DO BRAIN ACTIVITY AND EXECUTIVE FUNCTION PREDICT WEIGHT LOSS IN A 12-MONTH INTERVENTION?

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With almost 38% of the adult population as obese, weight loss is a public health imperative. We cannot yet predict who will succeed in losing weight through dietary interventions, though reward sensitivity and executive functioning (EF) may influence weight loss. The present study examined whether neural reward network responsivity to visual food cues or EF prior to a dietary intervention predicted weight loss in an overweight and obese sample. It also examined the relationship between brain activity during the visual presentation of food items and measures of EF, and tested whether EF statistically mediated the relationship between neural reward network activation and weight loss.

108 middle-aged, overweight and obese (mean BMI=30.93 $\pm$ 3.59 kg/m^2) adults completed functional neuroimaging and an EF assessment prior to a 12-month weight-loss intervention. Functional neuroimaging included a visual food cuing (VFC) task to examine neural responses to food stimuli that included high-caloric foods, low-caloric foods, and neutral images. The EF assessment included the Iowa Gambling Task (IGT) and Stroop task as metrics of strategic planning and inhibitory control, respectively. All analyses controlled for sex; analyses involving EF additionally controlled for years of education.

Following the intervention, participants lost approximately 9% of initial body weight (9.06% $\pm$ 6.86%); baseline weight was not associated with percentage of weight lost. During the visual food cue task, greater activation in the bilateral anterior cingulate cortex and less activation in the right caudate, dorsolateral prefrontal cortex, and orbitofrontal cortex was predictive of more

weight loss. Greater activation in the left nucleus accumbens and right caudate was also associated with better performance on the IGT. EF performance was not associated with weight loss.

Reduced neural sensitivity to visual food stimuli in reward regions and increased reactivity in areas associated with EF were predictive of greater success in a dietary weight-loss intervention in overweight and obese adults. Individuals who are less sensitive to rewarding food images and who do not need to inhibit impulsivity may be those who lose more weight. These individuals may be more effective at evaluating the consequences of their dietary choices to aid their successful weight loss.

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1.0 INTRODUCTION

1.1 OBESITY AND WEIGHT LOSS

Obesity is a heterogeneous disease with various etiologies that may be organic (e.g., metabolic dysfunction) or related to an individual's environment (Heindel, Newbold, & Schug, 2015; Kramer, Zinman, & Retnakaran, 2013). To meet criteria for obesity, individuals must have a body mass index (BMI), or a ratio of body weight to height (kilograms per meter squared; kg/m^2), of 30.0 kg/m^2 or more. A BMI between 25.0-29.9 kg/m^2 is categorized as overweight, while a BMI between 18.5-24.9 km/m^2 is categorized as healthy (Panel, 1998). Obesity is highly prevalent, with approximately 38% of American adults meeting criteria (Flegal, Kruszon-Moran, Carroll, Fryar, & Ogden, 2016). Within the obese population, there is considerable variability in the cause and development of the condition (Heindel et al., 2015). The underlying factors that influence obesity risk may contribute to the ability and/or likelihood of successful weight loss.

Dietary interventions often aim to meet the clinical recommendations of losing 10% of initial body weight (Goldstein, 1992). Meta-analyses showed that most successful weight loss interventions involve participants losing 5-9% of their body weight, though there is typically some regain of weight (between 2-3%) after the first six months of weight loss (Franz et al., 2007; Wu, Gao, Chen, & Van Dam, 2009); (Jakicic, Marcus, Lang, & Janney, 2008). However, it is rare that participants in weight loss interventions regain enough weight to return to baseline (Franz et al.,

2007). Problematically, most of the past work using dietary plans has included only short-term interventions, i.e., up to 16 weeks (Franz et al., 2007; Miller, Koceja, & Hamilton, 1997; Wu et al., 2009), and evidence shows that individuals often lose the most weight at the six-month time point (Jakicic et al., 2008). Therefore, these shorter-term interventions may have been too brief for participants to appreciate the full effects of their dietary plans.

Yet, not everyone is able to lose the recommended 10% of baseline body weight in an intervention, despite active participation (Jakicic et al., 2008). Obesity and weight loss can be influenced by a variety of demographic factors, including age, sex, race, and socioeconomic status (SES). These features are largely intrinsic, although some, like SES, affect obesity and weight loss in conjunction with environmental influences (Sobal & Stunkard, 1989; Wardle, Waller, & Jarvis, 2002). Individuals living in areas of lower SES are more likely to be obese (Wardle et al., 2002), and there is evidence that having limited access to fresh food and safe forms of physical activity are risk factors for obesity (Morland, Roux, & Wing, 2006; Sallis & Glanz, 2009). While these environmental contributions are important, they may be difficult to quantify (McLaren, 2007; Stunkard & Sorensen, 1993). Thus, we can look to the intrinsic factors that contribute to the variability in weight loss across individuals seeking obesity treatment.

The intrinsic factors that predict weight loss are not agreed upon in the literature and may be related to obesity risk and/or weight gain, such as age, race, or education (Bautista-Castano, Molina-Cabrillana, Montoya-Alonso, & Serra-Majem, 2004; Finkler, Heymsfield, & St-Onge, 2012; Karlsen, Søhagen, & Hjelmesæth, 2013). These characteristics are also related to psychosocial and cognitive functioning (Agüera et al., 2015). Examination of these factors in laboratory settings may extend our understanding of how they are associated with weight.

1.2 EXECUTIVE FUNCTIONING AND WEIGHT LOSS

The role of cognitive functioning in weight loss is not clear, as it may be one of many factors that can influence the success of a weight loss intervention (Espeland et al., 2014; Prickett, Brennan, & Stolwyk, 2015). For example, if someone is unable to contemplate future consequences, that person may not consider the differential health outcomes between eating an apple or a cookie. Another person with poor inhibitory control may find it difficult to stop eating snacks between meals because the food is readily available, despite knowing that this behavior hinders weight loss goals. These executive functions (e.g., planning, inhibition, impulsivity) are important cognitive components of the ability to adhere to a dietary intervention and lose weight.

Executive functioning (EF) is a cognitive domain encompassing higher-order processes including impulsive decision-making, inhibitory control, working memory, and set-shifting to attain goals (Sharma, Markon, & Clark, 2014; Welsh & Pennington, 1988). Measuring these processes can be done with a variety of behavioral tests. Tasks such as the Iowa Gambling Task (IGT; (Bechara, Damasio, Damasio, & Anderson, 1994) and the Stroop task (Stroop, 1935) are commonly used to examine the ability to make decisions related to future goals and control behavioral responses to stimuli. Performance on, and brain activity during, these tasks vary as a function of age (Cauffman et al., 2010), sex (Bolla, Eldreth, Matochik, & Cadet, 2004; van den Bos, Homberg, & de Visser, 2013), education (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006), and weight (see Fitzpatrick, Gilbert, & Serpell, 2013 for review). There is sufficient evidence that obese individuals perform poorly on cognitive tasks across several domains, and these effects may be greatest for EF (Fitzpatrick et al., 2013; Gunstad et al., 2007; Smith, Hay, Campbell, & Trollor, 2011). Using these tasks to examine planning and inhibition may shed light on how EF can predict weight loss through adherence to a prescribed diet.

The IGT is frequently used to test impulsive decision-making and planning for future goals through the development of advantageous strategies during the task (Bechara et al., 1994). In the task, participants try to win money by selecting cards from one of four decks. Two of the decks are advantageous and allow the participant to win money, and two of the decks are disadvantageous and cause the participant to lose money. The participants are given a monetary credit at the beginning of the task that they must pay back; their net total score at the end of the task is an indicator of strategic decision-making, such that low or negative scores are related to making disadvantageous choices (Bechara, 2007).

IGT performance correlates positively with performance on other EF tests (Toplak, Sorge, Benoit, West, & Stanovich, 2010), so it can serve as one metric for this domain of cognitive function. Compared with lean participants, obese participants perform worse on the IGT by selecting more cards from disadvantageous decks (Brogan, Hevey, & Pignatti, 2010; Davis, Patte, Curtis, & Reid, 2010; Pignatti et al., 2006). The failure to develop advantageous strategies to attain future goals, such as winning money, suggests that obese individuals may be less tactical in their decision-making across other facets of their lives, like losing weight (Davis et al., 2010). This could be a result of altered sensitivity in brain regions that would cause certain individuals to make maladaptive behavioral choices, such as discounting strategies to attain future rewards (Mathar, Horstmann, Plegar, Villringer, & Neumann, 2016).

In addition to the IGT, the Stroop task can be used as a metric of EF since it measures an individual's ability to control responses to visual color word cues (Stroop, 1935). Participants complete three task conditions (i.e., congruent, incongruent, and neutral) where the words presented on the screen match, do not match, or are not related to the color of the ink in which the words are written. The Stroop task elicits inhibitory control, or the ability to ignore stimuli that

would distract from a target action, which is a component of impulsivity and a key executive function related to the achievement of goals (Sharma et al., 2014).

The evidence surrounding performance differences between obese and healthy individuals on the Stroop task is mixed (Fitzpatrick et al., 2013). There is some evidence that obese individuals perform poorly on the Stroop task, such that they are less able to inhibit their responses during the incongruent condition (Fagundo et al., 2012; Maayan, Hoogendoorn, Sweat, & Convit, 2011; Xu et al., 2017). Yet, other studies have not shown differences in performance between obese and healthy participants (Balodis et al., 2013; Fitzpatrick et al., 2013). The conflicting evidence suggests that not enough work has been done to understand the complexity of the Stroop task in obese participants and that using only one metric of EF is not sufficient to determine the neurocognitive deficits associated with obesity. Using multiple tests to encapsulate the subcategories of EF may allow for the determination of how the relationship between EF and obesity contributes to weight loss.

Little work to date has examined the variability in EF within an entirely overweight and obese sample. Instead, most research has compared obese with lean participants to make claims about the risks associated with obesity. Between the two long-term weight loss studies that focus on obese populations [i.e., the Diabetes Prevention Program (D. P. P. D. R. Group, 2002) and the Look AHEAD trial (T. L. A. R. Group, 2003)], neither used cognition to understand or predict the trajectory of weight loss for their participants. An ancillary study from the Look AHEAD trial showed that a lifestyle intervention for weight loss was associated with improved cognitive functioning for overweight, but not obese, participants at an 8-year follow-up. However, this was one of the only studies to examine cognitive outcomes in a long-term weight loss intervention and it was unique to adults with Type 2 diabetes.

1.3 REWARD SENSITIVITY AND WEIGHT LOSS

Unlike some of the psychosocial factors that may influence obesity and healthy eating habits, such as social cuing, the cognitive risk factors for obesity have a neural basis (e.g., reward sensitivity, EF) (Burger & Berner, 2014; Nummenmaa et al., 2012; Yokum, Ng, & Stice, 2011). The behaviors that arise from these risk factors, such as overeating, may be due to increased cue-related reactivity in the neural reward network (Castellanos et al., 2009). The variability in neural responses to rewards within an obese sample may provide insight of why some individuals successfully lose weight under restricted diets, but others under the same conditions do not.

Reward sensitivity can be elicited through visual food cuing (VFC) – a type of behavioral task that utilizes images of high-caloric foods, low-caloric foods, and neutral objects. When presented with images of food, obese individuals attend to the images for a longer period of time than their lean counterparts and this attentional bias is not specific to high-caloric foods, but food in general (Castellanos et al., 2009; Yokum et al., 2011). This increased attention to food images may be due to intensified sensitivity to food rewards compared to other stimuli (Castellanos et al., 2009; Yokum et al., 2011). Additionally, this heightened attention to food images may result in a greater desire to eat. For instance, one study found that compared with lean individuals, obese individuals experienced greater motivation to eat after being exposed to food cues (Ferriday & Brunstrom, 2011). Although this study did not show evidence that the heightened motivation to eat resulted in overeating, individuals with greater desire to eat and lower inhibitory control may be at the greatest risk for overeating in response to food stimuli.

