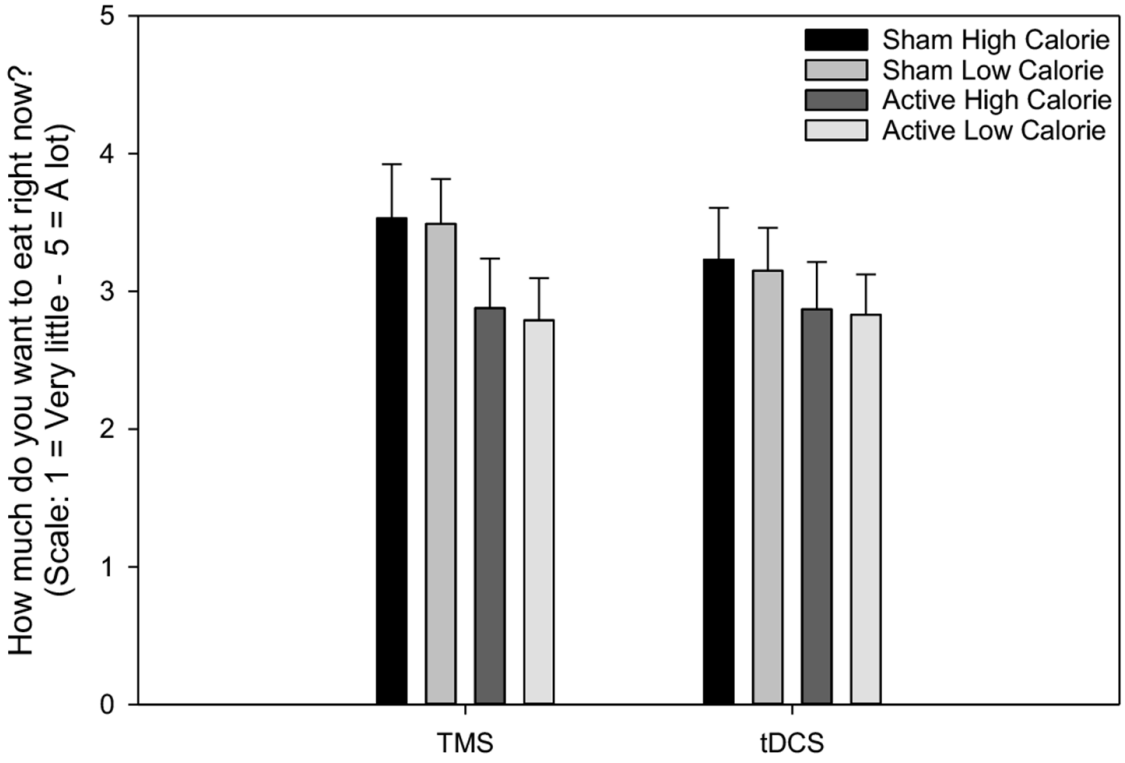

Fig 1. Plot demonstrating participants' desire to eat when shown images of high- and low-calorie foods following either sham or active neuromodulation.

Another question asked during the food preference task was, "How appealing do you find this item?" Analysis revealed that the overall appeal of items were less following active stimulation compared to sham stimulation ($p = <0.001$), $F(1,19) = 18.9765$. These results were primarily driven by the decrease in appeal of high calorie foods following active stimulation, as the change in appeal of low-calorie foods was not significant from sham to active stimulation.