However, some studies of reward processing revealed no differences in neural activation between anticipation of food versus monetary rewards in obese participants (Opel et al., 2015; Stice & Yokum, 2016; Stice, Yokum, Burger, Epstein, & Small, 2011). This implies that the

heightened sensitivity to rewards may be general, and not specific to food cues, which could provide additional opportunities for researchers to study the variability of responses to rewards within an obese population. If certain individuals are more sensitive to rewarding stimuli regardless of the specific cue, it is possible that obesity is just one manifestation of their hyper-sensitivity. In conjunction with poor EF, this hyper-sensitivity to rewarding stimuli may be used to predict future weight gain or loss (Demos, Heatherton, & Kelley, 2012; Lopez, Hofmann, Wagner, Kelley, & Heatherton, 2014; Murdaugh, Cox, Cook, & Weller, 2012; Nederkoorn, Houben, Hofmann, Roefs, & Jansen, 2010; Stice, Yokum, Bohon, Marti, & Smolen, 2010; Yokum, Gearhard, Harris, Brownell, & Stice, 2014; Yokum et al., 2011).

1.4 NEURAL RESPONSIVITY AND WEIGHT LOSS

Neuroimaging studies suggest alterations in brain structure and function in obese individuals relative to their healthy counterparts that may influence reward sensitivity and EF (Kishinevsky et al., 2012; Pannacciulli et al., 2006; Raji et al., 2010; Yokum, Ng, & Stice, 2012). Some of these studies used functional magnetic resonance imaging (fMRI) to detect subtle differences in blood oxygen level dependent (BOLD) activity as they related to a relevant behavioral task. The neural networks that control EF and reward processing involve multiple overlapping regions and structures, such as the striatum, prefrontal cortex (PFC), cingulate cortex, and others (Kenny, 2011; Marques-Iturria et al., 2015). The striatum – a subcortical forebrain structure that consists of the nucleus accumbens (NAcc), caudate, and putamen – is a key brain region for reward processing. The PFC is a cortical region associated with cognitive control and EF. These structures make up part of a corticostriatal circuit – a network responsible for integrating higher-order cognitive

processing with responses to reward (Kenny 2011). Projections between the PFC and the striatum have been implicated in anticipating reward and making goal-directed behavioral choices related to that anticipation (Balleine, Delgado, & Hikosaka, 2007; Rolls, 2000), making this piece of corticostriatal circuitry central to understanding the motivation to receive reward.

There is a large literature on brain circuitry between reward and EF networks in both healthy and clinical populations. The regions involved in reward processing have been linked to numerous disorders, such as addiction and obesity (see Berridge, Ho, Richard, & DiFeliceantonio, 2010; Stice & Yokum, 2016 for review). Obese participants show greater activation in reward regions (i.e., the striatum) and less activation in EF regions (i.e., the PFC) than their lean counterparts when viewing images of highly palatable foods (Castellanos et al., 2009; Cornier, Salzberg, Endly, Bessesen, & Tregellas, 2010; Rothemund et al., 2007; Stoeckel et al., 2009; Stoeckel et al., 2008). This heightened striatal sensitivity may put obese individuals at higher risk for future weight gain due to alterations in their responsivity to rewarding stimuli (Burger, Shearrer, & Sanders, 2015; Stice et al., 2011). One theory posits that the PFC can exert top-down control over reward sensitivity supported by the striatum so as to regulate decision-making by activating inhibitory control processes (Wallis, 2007). The PFC encodes rewarding stimuli as a foundation for behavioral learning about specific cues (Rolls 2000), and altered responsivity may make certain cues more salient than others. Lower PFC responsivity may reflect dysfunctional associations between visual cues and actions that lead to rewarding consequences (Maayan et al., 2011; Wallis, 2007; Yokum et al., 2011). The connections between the PFC and striatum balance EF and response to reward, and disruptions in them may be detrimental to achieving goals (Marques-Iturria et al., 2015; Rothemund et al., 2007; Stice et al., 2010; Stoeckel et al., 2009).

The cognitive tasks described above have been related to this same corticostriatal circuit. For example, the IGT is related to both EF and reward processing brain regions in healthy and patient populations (Buelow & Suhr, 2009; Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005; Lawrence, Jollant, O'Daly, Zelava, & Phillips, 2009; Li, Lu, D'Argembreau, Ng, & Bechara, 2010). Heightened activation in the orbitofrontal cortex (OFC), a region of the PFC, is found throughout the IGT, while heightened activation in the striatum is found when participants win money (Hsu et al., 2005; Lawrence et al., 2009; Li et al., 2010). Evidence suggests that performance on the IGT is related to the amount of activation in the PFC during the task, with better performance associated with greater activation (for review, see Buelow & Suhr, 2009). As the PFC is a crucial structure for decision-making processes, participants who show more activation in this region while selecting cards may choose more advantageous decks in the IGT. Studies show that patients who have brain lesions in the OFC perform poorly– they select more cards from the disadvantageous decks (Bechara, Damasio, Tranel, & Anderson, 1998; Buelow & Suhr, 2009). The brain regions linked to IGT performance in lesion patients are also those that are altered in obese populations (Appelhans, 2009; Brogan et al., 2010; Li et al., 2010). Individuals who cannot consider long-term consequences and are hyper-sensitive to rewards may be at highest risk for future weight gain, as the tendency to make disadvantageous choices may reflect the relationship between neural reward sensitivity and the propensity for weight loss.

Across the lifespan, brain responses to the incongruent and congruent conditions of the Stroop task differ in location and intensity (Banich et al., 2000; Milham et al., 2002; Xu et al., 2017). Often, regions associated with attention, inhibitory control, and impulsivity are those with the greatest differences in brain activity between conditions. These regions – namely, areas of the PFC, cingulate cortex, insular cortex, and striatum (Banich et al., 2000; Chen, Lei, Ding, Li, &

Chen, 2013; Kim, Chung, & Kim, 2010; Piai, Roelofs, Acheson, & Takashima, 2013; Verstynen, 2013) – are among those that show altered responsivity in obese individuals in response to visual food stimuli, as described above (Lopez et al., 2014). In a study examining the neural substrates of inhibitory control, obese participants had greater activity in the middle frontal gyrus, insula, and cingulate gyrus during the incongruent compared to the congruent condition (Balodis et al., 2013). These results indicate that obese participants may recruit more neural resources to complete more difficult task conditions compared with their lean counterparts. However, most of this work has been cross-sectional and did not examine the associations between task performance and weight loss in obese samples.

In fact, few studies have used EF to predict changes in weight over time. One study of adults in a supervised weight loss program found that better baseline set-shifting and faster response inhibition were associated with more weight loss at an 8-week follow-up (Galioto et al., 2016). Another showed that only the interaction between inhibitory control and ratings of liking food predicted weight loss within 52 weeks of an intervention (Brockmeyer et al., 2016). Together, this suggests that EF may influence weight loss over time, but these researchers did not incorporate neuroimaging. In a study that combined Stroop task performance and neural responsivity during the task to examine weight loss in a 4-week intervention of overweight and obese adolescents, more weight loss was associated with increases in oxygenated hemoglobin levels in PFC regions related to the Stroop effect (Xu et al., 2017). These results indicate that EF and attentional control, both of which are engaged during the Stroop task, and the differences in neural responsivity that the task elicits may be related to the ability to lose weight. While these results are promising, only functional near infrared spectroscopy (fNIRS) was used to quantify changes in hemodynamic

response, which has a lower spatial resolution than fMRI. Thus, more work is needed to understand how EF and neural responsivity are related to weight loss.

In addition to the IGT and Stroop task, VFC tasks can be used to evoke neural activation related to reward processing and EF. One study found that participants with greater activation in the NAcc while viewing food images correlated positively with subjective ratings of desire for food, higher likelihood to give into the temptation to eat, and eating larger quantities (Lopez et al., 2014). The researchers also found that heightened activation in the inferior frontal gyrus (IFG), a region implicated in cognitive control, during a response inhibition task was associated with better control over the temptation to eat and eating less overall. However, this work was cross-sectional, so the temporal associations between brain activity and change in weight are impossible to discern.

There have been several prospective studies that examined the relationship between reward and EF circuitry and weight change over time. FMRI work comparing obese with lean participants showed that heightened activation in regions supporting reward and attention processes was associated with future weight gain. Specifically, one study found that greater activation in the NAcc during a baseline session of viewing food stimuli correlated positively with increased BMI at a 6-month follow-up (Demos et al., 2012). Another study found heightened activation in the lateral OFC and ventrolateral PFC during an initial exposure to palatable food cues, and that this activation correlated positively with increases in BMI at a one-year follow-up (Yokum et al., 2011). These studies provide evidence that neural reward and EF regions may be target predictors of weight gain in intervention research, as increased activation in these areas was associated with an increase in BMI. Although the mechanisms by which the weight was gained were not discussed in these studies, it is possible that the individuals who were more responsive to rewarding stimuli

made poorer food-consumption decisions and/or were less successful in controlling their impulses to eat.

To date, there have been two studies examining the predictive power of neural responsivity on weight loss. One 12-week dietary intervention found that higher baseline BOLD activation in the NAcc and other reward regions when viewing images of high-caloric foods was associated with less successful weight loss at a 9-month follow-up (Murdaugh et al., 2012). The same study also found that greater activation in areas of the PFC that are associated with attention while exposed to images of food was associated with a lack of success in the intervention (Murdaugh et al., 2012). These findings suggest that some individuals are more sensitive to hedonic rewards associated with food, and cues related to food may drive future consumption. Another study used fNIRS during the Stroop task to predict weight loss after a 4-week fitness intervention (Xu et al., 2017). The authors found that better performance on the task and greater hemodynamic responses in the PFC were associated with more weight loss at the end of the intervention. Taken together, the evidence is not clear if heightened activation in PFC regions related to EF is associated with successful weight loss; however, increased activity in reward regions during exposure to food stimuli may predict weight loss in an intervention.

1.5 PREDICTING WEIGHT LOSS

Predicting future real-world outcomes based on brain regions of interest is becoming increasingly common in MRI research. In structural brain imaging research, responses to cancer treatment were predicted based on water motion within brain tumor tissue (Moffat et al., 2005). Other work in traumatic brain injury populations has shown that diffusion tensor imaging of white matter

integrity predicted Glasgow Coma Scale scores at 6-month follow-up (Yuh et al., 2014). In fMRI studies, obese individuals differ from lean individuals in relative activation of reward circuitry when exposed to food-related stimuli, and this variability predicts short-term changes in weight (Demos et al., 2012; Murdaugh et al., 2012; Stice, Burger, & Yokum, 2015; Yokum et al., 2014). However, there is limited research on the variability within an obese population, rather than examining differences between obese and lean participants.

Variability in brain activity during reward-related tasks and EF task performance has not been definitively associated with weight loss (Burger & Berner, 2014; Burger & Stice, 2011; Cornier et al., 2010; Demos et al., 2012; Stice et al., 2015; Stoeckel et al., 2009; Yokum et al., 2014). However, some obese individuals may be hyper-responsive to rewards, which impedes their ability to lose weight (Stice & Yokum, 2016). This may provide evidence for a subgroup of obese individuals who are especially reactive in the neural reward network and make impulsive, disadvantageous decisions that would enable overeating, and may not lose weight in an intervention. To date, only two studies have used brain imaging data to predict future weight loss using dietary changes, and these interventions were short (i.e., up to 12 weeks) and/or compared obese with lean participants (Murdaugh et al., 2012; Xu et al., 2017). To build on this limited literature, research within an entirely overweight and obese sample should use neural activation and EF task performance to predict weight loss after longer-term interventions. Combining this heightened sensitivity to rewarding stimuli with neurocognitive functioning may provide a fuller picture for why some individuals are not as effective at losing weight in a dietary intervention.

1.6 AIMS AND HYPOTHESES

The primary aim of the current study was to predict weight loss following a 12-month dietary intervention within an overweight and obese sample using the variability in neural reward network activation during a VFC task at baseline. We hypothesized that heightened brain activity in areas supporting reward processing while viewing images of food would be associated with less weight lost after the intervention. The second aim was to explore the relationship between brain activation during the VFC task and measures of EF at baseline. We hypothesized that heightened activation in reward regions while viewing images of food would be associated with poorer performance on EF tasks. The third aim of the current study was to examine whether baseline EF was predictive of weight lost at the 12-month follow-up. We hypothesized that poorer performance on EF tasks would be associated with less successful weight loss after the intervention. Our fourth and final aim was to test if EF statistically mediated the relationship between reward sensitivity and the amount of weight lost after the intervention. We hypothesized that EF task performance would statistically mediate this relationship, such that individuals who showed heightened activation in reward regions in response to food cues would perform poorly on EF tasks, and in turn, lose less weight. These results would implicate EF as a factor to predict weight loss beyond the variance that could be predicted with neural responsivity to food cues.

2.0 METHODS

2.1 PARTICIPANTS

Participants were recruited from a parent study (PI: Jakicic) at the University of Pittsburgh examining cardiac changes following a year of a dietary, and for some participants, physical activity, intervention to take part in an ancillary neuroimaging study. Participants were informed of this ancillary study during a session of the parent study immediately after enrollment. All eligible participants were given time to decide if they were interested in the neuroimaging component and given contact information to express interest. Participants interested in the neuroimaging component were required to have enrolled in this ancillary study prior to beginning the intervention.

Participants were eligible if they were between the ages of 18-55 and had a BMI between 25.0-39.9 kg/m^2. Exclusion criteria included: Females who were pregnant, breastfeeding, or planning to become pregnant; history of bariatric surgery; current medical condition that could affect body weight (e.g., cancer, diabetes mellitus); current cardiac conditions that increase risk of a cardiac event (e.g., congestive heart failure); resting systolic blood pressure >160 mmHg or resting diastolic blood pressure >90 mmHg; an eating disorder that would contraindicate weight loss or physical activity; alcohol or substance abuse; current treatment for psychological disorders, taking psychotropic medication within the past 12 months, or hospitalization for depression within

the past five years; report of exercise for more than three days per week for more than 20 minutes per day in the last three months; report of weight loss greater than 5% or participation in a weight reduction diet in the past 3 months; inability to attend at least 80% of the scheduled intervention sessions; contraindication to MRI (e.g., pacemaker, claustrophobia); history or presence of neurological disorder (e.g., dementia, stroke); history of developmental pathologies or traumatic brain injury; and left-handedness. Individuals with a history of welding work or tattoos with metal filings were subject to additional safety screening prior to participation. All participants were required to provide informed consent, complete all baseline sessions and procedures, and be randomized to their intervention group prior to neuroimaging.

2.2 PROCEDURES

Participants came into the laboratory for multiple baseline assessment visits to: 1) obtain demographic information, have their weight and height measured by the intervention staff, and undergo a dual-energy X-ray absorptiometry (DXA) scan, and 2) complete the EF tasks and undergo neuroimaging. Throughout the 12-month intervention, all participants had weekly behavioral weight control sessions that are described in detail below. The initial weight assessment took place prior to the cognitive and neuroimaging components, as this was part of the initial randomization visit of the parent study. Since an objective weight assessment was conducted prior to the cognitive and neuroimaging sessions, participants self-reported their weight. Objective weight data were not available at the time of conducting the analyses for this thesis, so only this subjective weight report was used. Participants were also asked to indicate demographic information, including age, sex, and years of education. Education was used in place of SES due

to the complexity of accurately quantifying SES (McLaren, 2007), and because individuals without a high school diploma are more than six times more likely to live in poverty than individuals with a college degree (De Vita & Farrell, 2014).

2.2.1 Weight Loss Intervention

Upon enrollment in the study, participants were randomized to one of three groups: energy restricted diet-only, diet + 150 minutes/week of moderate intensity physical activity, or diet + 250 minutes/week of moderate intensity physical activity. Participants were randomized equally across all groups and all assessments were conducted by blinded personnel. All weight assessments before, after, and during the intervention were conducted privately between the participants and the intervention staff. At the first pre-intervention assessment, participants had their weight and height measured and underwent a dual-energy X-ray absorptiometry (DXA) scan. DXA scans involve the participant laying on a table with an X-ray arm that beams two different energy rays at his or her body. The scans measure bone mineral density by creating fat-to-mass ratios from the difference between hard and soft tissue X-ray absorption. These ratios can be used to quantify adiposity (Kelly, Wilson, & Heymsfield, 2009). These measurements were taken again immediately after the completion of the intervention. Participants self-reported their height and weight to assessment staff at the pre- and post-intervention neuroimaging sessions. For the purposes of this thesis, self-reported weight was used to measure change in adiposity, as quantified through percentage of initial body weight lost.

Regardless of randomized group, all participants were prescribed an energy-restricted dietary intervention that previously has been shown to reduce body weight by 8-10% in the first 6 months of treatment (Goodpaster et al., 2010; Jakicic et al., 2008). All participants had their energy

intake reduced to 1200-2100 kilocalories per day based on their initial body weight. They had a targeted macronutrient composition for their diets (i.e., 20%-30% fat, 50%-55% carbohydrate, and 20%-25% protein). Participants recorded their meals in a food diary, which they gave to the intervention staff to monitor dietary adherence and receive feedback.

Throughout the intervention, all participants completed a behavioral weight control program. The program consisted of weekly, hour-long meetings with either a group of 15-20 participants or an individual meeting with intervention staff. In Months 1-6, three of the weekly meetings were in a group setting and involved an educational component related to weight loss, eating behaviors, or physical activity behaviors. The other week of the month was an individual meeting to focus on participant progress in the intervention. In Months 7-12, only two of the weekly meetings were in a group setting. During the other two weeks of the month, participants had individual phone calls with intervention staff to discuss their progress.

2.2.2 Executive Functioning Assessment

Before randomization, participants completed computerized versions of the Iowa Gambling Task (IGT; (Bechara et al., 1994; Bechara et al., 1998) and the Stroop task (Stroop, 1935). The IGT was administered outside of the MRI scanner prior to neuroimaging. At the beginning of the IGT, participants were given a $2000 credit with which they were instructed to play a game with the goal of winning as much money as possible. They were instructed to select cards one at a time from one of four decks (i.e., Deck A, B, C, or D) presented on the screen. They were told that some decks are better than others, but they were not told which decks were better. Participants were also told that the game was fair, so they should play as if they were using real money. Participants completed five blocks of 20 card selection trials, totaling 100 trials (Bechara, 2007; Bechara et al.,

1994). A Net Total score was calculated by subtracting the number of cards chosen from disadvantageous decks from the number of cards chosen from advantageous decks. A learning score was calculated by subtracting the net score of the first 20-card trial from the net score of the second 20-card trial. This metric was created to evaluate changes in strategy between the two initial trials.

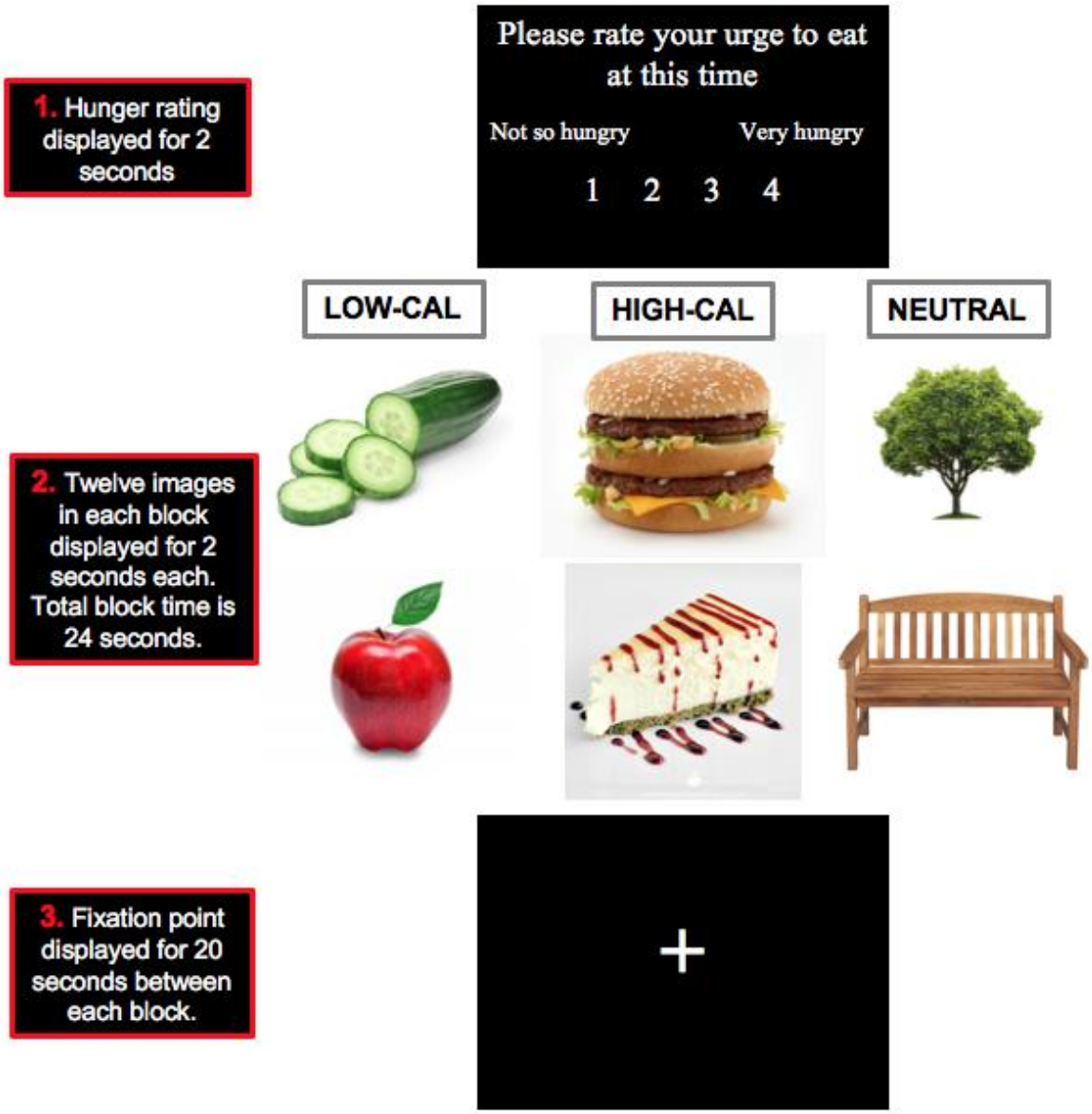
While in the scanner, participants completed the Stroop task (Stroop, 1935) to measure inhibitory control. Participants completed 182 trials and wore a glove on their right hand with buttons to indicate a response choice corresponding with each finger. During the Stroop task, they were asked to indicate the color of the text that was written on the screen, regardless of the word that was written. In the Congruent condition, the word presented matched the color of the text (e.g., "red" written in red ink). In the Incongruent condition, the word presented did not match the color of the text (e.g., "red" written in green ink). In the Neutral condition, the word presented was not a color name (e.g., "table" written in red ink). Comparison of these conditions can be quantified as the Stroop effect, a metric of interference between the incongruent and congruent conditions that quantifies inhibitory control (Van der Elst et al., 2006). The Stroop effect can be calculated with the equation: (incongruent – congruent) / congruent.

2.2.3 Visual Food Cuing Task

While in the scanner, participants viewed images of high-caloric foods, low-caloric foods, and neutral images (i.e., flowers, furniture). These images were presented in blocks, such that one block of images was all high-caloric foods, one was all neutral images, and so on. The blocks were fixed so that each participant viewed all the images in the same order. Participants were instructed to remain focused on the pictures on the screen and asked to rate their hunger before each block

on a 1-4 Likert scale, using their right-hand fingers to indicate their choice. Each block lasted approximately 45 seconds, yielding a total task duration of approximately ten minutes, including time for instructions (see Figure 1).

Figure 1. Visual Food Cuing Task Design



2.2.4 MRI Data Acquisition

Data were collected using a Siemens Verio 3-Tesla magnet with a 32-channel transmit-receive head coil. Head motion was restricted using foam inserts placed inside of the head coil. Each imaging session consisted of fMRI scans while the participant was at rest and during the VFC task. Neuroimaging also included a high-resolution anatomical scan. Functional MR images were acquired using single-shot T2-weighted echo-planar imaging (EPI) with BOLD contrast imaging to quantify the changes in blood oxygenation, or hemodynamic response, in the brain [echo time (TE) = 35ms; repetition time (TR) = 2.0s; flip angle = 75°]. We acquired 34 axial-oblique slices 3.5 mm thick with a 1 mm gap at a scan resolution of 64 x 64, reconstructed to 128 x 128, and 240 x 240 x 149mm FOV. The high-resolution structural scan was acquired using a sagittal T1-weighted image with magnetization-prepared rapid gradient echo [256 slices; 1mm thick; TE = 2.93ms, TR = 1.9s, flip angle = 9°, and 256 x 256 x 176mm FOV].