Figure 2. Appeal of Food

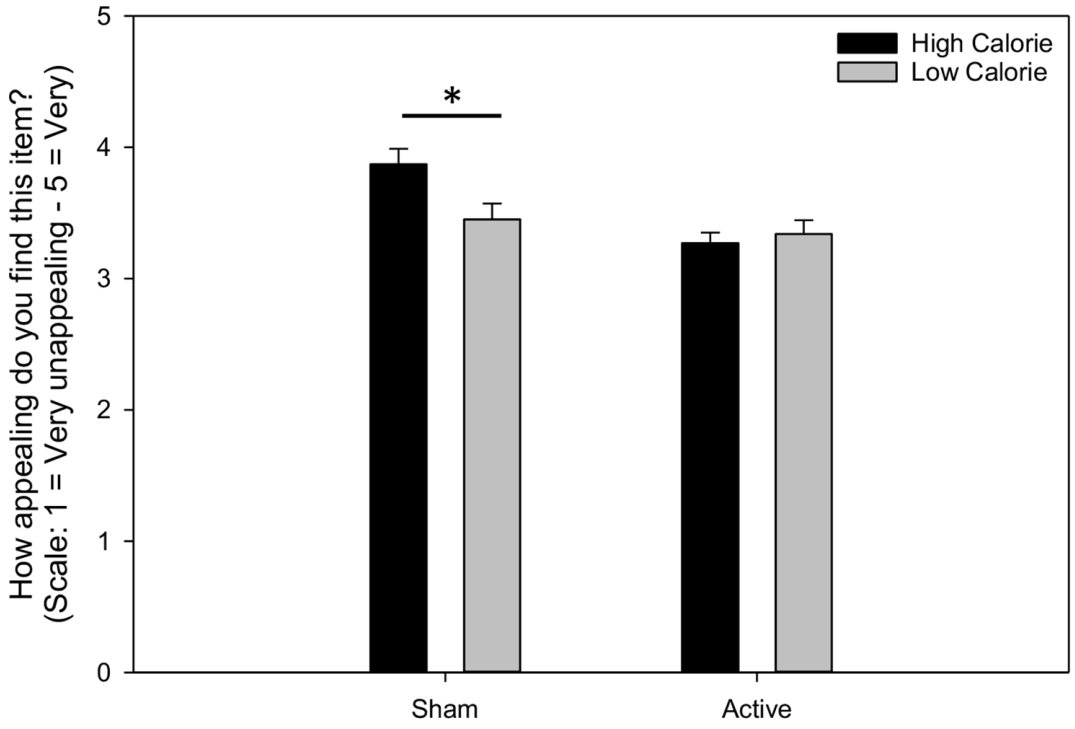

Fig 2. Plot demonstrating the appeal of food when shown images of high- and low-calorie foods following either sham or active neuromodulation. Overall appeal of food was less following active stimulation when compared to sham stimulation.

4.2 Food Craving Questionnaire

Participants were asked to fill out a food cravings questionnaire (FCQ-S) at the beginning and end of each session. Within this questionnaire were statements related to feelings of lack of control that participants were asked to score. The statements included: "If I had food, I could stop eating it," "My desire to eat seems overpowering," "I know I'm going to keep on thinking about food until I actually have it." Analysis revealed that responses to the FCQ-S did not change significantly during session 1 ($F(1,10) = 1.9692$, $p = 0.191$) and session 2 ($F(1,11) = 0.162$, $p = 0.695$). However, the FCQ-S responses to feelings of lack of control significantly declined at the end of session 3 ($F(1,11) = 8.57$, $p = 0.014$).

Figure 3. FCQ-S Session 1

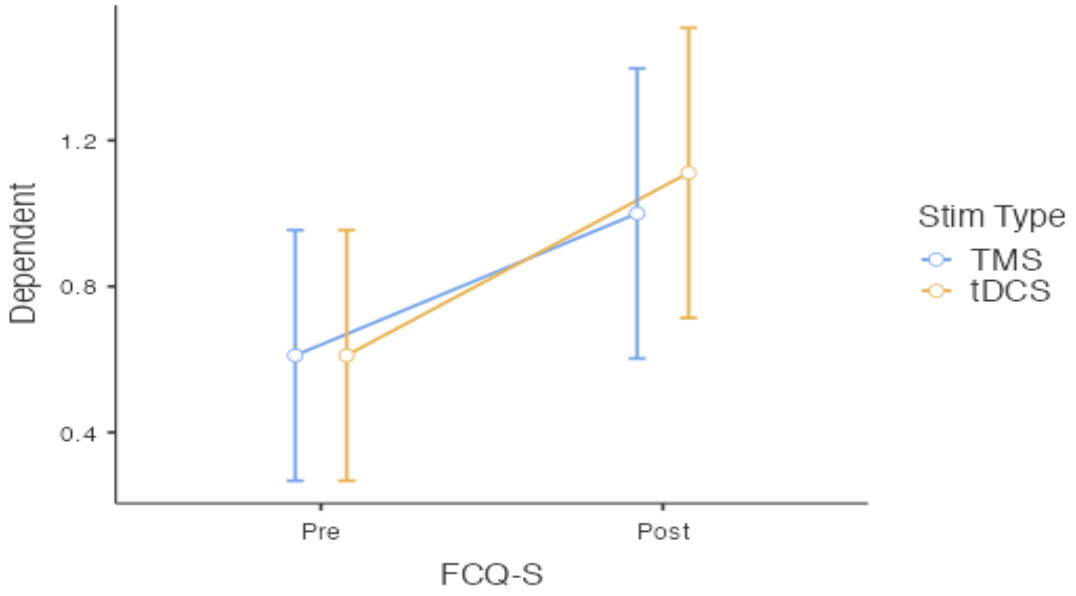

Fig 3. Plot comparing FCQ-S responses to feelings of lack of control before and after sham stimulation during session 1. While it appears there is an increase in feeling of lack of control following sham stimulation, the increase is not significant ($p = 0.191$)