Stimuli were presented on a visual display that projects from a computer running E-prime software to the participant via a rear-projecting mirror mounted on the head coil. Button presses were recorded using MRI-compatible gloves with buttons on each finger.

2.3 STATISTICAL ANALYSES

2.3.1 Descriptive Statistics

The relationships between weight loss and initial body weight, age, sex, race, and education were examined using bivariate correlations. All variables related to weight loss and EF were tested for normality of distribution and found to be normally distributed. Variability in Stroop task performance was analyzed using paired t-tests to compare response time (RT) between the conditions and verify the Stroop effect within this sample.

Investigators remained blind to intervention group assignment; therefore, secondary analyses controlling for intervention group were not completed. Two of the three intervention groups were also prescribed a physical activity regimen and physical activity has been shown to be a contributing factor for weight loss, though to a significantly smaller extent than dietary changes (Jakicic et al., 2014). These analyses will be completed when investigators are unblinded to group assignment.

2.3.2 Neuroimaging

FMRI data were analyzed using general linear models with FSL software (FMRIB, Oxford, UK). Standard preprocessing steps were conducted on each subject prior to statistical analyses. Rigid body motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002) was done

with realignment to the center image in the time series. High-pass temporal filtering was completed using a threshold of 100 seconds. Spatial smoothing using a full weight at the half maximum Gaussian kernel of 5 millimeters was employed to accommodate variability between participants. Statistical parameter maps were constructed for each participant and each condition and contrast at each voxel using a gamma function.

Five individual-level contrasts were used, including: each condition of the VFC task (i.e., low-caloric foods, high-caloric foods, or neutral images) compared to a fixation period, high-caloric compared with low-caloric foods, and high- + low-caloric foods compared with neutral images. Lower-level contrasts were forwarded to a higher-level analysis where the images were used to examine associations with weight loss and EF. Thresholds were set using a family-wise error rate correction using a voxel-wise threshold ($p<.01$) and cluster-based threshold ($p<.05$). Neural activation was examined using a whole-brain, voxel-wise approach with *a priori* hypotheses for corticostriatal regions related to reward processing and EF.

2.3.3 Testing Aim 1

To test Aim 1, we conducted hierarchical linear regressions to test the association between BOLD activation at baseline and weight loss following the intervention. Weight loss was quantified as percentage of initial body weight lost at the end of the intervention. BMI does not correlate strongly with percentage of body fat in overweight participants (Romero-Corral et al., 2008), therefore using the percentage of initial body weight lost may more accurately reflect changes in adiposity. Sex was included as a covariate in these analyses.

Due to the implications of corticostriatal circuitry across multiple disorders, including obesity, we focused our reported results on regions contained within this corticostriatal pathway.

2.3.4 Testing Aim 2

Aim 2 was tested with hierarchical linear regressions to examine the associations between BOLD activation during the VFC task and EF task performance at baseline. Sex and years of education were included as a covariate in these analyses. To reduce the number of statistical comparisons, we chose to focus only on the regions within the corticostriatal pathway that were associated with weight loss in Aim 1.

2.3.5 Testing Aim 3

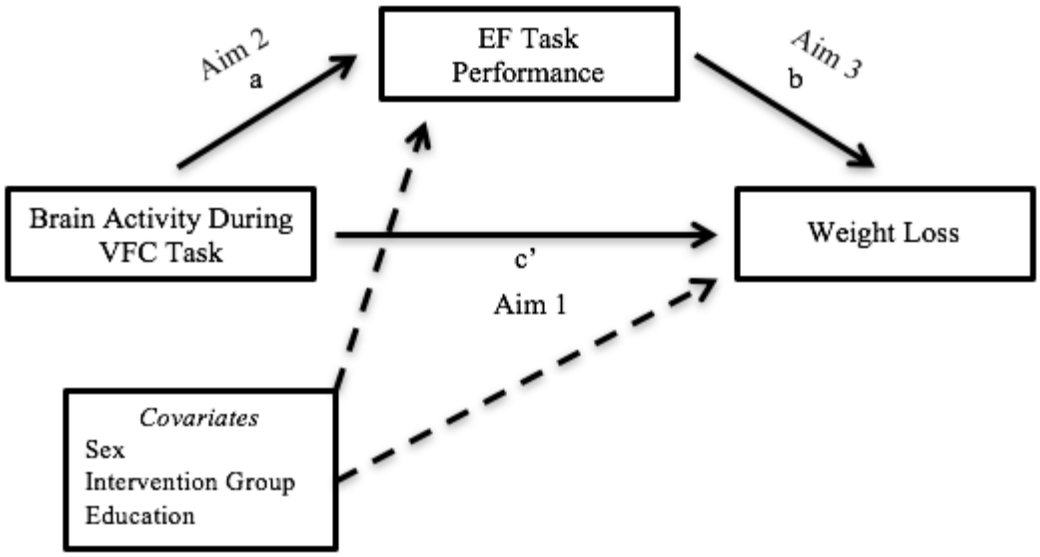
Aim 3 was tested with hierarchical linear regression models between weight loss and EF task performance. Sex and years of education were entered as covariates in these models. Given the relationship between sex and performance on cognitive tasks in different cognitive domains (Bolla et al., 2004; van den Bos et al., 2013; Van der Elst et al., 2006), interaction terms with sex were created for each cognitive variable and included in the regression models. When these terms did not significantly contribute to the variance in weight loss, they were dropped from the regression models.

2.3.6 Testing Aim 4

To test Aim 4, we confirmed that the assumptions to conduct statistical mediation were met by examining the results of Aims 2 and 3 (i.e., the *a* and *b* paths of a mediation model, respectively; see Figure 2). If they were met, we would use PROCESS (Hayes, 2013) to test if EF at baseline

statistically mediated the relationship between BOLD activation during the VFC task at baseline and weight loss following the intervention.

Figure 2. Conceptual Model of Aim 4



3.0 RESULTS

3.1 PARTICIPANTS

125 participants were enrolled in the neuroimaging arm of the intervention. 115 completed all study procedures and returned for follow-up testing. Of these, seven participants were excluded from analyses due to: not completing the VFC task at baseline (n=3), inaccurate or lack of weight reporting at baseline or follow-up (n=4). The final study sample was 108 community-dwelling adults.

Participants had a mean age of 44.75 $\pm$ 8.55 years, weighed ~193 pounds (192.55 $\pm$ 28.77), and had a BMI of ~31 kg/m^2 (30.93 $\pm$ 3.59) on average at baseline. They were highly educated, with an average of 16.54 $\pm$ 2.55 years of education, 96% right-handed, and 77% female (see Table 1). The sample was 76% Caucasian, 18% African American, 3% Asian, and 3% multiracial, which is similar to the racial makeup of Pittsburgh (Pittsburgh, 2011).

Table 1. Demographic Information.

	Mean	***St. Dev.***
Baseline Age	44.75	8.55
Sex (%Female)	76.9	-
Education (years)	16.54	2.55
Race (%Caucasian)	75.9	-
Baseline Weight (lbs)	192.55	28.77
Follow-up Weight (lbs)	174.97	28.68
Weight Change (%)	9.06	6.86
Baseline BMI	30.93	3.59
Follow-up BMI	28.19	3.95
BMI Change	2.74	2.23

Prior to the intervention, participants' baseline weight was significantly associated with sex [r(108)=-.435, p<.001], such that males had a higher weight than females. However, baseline BMI was not associated with sex (p=.668). Baseline weight and BMI were not significantly associated with participants' age, race, or years of education (all p-values>.220; see Table 2).

Table 2. Relationships Between Baseline Weight, BMI and Demographic Information.

		Age	***Gender***	***Race***	***Education***	***Weight***	***BMI***
Weight (lbs)	r	-.080	-.435	-.004	.013	1.000	.740
	p	.412	<.001*	.968	.892	-	<.001***
BMI (kg/m^2)	r	-.106	.042	-.092	.017	.740	1.000
	p	.276	.668	.352	.865	<.001***	-

*p < .05, **p < .01, ***p < .001

3.2 AIM 1

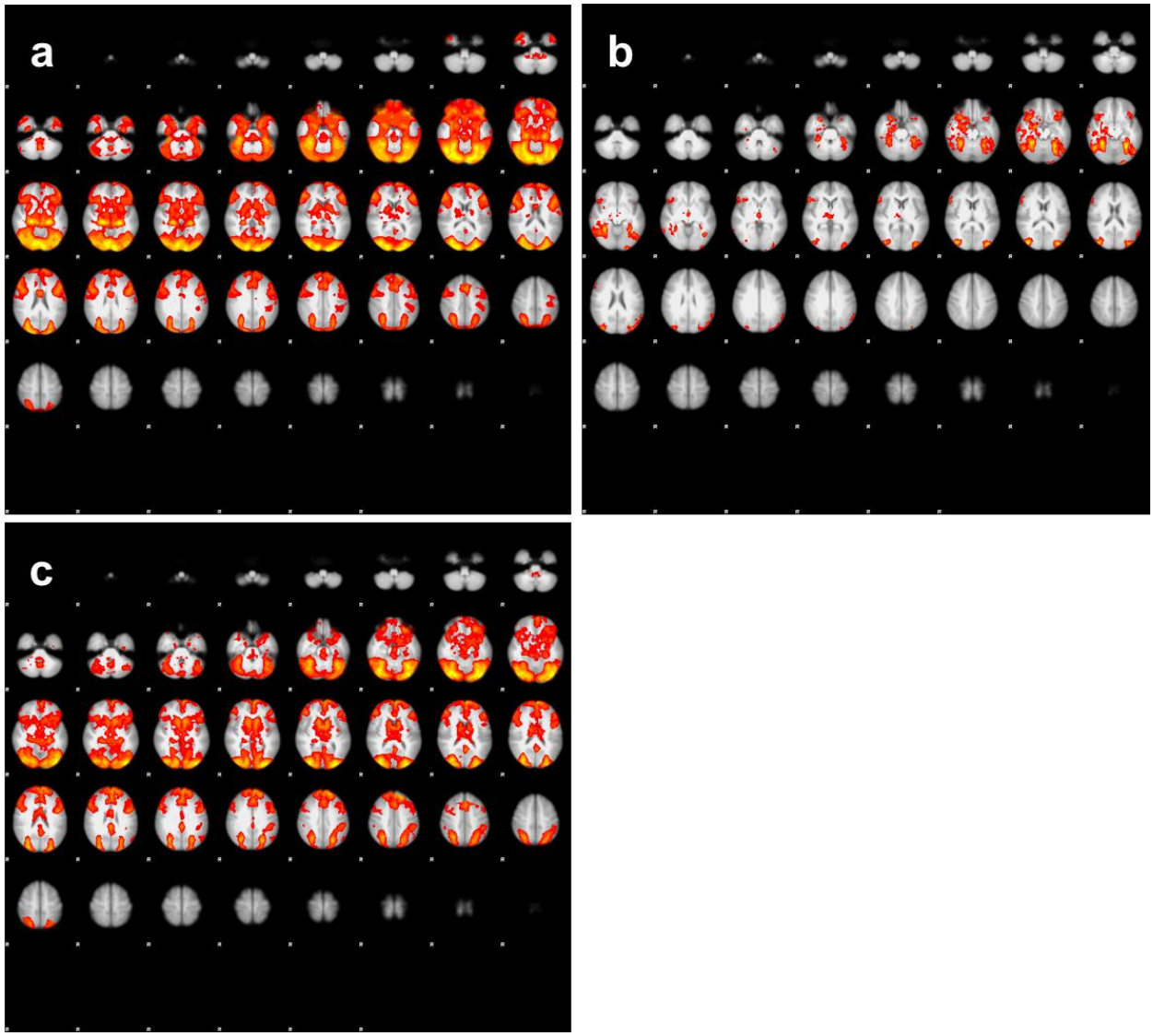
At the 12-month follow-up, participants had lost an average of ~18 pounds (17.58 $\pm$ 14.12), or 9% of their initial body weight (9.06% $\pm$ 6.86%). This weight loss is equivalent to a 2.7 kg/m^2 decrease in BMI, with an average follow-up BMI of 28.19 kg/m^2 (see Table 1). There was no association between baseline weight and percentage of weight lost [r(108)=.067, p=.490]; therefore, analyses and results described below did not include initial weight as a covariate.

First, we conducted whole-head, voxel-wise analyses to determine which regions showed activation during the VFC task conditions. The most robust differences in neural activation occurred during the high-caloric foods versus fixation, high-caloric versus low-caloric foods, and food versus neutral images contrasts. This is consistent with prior work using similar food-cuing

paradigms (Pursey et al., 2014) and supported our hypothesis that our participants would show more neural responsivity to food stimuli, and specifically high-caloric foods (see Figure 3).

Figure 3. Differences in Neural Activation by VFC Contrast.

Whole-brain activation in the VFC task in our contrasts of interest: (a) high-caloric foods vs. fixation; (b) high-caloric vs. low-caloric food images; (c) food vs. neutral images.



The primary aim of this thesis was to test whether neural reward network responsivity to visual food cues at baseline predicted weight loss in a dietary intervention. Consistent with our

predictions, we found that weight lost over the 12-month period was correlated with baseline activation during the VFC task. While participants viewed images of high-caloric foods or any food, five clusters were significantly associated with weight loss: two in the right cingulate cortex (one extending from the right subgenual cingulate cortex to the left dorsal anterior cingulate cortex (ACC) and one in the medial ACC), one extending from the right precentral gyrus to the right dorsolateral PFC (dlPFC), one in the right OFC, and one extending from the right caudate into the right NAcc (see Table 3, Figures 4-5). Participants who lost more weight showed greater differences in activity in the ACC clusters while viewing pictures of high-caloric foods versus fixation [$r(108)=.387$, $p<.001$] and versus low-caloric foods [$r(108)=.192$, $p=.046$].

Table 3. Regions Showing Differential Activation During the Visual Food Cuing Task in Relation to Weight Loss and EF.

ROI	*Task*	*Contrast*	*Dir.*	*# Voxels*	*Peak X*	*Peak Y*	*Peak Z*	*Add'l Regions*
L. ACC	VFC	High-Cal > Fixation	Pos.	690	45	68	29	R. subcallosal cortex
R. ACC	VFC	High-Cal > Low-Cal	Pos.	65	44	83	42	
R. dlPFC	VFC	Food > Neutral	Neg.	484	14	77	39	R. precentral gyrus, IFG
R. OFC	VFC	Food > Neutral	Neg.	121	32	94	28	
R. Caudate	VFC	Food > Neutral	Neg.	106	36	73	40	R. NAcc
L. NAcc	IGT Learn	High-Cal > Low-Cal	Pos.	12	48	69	35	
R. Caudate	IGT Net Total	High-Cal > Low-Cal	Pos.	60	38	61	46	

Figure 4. Activation Clusters in the Caudate Nucleus and Anterior Cingulate Cortex.

(a) Negative association between weight loss and differences in activation in the right caudate nucleus in the food vs. neutral images contrast; (b) Positive associations between weight loss and differences in activation in the bilateral anterior cingulate cortex in the high-caloric foods vs. fixation contrast (red), and between weight loss and differences in activation in the right anterior cingulate cortex in the high-caloric vs. low-caloric foods contrast (green).

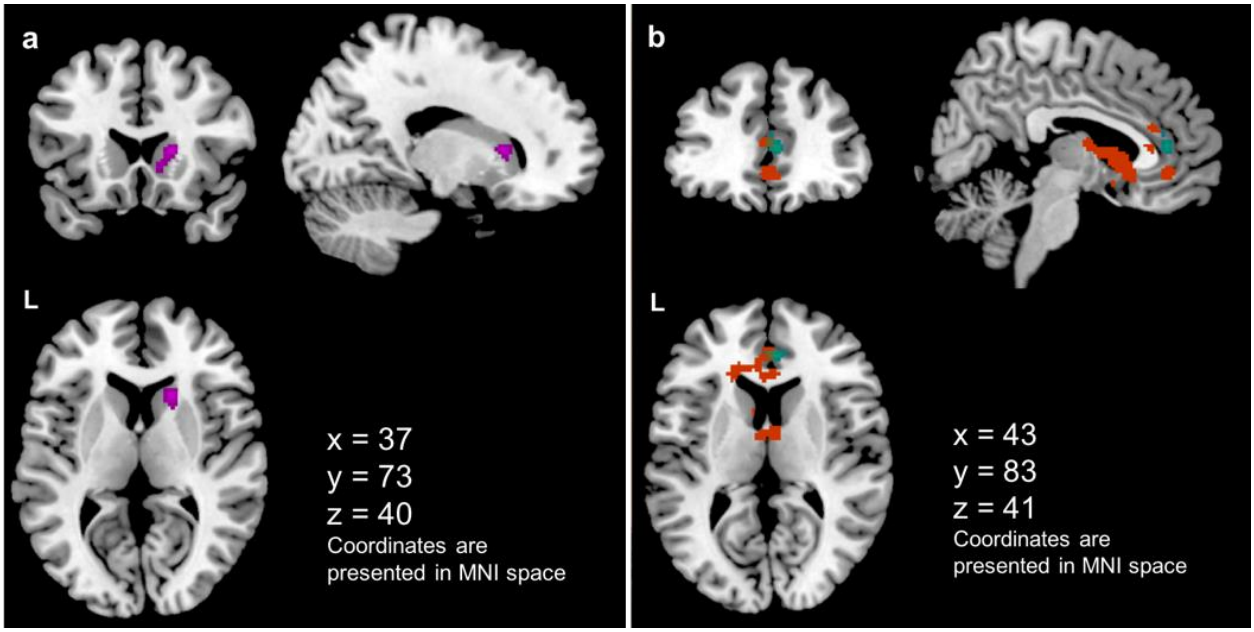
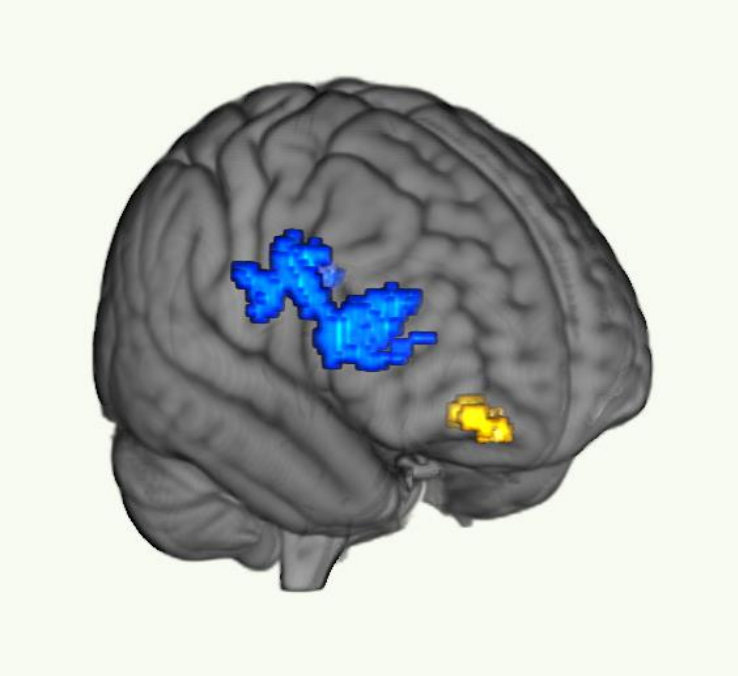


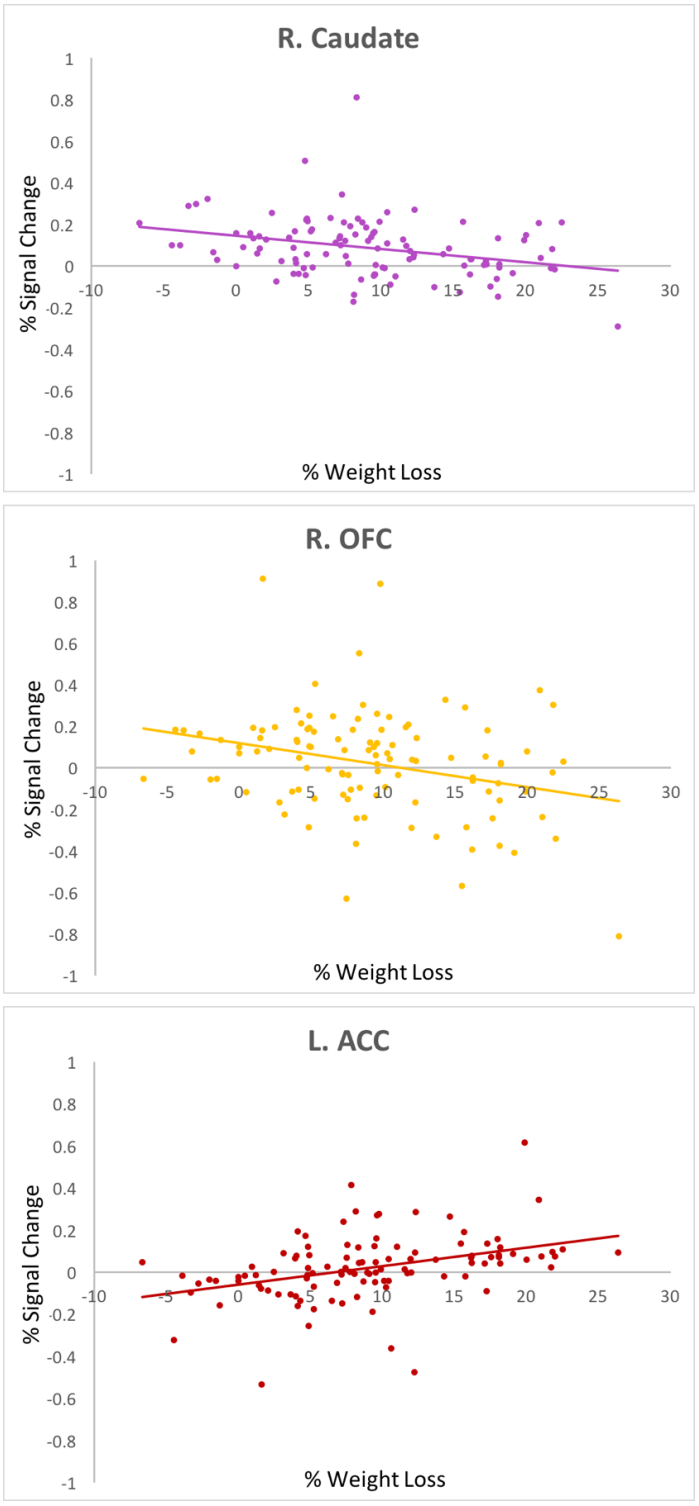
Figure 5. Activation Clusters in the Dorsolateral Prefrontal Cortex and Orbitofrontal Cortex.

Negative associations between weight loss and differences in activation during the food vs. neutral images contrast in the dlPFC (blue) and OFC (yellow) on the right.



In contrast with the findings described above for the ACC, weight loss was negatively associated with changes in brain activity in the right caudate, which is involved in reward processing, and the right dlPFC and right OFC, which are involved in inhibitory and attentional control. Participants who lost more weight at the end of the intervention showed *less* of a difference in activity in the right caudate [r(108)=-.308, p=.001] and in these right frontal regions [dlPFC r(108)=-.301, p=.002; OFC [r(108)=-.290, p=.002] while viewing images of food compared to neutral images (see Figure 6).