Figure 4. FCQ-S Session 2

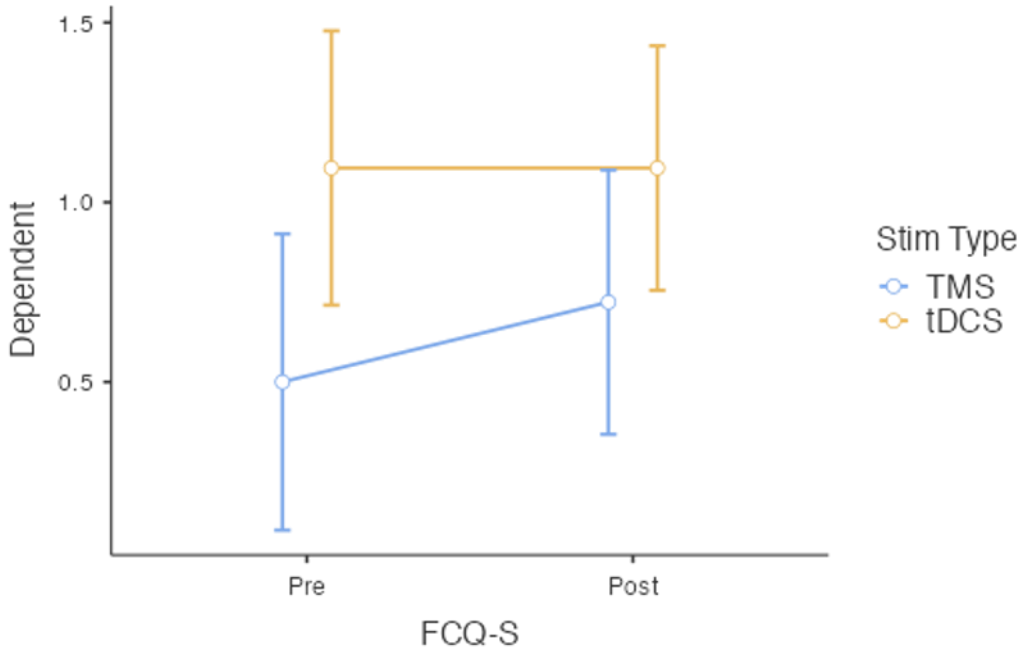

Fig 4. Plot comparing FCQ-S responses to feelings of lack of control before and after active stimulation during session 2. There is not a significant change in feelings of lack of control during session 2 ($p = 0.695$)