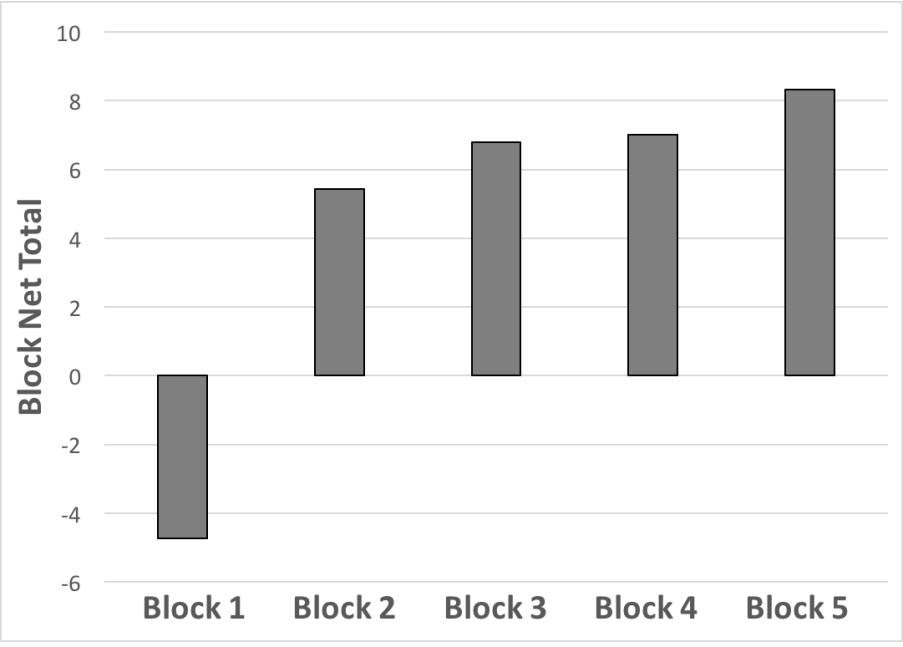
Figure 6. Relationships between Weight Loss and BOLD Activity in the Caudate, OFC, and ACC.



3.3 AIM 2

Consistent with the literature and our predictions, participants selected more cards from the advantageous (61.06 ± 13.93) rather than disadvantageous (38.56 ± 13.85) decks of the IGT. Our participants selected cards using successful strategic planning during the task, as indicated by an average Net Total score of 23 (22.87 ± 27.70; see Table 4). In line with earlier work, the participants' learning trajectories varied between trial blocks, with the largest improvement in task strategy between blocks 1 and 2 (see Figure 7). This improvement early in the task denotes a learning curve that may reflect a lack of EF deficits in this younger adult population.

Figure 7. IGT Learning Across Blocks.



Participants also performed in line with our predictions and prior research by responding significantly faster in the Stroop task during the Congruent (759.78 ± 74.51ms) condition compared to the Neutral (793.25 ± 82.94ms) or Incongruent (899.86 ± 117.49ms) conditions (all t>11.21, all p-values <.001; see Tables 4 and 5 for details). They also responded significantly faster during the Neutral condition compared to the Incongruent condition (t=16.54, p<.001). Consistent with our predictions and prior literature, participants responded more accurately during the Congruent and Neutral conditions (0.97 ± 0.04) compared to the Incongruent condition (0.89 ± 0.12; all t>6.83, all p-values>.001). There was no difference in response accuracy between the Congruent and Neutral conditions.

Table 4. Executive Functioning Task Performance.

	Mean	***St. Dev.***
IGT Net Total	22.87	27.70
IGT Learning (B1 to B2)	10.17	13.15
Stroop CON RT	759.78	74.51
Stroop NEU RT	793.25	82.94
Stroop INC RT	899.86	117.49
Stroop CON ACC	0.97	0.04
Stroop NEU ACC	0.97	0.04
Stroop INC ACC	0.89	0.12

Table 5. Stroop Task Performance Comparison by Condition.

		t	*Significance*
Response Time			
CON	**INC**	-20.08	<.001***
CON	**NEU**	11.21	<.001***
INC	**NEU**	16.54	<.001***
Accuracy			
CON	**INC**	7.18	<.001***
CON	**NEU**	-1.80	.075
INC	**NEU**	-6.83	<.001***

*p < .05, **p < .01, ***p < .001

Aim 2 of this thesis was designed to test if brain regions that are active while viewing images of food were related to performance on EF tasks. Within the regions of the corticostriatal circuit where activation during the VFC task was associated with weight loss, there were no activation clusters significantly associated with Stroop task performance. However, differences in activation in regions related to reward processing were positively associated with IGT performance in the high-caloric versus low-caloric foods contrast. Individuals with higher Net Total scores showed heightened activation in the right caudate [r(108)=.271, p=.005] and those who improved more across the first two trials of the task showed heightened activation in the left NAcc [r(108)=.198, p=.040] (see Table 3 for details). However, the right caudal activation cluster did not overlap with the cluster significantly associated with weight loss. While the right caudate was activated in response to food cues relative both to EF and weight loss, it is not clear if this relationship between EF and reward responsivity is related to weight loss.

3.4 AIM 3

Aim 3 of this thesis was designed to examine whether EF before randomization into the weight loss intervention was predictive of the amount of weight lost. Although we predicted that weight loss would be significantly associated with EF, hierarchical regression models of these relationships were not significant for any EF variables, including IGT Net Total, IGT learning, and Stroop incongruent condition accuracy (see Table 6 for details). The interaction term of sex and each cognitive variable was not significant and subsequently dropped from the regression models. After dropping the interaction term, the Stroop interference accuracy accounted for a significant

proportion of the variance in weight loss [β=-.206, t(100)=-2.142, p=.035]; however, this was no longer significant after correcting for multiple comparisons (see Table 6).

Table 6. Weight Loss and Neurocognitive Task Performance.

	β	***t***	***Significance***
IGT Net Total	.154	1.614	.109
IGT Learning (B1 to B2)	-.037	-.381	.704
Stroop CON RT	-.070	-.708	.481
Stroop INC RT	-.051	-.511	.610
Stroop Interference RT	.019	.190	.850
Stroop CON ACC	.015	.149	.882
Stroop INC ACC	-.190	-1.968	.052
Stroop Interference ACC	-.206	-2.142	.035*

*p < .05, **p < .01, ***p < .001
Note: IGT=Iowa Gambling Task, B1=block 1, B2=block 2, INC=incongruent condition, CON=congruent condition, RT=response time in milliseconds, ACC=accuracy; all cognitive measures reported were assessed at baseline. All regression models controlled for sex and years of education.

3.5 AIM 4

Aim 4 of this thesis was to test if EF statistically mediated the relationship between brain activation while viewing images of food and weight lost over a 12-month dietary intervention (see Figure 2). Testing for statistical mediation requires that the relationships between the independent variable and mediator (*a* path), and the mediator and dependent variable (*b* path) are statistically significant (Hayes, 2013). Aim 1 described above tested the *c'* path and showed a significant relationship between BOLD activation in reward regions during the VFC task and weight loss. Aim 2 described above tested the *a* path and showed that there was a significant relationship between BOLD activation in regions related to reward processing during the VFC task and EF task performance.

Aim 3 tested the *b* path and did not show any significant relationships between EF task performance and weight loss. Since the *b* path did not support our hypothesis that EF was related weight loss, the assumptions necessary for statistical mediation were not met and those analyses were not conducted.

4.0 DISCUSSION

This thesis sought to examine the predictive power of brain activation in reward regions during a VFC task and EF task performance on weight loss after a 12-month dietary intervention. We also sought to explore if EF would statistically mediate the relationship between BOLD activity during the VFC task and weight loss, which would indicate that cognition contributes to weight loss above and beyond neural reward sensitivity. We found evidence consistent with our hypotheses that neural responsivity to food cues predicted long-term weight loss and was related to EF task performance. However, EF did not predict weight loss, and therefore statistical mediation could not be tested.

Multiple brain areas showed reduced differences in activation while viewing food compared to non-food images that were associated with weight loss. These regions included those involved in reward processing (i.e., the caudate), and those involved in EF (i.e., the dlPFC and OFC). Notably, individuals who lost more weight over the course of the intervention showed reduced neural sensitivity to visual food stimuli in regions associated with reward processing. These results could indicate that overweight and obese individuals who do not react as strongly to visual food cues in reward-related brain circuitry could be the most responsive to dietary interventions. Contrary to our predictions, the individuals who showed less sensitivity in brain regions related to EF, including the OFC and dlPFC, were more successful at losing weight. Although this reduced difference in activity of the OFC and dlPFC is often associated with reduced inhibitory control and increased impulsive decision-making (Brooks, Cedernaes, & Schioth, 2013; Fitzpatrick et al., 2013; Gunstad et al., 2007; Smith et al., 2011), one other weight loss intervention also found that successful weight loss was associated with reduced activation in the PFC

(Murdaugh et al., 2012). Here, the individuals who lose more weight may not need to inhibit impulsive decision-making when viewing images of food to adhere to their dietary intervention. Taken together, it is possible that the individuals losing more weight recruited fewer EF resources because they were less sensitive to the rewarding food stimuli.

We also found that increased activity in the ACC while viewing images of high-caloric food was associated with more weight lost over the intervention. Notably, there were no main effects of activation in these regions in response to the food cues, just as the activation related to weight loss. As the ACC is implicated in processing conflicts (Botvinick, Nystrom, Fissel, Carter, & Cohen, 1999), heightened activity in this region in response to visual food cues may be related to the evaluation of outcomes related to eating. One meta-analysis of fMRI studies examining the differences in activation between obese and lean participants in response to food cues posited that this ACC activity may reflect the balance between a desire to eat and a desire to control appetite (Brooks et al., 2013). Since significant activation clusters in the ACC were only seen relative to weight loss, it is possible that this conflict evaluation is only elicited in obese participants when they are prompted with potentially conflicting cues (i.e., eating high-caloric foods and losing weight in an intervention). This function can also work in conjunction with the dlPFC role in making decisions related to goals. The unique anatomical proximity of the ACC to the striatum and PFC allows this region to function as part of a corticostriatal circuit that incorporates reward sensitivity and decision-making about future behaviors (Pannacciulli et al., 2006; Raji et al., 2010; Verstynen, 2013). Our findings that reduced neural sensitivity to images of food in reward and EF regions and increased sensitivity in the ACC may reflect an ability to analyze costs and benefits as they relate to impulsive behaviors and long-term goals, such as losing weight.

We measured EF with two tasks: the IGT as a measure of impulsive decision-making related to future goals, and the Stroop task as a measure of inhibitory control. We found that activity in the right caudate and left NAcc while viewing images of food was positively associated only with the IGT variables. Specifically, better total performance and learning across the first two trials – metrics related to risk aversion and adaptive planning – were associated with increased activation in these reward regions. This could indicate that increased sensitivity in reward regions during a VFC task is more closely related to stronger abilities to avoid making maladaptive choices. However, these activation clusters did not overlap with those associated with weight loss. In conjunction with finding no activation clusters within this corticostriatal circuit that were related to Stroop task performance, this suggests that the neural processes elicited by a VFC task are differentially related to weight loss and EF.

Contrary to our predictions, EF task performance at baseline was not associated with the amount of weight lost over the 12-month dietary intervention. Although previous work has shown that cognition may predict future weight loss, these studies employed shorter interventions and diverse metrics of EF (Brockmeyer et al., 2016; Galioto et al., 2016; Xu et al., 2017). In trying to understand the factors that predict weight loss, our evidence showed that EF does not account for variance above and beyond that of neural reward region activation in response to visual food cues. With our younger sample that did well on our EF tasks, we may have had limited variability of IGT and Stroop performance to show significant relationships with weight loss. It is also possible that these metrics of EF, while well-studied and frequently used, are not as closely related to weight loss as they are to obesity (Fitzpatrick et al., 2013; Gunstad et al., 2007). While obese individuals show deficits on EF tasks compared to healthy controls, it is not clear if this behavioral task performance can predict future weight loss.

Since we were not able to test for statistical mediation in this sample, it is not clear if EF mediates the relationship between neural reward sensitivity and weight loss. Although EF was related to brain activity during the VFC and there is literature to suggest that it is related to weight loss, no studies to date have tested this mediation model.

There are several reasons why predicting weight loss is difficult, including the relatively low proportion of variance accounted for by individual predictors and differences across study populations and results (Stubbs et al., 2011). Although weight loss has been studied in long-term interventions, we still do not fully understand the cognitive processes that facilitate adherence to dietary or physical activity regimens. The biological risk factors for obesity (e.g., metabolic functioning, cardiovascular disease) interact with each other to create varying levels of risk, which can be difficult to quantify or control. Additionally, restricting our sample to individuals with a truncated BMI range (i.e., 25.0 kg/m^2 or higher) may have limited the variability we could see in our results. Although our sample had a normal distribution of baseline BMI and percentage of initial weight lost, this restricted range could reduce the sensitivity with which we were able to detect relationships between weight loss and our cognitive variables of interest. With these considerations, it may not be surprising that we did not find evidence to corroborate some previous literature using behavioral metrics to predict weight loss.

Though we found compelling evidence that neural responses in reward regions to visual food cues are related to future weight loss, this study is not without its limitations. Our sample was taken from one area in Western Pennsylvania, highly educated, and was 76% Caucasian. This may limit the generalizability of our results, particularly to more racially-diverse areas. FMRI analyses do not allow for temporal resolution that may tell us which brain regions are first activated upon seeing food images versus which are activated in response to that activation. As this makes fMRI

data difficult to interpret, we did so cautiously. There was no long-term follow-up of participants beyond the 12-month assessment and it has been shown that weight loss intervention participants typically re-gain 2-3% of their initial body weight after the intervention (Franz et al., 2007; Wu et al., 2009). Additionally, percentage of initial body weight lost is a crude estimate of weight loss and was reported subjectively by our participants. While this percentage may be a better reflection of weight loss than BMI (Romero-Corral et al., 2008), objective metrics of adiposity should be used in future work to ensure that the measurement of weight loss is as objective as possible. The use of two EF metrics may not have been sufficient to capture all the various processes typically associated with EF (e.g., working memory). Though we used multiple variables within the IGT and Stroop task, other tasks should be used to confirm and follow-up on associations between EF and weight loss.

Notably, we are still blinded to group assignment and were not able to assess how the intervention groups may have influenced weight loss. Although all groups engaged in an energy-restricted diet, two-thirds of our participants also engaged in increased physical activity that could not be accounted for in our analyses. Despite evidence that only high levels of physical activity contribute to a significant proportion of weight lost in interventions (Jakicic et al., 2008), it is possible that these participants engaged in other behaviors that could be related to weight loss, such as eliminating certain unhealthy foods from their diets. With the additional motivation of exercise, two of the three intervention groups may have lost more weight than the diet-only group. However, most weight loss interventions include both dietary and physical activity changes to promote healthier lifestyles. Thus, our study likely represents the real-world implications of dietary interventions.

Although we do not know if our participants show the same differences in activation after the intervention, future work will examine changes in VFC activity and EF task performance over time. It is possible these changes are related to weight loss even though baseline EF did not predict the amount of weight lost. Additionally, we can examine brain activity during the Stroop task to see how it is related to activity during the VFC, EF task performance, and weight loss. With the wide range of cognitive processes elicited by the Stroop task, we may see differential relationships with reward region sensitivity that could not be explored with behavioral metrics alone. Future work should examine the ability of these predictions to be successful in clinical populations with explicit comorbid medical and/or psychiatric conditions.

This study was the first to examine whether fMRI activity during a VFC task and measures of EF predict weight loss following a 12-month dietary intervention in an overweight and obese sample. Although other lifestyle interventions have examined the predictive value of neural responses or EF on weight loss, none have focused on weight loss in an obese sample over a 12-month period. Instead, many prospective intervention studies have been of shorter durations (i.e., 4- or 12-weeks) and most have not examined both neural responsivity and EF as contributing factors (Murdaugh et al., 2012; Xu et al., 2017). We examined how cognitive processes interacted with neural activation to rewarding food stimuli to influence future weight loss. While past work has found that differences in brain activity in these areas in response to food cues is predictive of weight loss (Pursey et al., 2014), our evidence incorporates EF to show that sensitivity in these areas is also related to cognition. Our results can inform future research by further corroborating and expanding on previous literature implicating reward regions of the brain in successful weight loss in a dietary intervention.

While brain activity is typically used as a targeted outcome or mediator, we used the 'brain-as-predictor' approach to examine neural metrics (e.g., task-related activation during a VFC task) as predictors of real-world outcomes (Berkman & Falk, 2013). Focusing on this heterogeneity in neural responsivity, which may partially underlie the etiology of conditions like obesity, may allow for the distinction of vulnerable individuals who are at higher risk for developing these harmful conditions (Erickson, Creswell, Versynen, & Gianaros, 2014). With this additional delineation of how individuals respond to weight loss protocols, individualized treatments can be created to aid in weight loss and improve the health of the 38% of Americans afflicted by obesity.

BIBLIOGRAPHY

Agüera, Z., García-Ruiz-de-Gordejuela, A., Vilarrasa, N., Sanchez, I., Baño, M., Camacho, L., . . . Menchon, J. M. (2015). Psychological and personality predictors of weight loss and comorbid metabolic changes after bariatric surgery. *European Eating Disorders Review, 23*(6), 509-516.

Appelhans, B. M. (2009). Neurobehavioral Inhibition of Reward-driven Feeding: Implications for Dieting and Obesity. *Obesity, 17*(4), 640-647.

Balleine, B. W., Delgado, M. R., & Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision-making. *The Journal of Neuroscience, 27*(31), 8161-8165.

Balodis, I. M., Molina, N. D., Kober, H., Worhunsky, P. D., White, M. A., Sinha, R., . . . Potenza, M. N. (2013). Divergent neural substrates of inhibitory control in binge eating disorder relative to other manifestations of obesity. *Obesity, 21*(2), 367-377.

Banich, M. T., Milham, M. P., Atchley, R., Cohen, N. J., Webb, A., Wszalek, T., . . . Magin, R. (2000). fMRI studies of Stroop tasks reveal unique roles of anterior and posterior brain systems in attentional selection. *Journal of Cognitive Neuroscience, 12*(6), 988-1000.

Bautista-Castano, I., Molina-Cabrillana, J., Montoya-Alonso, J. A., & Serra-Majem, L. (2004). Variables predictive of adherence to diet and physical activity recommendations in the treatment of obesity and overweight, in a group of Spanish subjects. *International Journal of Obesity, 28*(5), 697-705.

Bechara, A. (2007). *Iowa gambling task professional manual*: Lutz: Psychological Assessment Resources.

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(13), 7-15.

Bechara, A., Damasio, H., Tranel, D., & Anderson, S. W. (1998). Dissociation of working memory from decision making within the human prefrontal cortex. *The Journal of Neuroscience, 18*(1), 428-437.

Berkman, E., & Falk, E. (2013). Beyond brain mapping using neural measures to predict real-world outcomes. *Current Directions in Psychological Science, 22*(1), 45-50.

Berridge, K., Ho, C., Richard, J., & DiFeliceantonio, A. (2010). The temped brain eats: Pleasure and desire circuits in obesity and eating disorders. *Brain Research, 1350*, 43-64.

Bolla, K., Eldreth, D., Matochik, J., & Cadet, J. (2004). Sex-related differences in a gambling task and its neurological correlates. *Cerebral Cortex, 14*(11), 1226-1232.

Botvinick, M., Nystrom, L., Fissel, K., Carter, C., & Cohen, J. D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature, 402*(6758), 179-181.

Brockmeyer, T., Sinno, M. H., Skunde, M., Wu, M., Woehning, A., Rudofsky, G., & Friederich, H. C. (2016). Inhibitory control and hedonic response towards food interactively predict success in a weight loss programme for adults with obesity. *Obesity Facts, 9*(5), 299-309.

Brogan, A., Hevey, D., & Pignatti, R. (2010). Anorexia, bulimia, and obesity: shared decision making deficits on the Iowa Gambling Task (IGT). *Journal of the International Neuropsychological Society, 16*(4), 711-715.

Brooks, S., Cedernaes, J., & Schioth, H. (2013). Increased prefrontal and parahippocampal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: a meta-analysis of fMRI studies. *PLoS ONE, 8*(4), e60393.

Buelow, M., & Suhr, J. (2009). Construct validity of the Iowa gambling task. *Neuropsychology review, 19*(1), 102-114.

Burger, K., & Berner, L. (2014). A functional neuroimaging review of obesity, appetitive hormones and ingestive behavior. *Physiology & Behavior, 136*, 121-127.

Burger, K., Shearrer, G., & Sanders, A. (2015). Brain-Based Etiology of Weight Regulation. *Current Diabetes Reports, 15*(11), 1-9.

Burger, K., & Stice, E. (2011). Variability in reward responsivity and obesity: evidence from brain imaging studies. *Current Drug Abuse Reviews, 4*(3), 182-189.

Castellanos, E., Charboneau, E., Dietrich, M., Park, S., Bradley, B., Mogg, K., & Cowan, R. (2009). Obese adults have visual attention bias for food cue images: evidence for altered reward system function. *Obesity, 33*(9), 1063-1073.

Cauffman, E., Shulman, E. P., Steinberg, L., Claus, E., Banich, M. T., Graham, S., & Woolard, J. (2010). Age differences in affective decision making as indexed by performance on the Iowa Gambling Task. *Developmental Psychology, 46*(1).

Chen, Z., Lei, X., Ding, C., Li, H., & Chen, A. (2013). The neural mechanisms of semantic and response conflicts: An fMRI study of practice-related effects in the Stroop task. *NeuroImage, 66*, 577-584.

Cornier, M., Salzberg, A., Endly, D., Bessesen, D., & Tregellas, J. (2010). Sex-based differences in the behavioral and neuronal responses to food. *Physiology & Behavior, 99*(4), 538-543.

Davis, C., Patte, K., Curtis, C., & Reid, C. (2010). Immediate pleasures and future consequences. A neuropsychological study of binge eating and obesity. *Appetite, 54*(1), 208-213.

De Vita, C. J., & Farrell, M. R. (2014). Poverty and income security in the Pittsburgh Metropolitan Area. Retrieved from

Demos, K., Heatherton, T., & Kelley, W. (2012). Individual Differences in Nucleus Accumbens Activity to Food and Sexual Images Predict Weight Gain and Sexual Behavior. *Journal of Neuroscience, 32*(16), 5549-5552.

Erickson, K., Creswell, J., Versynen, T., & Gianaros, P. (2014). Health Neuroscience: Defining a New Field. *Current Directions in Psychological Science, 23*(6), 446-453.

Espeland, M., Rapp, S., Bray, G., Houston, D., Johnson, K. C., Kitabchi, A., . . . Kritchevsky, S. (2014). Long-term impact of behavioral weight loss intervention on cognitive function. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 69*(9), 1101-1108.

Fagundo, A. B., De la Torre, R., Jiménez-Murcia, S., Agüera, Z., Granero, R., Tárrega, S., . . . Fernandez-Aranda, F. (2012). Executive functions profile in extreme eating/weight conditions: from anorexia nervosa to obesity. *PLoS ONE, 7*(8), e43382.

Ferriday, D., & Brunstrom, J. (2011). 'I just can't help myself': effects of food-cue exposure in overweight and lean individuals. *International Journal of Obesity, 35*, 142-149.

Finkler, E., Heymsfield, S. B., & St-Onge, M. P. (2012). Rate of weight loss can be predicted by patient characteristics and intervention strategies. *Journal of the Academy of Nutrition and Dietetics, 112*(1), 75-80.

Fitzpatrick, S., Gilbert, S., & Serpell, L. (2013). Systematic review: are overweight and obese individuals impaired on behavioural tasks of executive functioning? *Neuropsychology review, 23*(2), 138-156.

Flegal, K., Kruszon-Moran, D., Carroll, M., Fryar, C., & Ogden, C. (2016). Trends in Obesity Among Adults in the United States, 2005 to 2014. *Journal of the American Medical Association, 315*(21), 2284-2291.

Franz, M. J., VanWormer, J. J., Crain, A. L., Boucher, J. L., Histon, T., Caplan, W., . . . Pronk, N. P. (2007). Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *Journal of the American Dietetic Association, 107*(10), 1755-1767.

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.

Goldstein, D. (1992). Beneficial health effects of modest weight loss. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity, 16*(6), 397-415.

Goodpaster, B. H., DeLany, J. P., Otto, A. D., Kuller, L., Vockley, J., South-Paul, J. E., . . . Jakicic, J. M. (2010). Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults. *Journal of the American Medical Association, 304*(16), 1795-1802.

Group, D. P. P. D. R. (2002). The Diabetes Prevention Program (DPP) description of lifestyle intervention. *Diabetes Care, 25*(12), 2165-2171.

Group, T. L. A. R. (2003). Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Controlled Clinical Trials, 24*(5), 610-628.

Gunstad, J., Paul, R. H., Cohen, R. A., Tate, D. F., Spitznagel, M. B., & Gordon, E. (2007). Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Comprehensive Psychiatry, 48*(1), 57-61.

Hayes, A. (2013). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. New York, NY: The Guilford Press.

Heindel, J. J., Newbold, R., & Schug, T. T. (2015). Endocrine disruptors and obesity. *Nature Reviews Endocrinology, 11*(11), 653-661.