Figure 5. FCQ-S Session 3

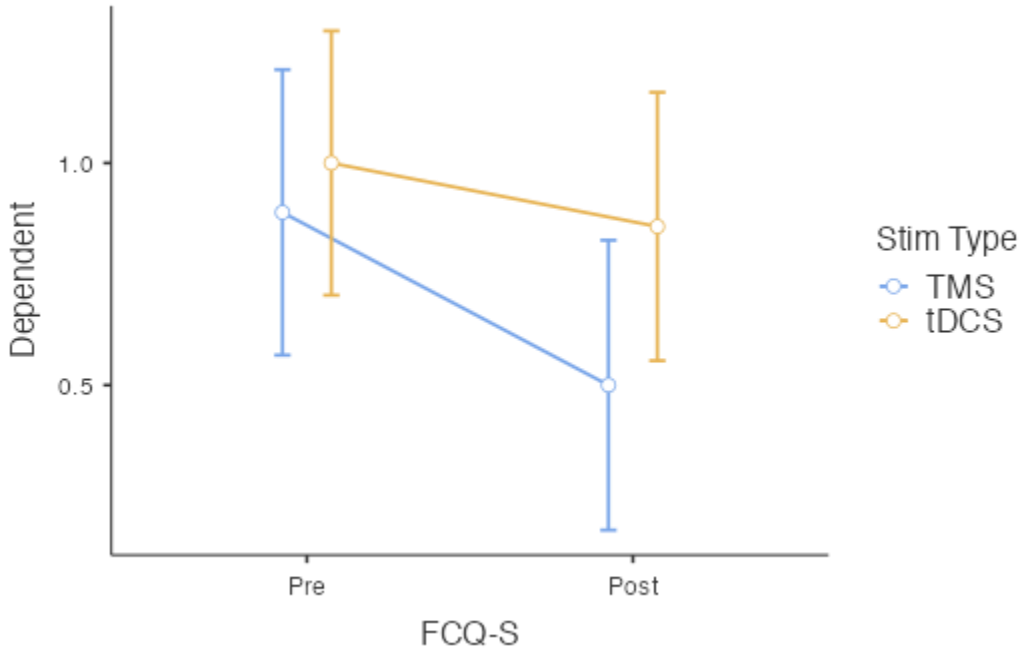

Fig 5. Plot comparing FCQ-S responses to feelings of lack of control before and after active stimulation during session 3. There is a significant decline in feelings of lack of control following stimulation in session 3 (p = 0.014)

4.3 Genetic Results

Several SNPs were analyzed to see if they play a role in neuromodulation efficacy. In the BDNF gene SNP (rs6265), G codes for valine while A codes for methionine. The genotype GG is considered the lower risk (risk=0) genotype while AA is considered the highest risk (risk=2) genotype. The genotype AG is assigned a risk of 1. The risk scores were assigned based on prior studies finding a relationship with the A allele and increased depression and suicidality (Kim et al., 2007). Analysis revealed a positive correlation between risk score and percent change in FCQ-S, R^2 = 0.207, beta = 50.9, although not significant (p = 0.076).

Figure 6. Risk rs6265

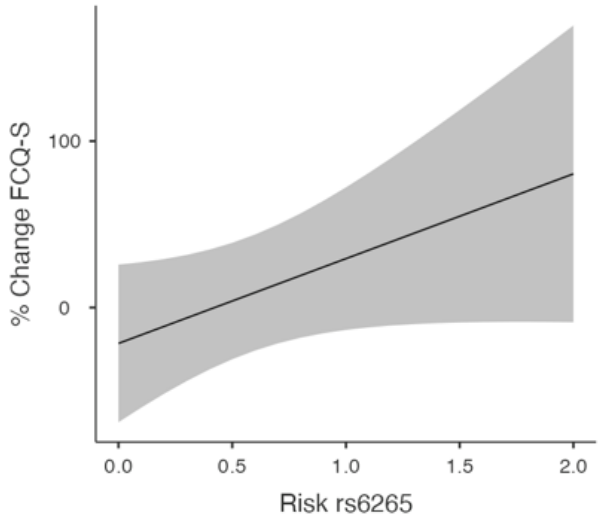

Fig 6. A plot of the risk scores for rs6265 against the percent change in the FDQ-S responses. While insignificant (p = 0.076), there is a trend showing that the GG genotype was less responsive to neuromodulation than AA.

The G allele in the HTR1A gene (rs6295) has been linked to greater levels of impulsivity, depression, and anxiety (Benko et al., 2010; Mekli et al., 2011). The GG genotype was assigned a risk score of 0, CG genotype was assigned a risk of 1, and CC assigned a risk of 2. Analysis revealed that the GG genotype is more impulsive in general and showed the greatest percent increase in control in FCQ-S following stimulation, R^2 = 0.281, beta = -53.0, and p = 0.035.

Figure 7. Risk rs6295

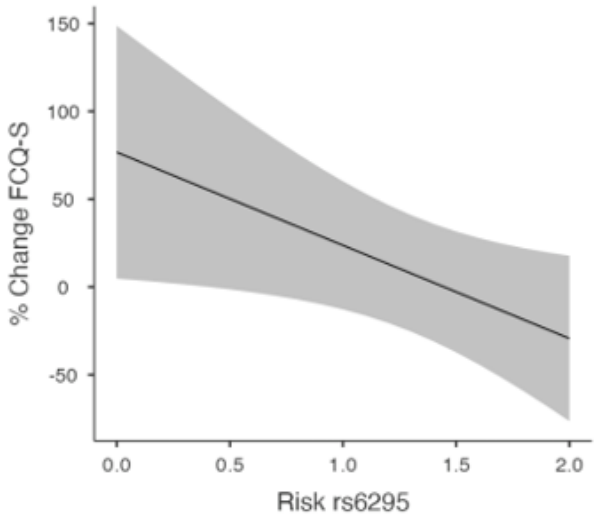

Fig 7. A plot of the risk scores for rs6295 against the percent change in the FDQ-S responses. The GG genotype showed the greatest percent increase in control in FCQ-S following stimulation.