Hsu, M., Bhatt, M., Adolphs, R., Tranel, D., & Camerer, C. (2005). Neural systems responding to degrees of uncertainty in human decision-making. *Science, 310*, 1680-1683.

Jakicic, J. M., Marcus, B. H., Lang, W., & Janney, C. (2008). Effect of exercise on 24-month weight loss maintenance in overweight women. *Archives of internal medicine, 168*(14), 1550-1559.

Jakicic, J. M., Tate, D. F., Lang, W., Davis, K. K., Polzien, K., Neiberg, R. H., . . . Erickson, K. (2014). Objective physical activity and weight loss in adults: The Step-Up Randomized Clinical Trial. *Obesity, 22*(11), 2284-2292.

Jenkinson, M., Bannister, P., Brady, J. M., & Smith, S. M. (2002). Improved Optimisation for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage, 17*(2), 825-841.

Karlsen, T. I., Søhagen, M., & Hjelmesæth, J. (2013). Predictors of weight loss after an intensive lifestyle intervention program in obese patients: a 1-year prospective cohort study. *Health and Quality of Life Outcomes, 11*(1).

Kelly, T., Wilson, K., & Heymsfield, S. (2009). Dual energy X-Ray absorptiometry body composition reference values from NHANES. *PLoS ONE, 4*(9), e7083.

Kenny, P. (2011). Reward Mechanisms in Obesity: New Insights and Future Directions. *Neuron, 69*(4), 664-679.

Kim, C., Chung, C., & Kim, J. (2010). Multiple cognitive control mechanisms associated with the nature of conflict. *Neuroscience Letters, 476*(3), 156-160.

Kishinevsky, F. I., Cox, J. E., Murdaugh, D. L., Stoeckel, L. E., Cook III, E. W., & Weller, R. E. (2012). fMRI reactivity on a delay discounting task predicts weight gain in obese women. *Appetite, 58*(2), 582-592.

Kramer, C. K., Zinman, B., & Retnakaran, R. (2013). Are metabolically healthy overweight and obesity benign conditions? A systemic review and meta-analysis. *Annals of internal medicine, 159*(11), 758-769.

Lawrence, N., Jollant, F., O'Daly, O., Zelava, F., & Phillips, M. (2009). Distinct roles of prefrontal cortical subregions in the Iowa Gambling Task. *Cerebral Cortex, 19*(1134-1143).

Li, X., Lu, Z., D'Argembreau, A., Ng, M., & Bechara, A. (2010). The Iowa Gambling Task in fMRI Images. *Human Brain Mapping, 31*(3), 410-423.

Lopez, R., Hofmann, W., Wagner, D., Kelley, W., & Heatherton, T. (2014). Neural Predictors of Giving in to Temptation in Daily Life. *Psychological Science, 25*(7), 1337-1344.

Maayan, L., Hoogendoorn, C., Sweat, V., & Convit, A. (2011). Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. *Obesity, 19*(7), 1382-1387.

Marques-Iturria, I., Scholtens, L., Garolera, M., Pueyo, R., Garcia-Garcia, I., Gonzalez-Tartiere, P., . . . van den Heuvel, M. (2015). Affected connectivity organization of the reward system structure in obesity. *NeuroImage, 111*, 100-106.

Mathar, D., Horstmann, A., Plegar, B., Villringer, A., & Neumann, J. (2016). Is it worth the effort? Novel insights into obesity-associated alterations in cost-benefit decision-making. *Frontiers in Behavioral Neuroscience*. doi:10.3389/fnbeh.2015.00360

McLaren, L. (2007). Socioeconomic status and obesity. *Epidemiologic reviews, 29*(1), 29-48.

Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., Wszalek, T., & Cohen, N. J. (2002). Attentional control in the aging brain: insights from an fMRI study of the Stroop task. *Brain and Cognition, 49*(3), 277-296.

Miller, W. C., Koceja, D. M., & Hamilton, E. J. (1997). A meta-analysis of the past 25 years of weight loss research using diet, exercise or diet plus exercise intervention. *International Journal of Obesity, 21*(10), 941-947.

Moffat, B., Chenevert, T., Lawrence, T., Meyer, C., Johnson, T., Dong, Q., . . . Ross, B. (2005). Functional diffusion map: A noninvasive MRI biomarker for early stratification of clinical brain tumor response. *Proceedings of the National Academy of Sciences, 102*(15), 5524-5529.

Morland, K., Roux, A. V. D., & Wing, S. (2006). Supermarkets, other food stores, and obesity: the atherosclerosis risk in communities study. *American Journal of Preventative Medicine, 30*(4), 333-339.

Murdaugh, D., Cox, J., Cook, E., & Weller, R. (2012). fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight loss program. *NeuroImage, 59*(3), 2709-2721.

Nederkoorn, C., Houben, K., Hofmann, W., Roefs, A., & Jansen, A. (2010). Control yourself or just eat what you like? Weight gain over a year is predicted by an interactive effect of response inhibition and implicit preference for snack foods. *Health Psychology, 29*(4), 389-393.

Nummenmaa, L., Hirvonen, J., Hannukainen, J., Immonen, H., Lindroos, M., Salminen, P., & Nuutila, P. (2012). Dorsal Striatum and Its Limbic Connectivity Mediate Abnormal Anticipatory Reward Processing in Obesity. *PLoS ONE, 7*(2), e31089.

Opel, N., Redlich, R., Grotegerd, D., Dohm, K., Haupenthal, C., Heindel, W., . . . Dannlowski, U. (2015). Enhanced Neural Responsiveness to Reward Associated with Obesity in the Absence of Food-Related Stimuli. *Human Brain Mapping, 36*(6), 2330-2337.

Panel, N. O. E. I. E. (1998). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults.

Pannacciulli, N., Del Parigi, A., Chen, K., Le, D., Reiman, E., & Tataranni, P. (2006). Brain abnormalities in human obesity: A voxel-based morphometric study. *NeuroImage, 31*(4), 1419-1425.

Piai, V., Roelofs, A., Acheson, D. J., & Takashima, A. (2013). Attention for speaking: domain-general control from the anterior cingulate cortex in spoken word production. *Frontiers in Human Neuroscience, 7*.

Pignatti, R., Bertella, L., Albani, G., Mauro, A., Molinari, E., & Semenza, C. (2006). Decision-making in obesity: a study using the Gambling Task. *Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity, 11*(3), 126-132.

Pittsburgh, C. o. (2011). *PGHSNAP*. Pittsburgh, PA.

Prickett, C., Brennan, L., & Stolwyk, R. (2015). Examining the relationship between obesity and cognitive function: a systematic literature review. *Obesity Research & Clinical Practice, 9*(2), 93-113.

Pursey, K. M., Stanwell, P., Callister, R. J., Brain, K., Collins, C. E., & Burrows, T. L. (2014). Neural responses to visual food cues according to weight status: a systematic review of functional magnetic resonance imaging studies. *Frontiers in Nutrition, 1*.

Raji, C., Ho, A., Parikshak, N., Becker, J., Lopez, O., Kuller, L., . . . Thompson, P. (2010). Brain structure and obesity. *Human Brain Mapping, 31*(3), 353-364.

Rolls, E. (2000). The orbitofrontal cortex and reward. *Cerebral Cortex, 10*, 284-294.

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Thomas, R. J., Collazo-Clavell, M. L., Korinek, J., . . . Lopez-Jimenez, F. (2008). Accuracy of body mass index in diagnosing obesity in the adult general population. *International Journal of Obesity, 32*(6), 959-966.

Rothemund, Y., Preuschhof, C., Bohner, G., Bauknecht, H.-C., Klingebiel, R., Flor, H., & Klapp, B. (2007). Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *NeuroImage, 37*(2), 410-421.

Sallis, J. F., & Glanz, K. (2009). Physical activity and food environments: solutions to the obesity epidemic. *Milbank Quarterly, 87*(1), 123-154.

Sharma, L., Markon, K., & Clark, L. (2014). Toward a theory of distinct types of "impulsive" behaviors: A meta-analysis of self-report and behavioral measures. *Psychological Bulletin, 140*(2), 374-408.

Smith, E., Hay, P., Campbell, L., & Trollor, J. (2011). A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obesity Reviews, 12*, 74-755.

Sobal, J., & Stunkard, A. J. (1989). Socioeconomic status and obesity: a review of the literature. *Psychological Bulletin, 105*(2).

Stice, E., Burger, K., & Yokum, S. (2015). Reward region responsivity predicts future weight gain and moderating effects of the TaqIAallele. *The Journal of Neuroscience, 35*, 10316-10324.

Stice, E., & Yokum, S. (2016). Neural vulnerability factors that increase risk for future weight gain. *Psychological Bulletin, 142*(5), 447-471.

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.

Stice, E., Yokum, S., Burger, K., Epstein, L., & Small, D. (2011). Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. *Journal of Neuroscience, 31*(12), 4360-4366.

Stoeckel, L., Kim, J., Weller, R., Cox, J., Cook III, E., & Horwitz, B. (2009). Effective connectivity of a reward network in obese women. *Brain Research Bulletin, 79*(6), 388-395.

Stoeckel, L., Weller, R., Cook III, E., Twieg, D., Knowlton, R., & Cox, J. (2008). Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *NeuroImage, 41*(2), 636-647.

Stroop, J. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18*(6), 643-662.

Stubbs, J., Whybrow, S., Teixeira, P., Blundell, J., Lawton, C., Westenhoefer, J., . . . Raats, M. (2011). Problems in identifying predictors and correlates of weight loss and maintenance: implications for weight control therapies based on behaviour change. *Obesity Reviews, 12*(9), 688-708.

Stunkard, A. J., & Sorensen, T. I. (1993). Obesity and socioeconomic status--a complex relation. *New England Journal of Medicine, 329*(14), 1036-1037.

Toplak, M., Sorge, G., Benoit, A., West, R., & Stanovich, K. (2010). Decision-making and cognitive abilities: A review of associations between Iowa Gambling Task performance, executive functions, and intelligence. *Clinical Psychology Review, 30*(5), 562-581.

van den Bos, R., Homberg, J., & de Visser, L. (2013). A critical review of sex differences in decision-making tasks: Focus on the Iowa Gambling Task. *Behavioural Brain Research, 238*, 95-108.

Van der Elst, W., Van Boxtel, M. P., Van Breukelen, G. J., & Jolles, J. (2006). The Stroop Color-Word Test influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment, 13*(1), 67-79.

Verstynen, T. (2013). The organization and dynamics of corticostriatal pathways link the medial orbitofrontal cortex to future behavioral responses. *Journal of Neurophysiology, 112*(10), 2457-2469.

Wallis, J. D. (2007). Orbitofrontal Cortex and Its Contribution to Decision-Making. *Annual Review of Neuroscience, 30*, 31-56.

Wardle, J., Waller, J., & Jarvis, M. J. (2002). Sex differences in the association of socioeconomic status with obesity. *American Journal of Public Health, 92*(8), 1299-1304.

Welsh, M. C., & Pennington, B. F. (1988). Assessing frontal lobe functioning in children: Views from developmental psychology. *Developmental Neuropsychology, 4*(3), 199-230.

Wu, T., Gao, X., Chen, M., & Van Dam, R. M. (2009). Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: a meta-analysis. *Obesity Reviews, 10*(3), 313-323.

Xu, X., Deng, Z. Y., Huang, Q., Zhang, W. X., Qi, C. Z., & Huang, J. A. (2017). Prefrontal cortex-mediated executive function as assessed by Stroop task performance associates with weight loss among overweight and obese adolescents and young adults. *Behavioural Brain Research, 321,* 240-248.

Yokum, S., Gearhard, A., Harris, J., Brownell, K., & Stice, E. (2014). Individual differences in striatum activity to food commercials predict weight gain in adolescents. *Obesity, 22*, 2544-2551.

Yokum, S., Ng, J., & Stice, E. (2011). Attentional bias to food images associated with elevated weight and future weight gain: an fMRI study. *Obesity, 19*(9), 1775-1783.

Yokum, S., Ng, J., & Stice, E. (2012). Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. *International Journal of Obesity, 36*(656-664).

Yuh, E., Cooper, S., Mukherjee, P., Yue, J., Lingsma, H., Gordon, W., . . . Sinha, T. (2014). Diffusion tensor imaging for outcome prediction in mild traumatic brain inury: A TRACK-TBI study. *Journal of Neurotrauma, 31,* 1457-1477.