The FTO gene (rs9939609) is strongly linked to obesity due to its role in regulating food intake by acting on the hypothalamus (Abdella et al., 2019). The A allele is considered high risk for increased fat intake and food cravings (Sonestedt et al., 2009), so it was assigned a higher risk score. The genotype AA was given a risk score of 2, AT a score of 1, and TT a score of 0. Analysis revealed that the AA genotype showed the greatest reduction in impulsivity following neuromodulation, R^2 = 0.397, beta = 57.5, and p = 0.009.

Figure 8. Risk rs9939609

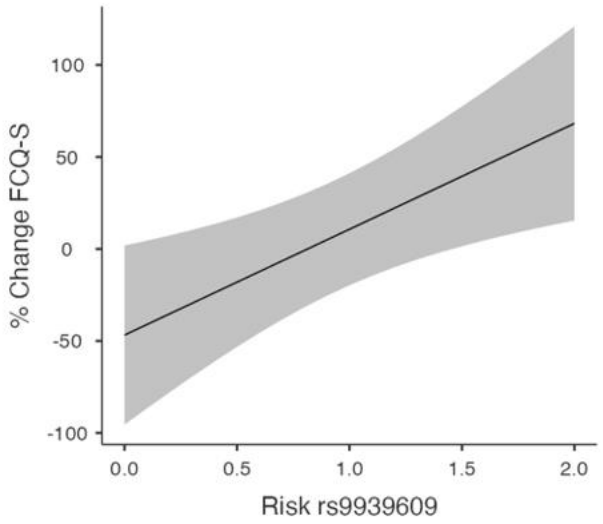

Fig 8. A plot of the relationship between the risk scores for rs9939609 against the percent change in FDQ-S responses. The plot demonstrates that the genotype AA had a significant reduction in the state food cravings compared to TT following neuromodulation according to the FCQ-S.

5. Preliminary Conclusions

In this study, we examined the use of tDCS and TMS as a means of modulating food cravings and impulsivity. Based on the results from the food preference test, both active tDCS and TMS decreased people's desire to eat in general. This is consistent with many prior studies (Fregni et al., 2008; Goldman et al., 2011; Ray et al., 2017). To build off the study where Goldman et al. found reduced cravings for sweet foods and carbohydrates, this study proposed that the effect might be related to caloric content. It was found that neuromodulation techniques can selectively decrease the appeal of high calorie foods through activation of the dorsolateral prefrontal cortex. The food craving questionnaire results indicate that the reduction in wanting to eat may be through modifications of feelings of lack of control because participants reported increased

feelings of control after neuromodulation. It is also important to note that neuromodulation itself may be off-putting, which could result in participants experiencing decreased food cravings.

We also examined genetic factors to look for relationships that can help predict the effectiveness of neuromodulation methods. Results from the BDNF gene suggest that people with the genotype GG may be more responsive to neuromodulation than people with the AA genotype. The HTR1A gene findings indicate that people with the GG genotype are able to better control their state food cravings following neuromodulation. Perhaps because they start out with higher levels of impulsivity, neuromodulation is able to produce a larger effect on this group. The results from the FTO gene show that the AA genotype showed the greatest reduction in impulsivity as measured by changes in state food cravings following neuromodulation. This indicates that neuromodulation may be an effective treatment for people with this genotype.

6. Future Directions

Further investigation of this study will include collecting data from the final participant. Additionally, EEG data collected during the Food Preference Task and Go/No-Go Task can be analyzed to measure reaction times between high-calorie and low-calorie food groups as well as reaction time for the Go/No-Go trials. This will help identify whether wanting to eat is moderated by general levels of impulsivity. Because impulsivity and feelings of lack of control are closely related, this data could provide further insight on whether the modifications in food cravings are related to changes in feelings of lack of control. Analyzing the brain activity while the participant underwent the tasks can help confirm their responses during the Food Preference Task and Food

Craving Questionnaire. Further investigation of genes, SNPs, and hormone/taste/neurotransmitter receptors can also help researchers gain more insight on predicting the efficacy of neuromodulation for individuals. Lastly, it will be critical to expand this study to the patient population. Because some of the participants met criteria for having eating disorders, it would be beneficial to compare the findings of those participants against the results from the participants without eating disorders.

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