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Inhibitory Control Efficiency In Successful Weight Loss Participants

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INHIBITORY CONTROL EFFICIENCY IN SUCCESSFUL WEIGHT LOSS PARTICIPANTS

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Abstract

Eating unhealthy foods and eating past satiety are inappropriate behaviors that promote obesity. The ability to effectively inhibit an inappropriate behavior is a key component of cognitive restraint and its impairment has been previously linked to obesity. In this study, a Go/No-Go fMRI task was completed by a cohort of adult women that had experienced initial weight loss followed by various levels of weight regain or continued weight loss. Region of interest fMRI analysis revealed that greater total weight loss was significantly related to decreasing activation in the right inferior frontal gyrus and the right superior frontal gyrus. These results suggest that as weight loss increases fewer cognitive resources are needed in order to maintain levels of inhibitory control. This cognitive efficiency, though only partially supported by better task performance, is supported by greater exercise. An analysis of resting state patterns of correlation between task-activated regions revealed a significant correlation between the right inferior frontal gyrus and the left middle temporal gyrus. The strength of this relationship was significantly correlated with increasing total weight loss and continued weight loss over time. Cognitive restraint was also associated with this fronto-temporal correlation and provides support for cognitive efficiency. Right inferior frontal gyrus was also correlated with left inferior frontal gyrus and this relationship was positively correlated with initial weight loss suggesting that fewer neurocognitive resources were required by those who were able to achieve greater initial weight loss.

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Background & Significance

Health Risks of Obesity

In the medical community, obesity is defined as an individual with a body mass index of 30 kg/m^2 or greater. Energetically speaking, obesity is caused by an imbalance in the energy consumed with the energy expended. In other words, obesity is the result of overconsumption of calories with a decrease in physical activity. It is a widely accepted notion that living in a society where highly-palatable processed foods are freely available in combination with a sedentary lifestyle is responsible for the egregiously high prevalence of obesity. Thus, it is no secret that the United States as a wealthy nation continues to struggle with widespread obesity. In fact, nearly 60% of adults in the US are overweight or obese (Kuczmarski, Carroll, Flegal et al., 1997; Yanovski & Yanovski, 2002) with obesity as the fifth leading cause of death. Financially, obesity is responsible for a staggering amount of direct and indirect costs to society (Wang, Beydoun, Liang et al., 2008; Raebel, Malone, Conner et al., 2004). Globally, obesity is the third leading preventable cause of death in the world (Danaei, Ding, Mozaffarian et al., 2009) and it has been estimated that approximately 3.28 billion people world-wide will be overweight/obese by 2030 (Kelly, Yang, Chen et al., 2008). Dubbed an 'obesogenic' society, obesity and its deleterious effects have reached epidemic proportions in the US (Blackburn & Walker, 2005; Flegal, Carroll, Kit et al., 2012).

The physical health problems associated with obesity are vast and lethal. With regards to the heart and cardiovascular system, obesity is linked to cardiovascular disease and heart failure. Specifically, excessive fat causes plaques to build up in the artery walls (atherosclerosis) causing restricted blood flow throughout the body and heart. As a result

of poor circulation caused by obstructed arteries, obese individuals are especially at risk for heart attack and stroke which are the result of blood clots occurring in the heart or brain, respectively. In addition, excessive fat around the heart can cause myocardial cell degeneration leading to cardiac dysfunction. High blood pressure, or hypertension, is also related to obesity. Because of the increased resistance in the arteries that accompanies obesity, the heart must pump blood more forcefully often resulting in cardiac hypertrophy. To complete the obesity heart disease cycle, hypertension itself has also been associated with an increased risk for stroke and heart attack.

Overconsumption of high-calorie foods, as typically seen in obesity, is a risk factor for type-2 diabetes. Type-2 diabetes is a disease in which, as a result of excessive glucose, the body's insulin receptors become insensitive to circulating insulin. This insensitivity results in the distortion of satiety signals and in the dysregulation of glucose consumption by the body. Left untreated, diabetes can cause vascular disease resulting in stroke, digit and limb loss, blindness, neuropathy, kidney damage, and Alzheimer's disease.

Finally, obesity has been linked to numerous types of cancer (for review, Calle & Thun, 2004). Though still being investigated because of the various types of cancers, the common cause of obesity-related cancers revolves around insulin and Insulin-like growth factors (IFGs) and their propensity to induce abnormal, uncontrolled cell growth (Giovannucci, Ascherio, Rimm et al., 1995; Macaulay,1992; LeRoith, Baserga, Helman, et al.,1995). An increase in circulating insulin, especially in the case of type-2 diabetes, can easily precipitate an increased risk for malignant growths.

In addition to numerous physical health issues associated with obesity, mental health may also be of concern for those that are obese and overweight (for review, Lopresti & Drummond, 2013). Independent of age, gender, and race, individuals with bipolar disorder were twice as likely to be obese compared to non-clinical controls (Goldstein, Liu, Zivkovic et al., 2011). Another study found that obesity significantly increased the odds of having any anxiety, mood, personality, and/or alcohol use disorder (Petry, Barry, Pietrzak et al., 2008). Luppino and colleagues brought to light the bidirectional relationship between obesity and depression. In their 15 study meta-analysis, they revealed that depression was a risk factor for obesity as well as the reverse—obese individuals were at greater risk for depression (Luppino, de Wit, Bouvy et al., 2010).

Dysregulation of bodily systems is common in obese populations including widespread inflammatory and oxidative stress as well as neurotransmitter imbalance. High accumulation of adipose tissue increases the secretion of inflammatory cytokines and escalates the peroxidation of lipids and proteins (Vincent, Innes & Vincent, 2007). Kynurenine, a metabolite of tryptophan, is abnormally up-regulated in obesity. Because of its close association with serotonin, the dysregulation of kynurenine has been implicated in major depressive disorder, schizophrenia, and bipolar disorder (Myint, Schwarz & Muller, 2012). Overproduction of this pathway is also linked to increased oxidative stress (Myint et al., 2012) and an impairment of serotonin release in the hypothalamus is known to be associated with overeating (Svec, Thompson, Corll et al., 2002). Taken together, the aforementioned physical and mental deficiencies in obesity

make for a compelling reason to investigate not only weight loss, but more importantly, weight loss maintenance.

Obesity & Addiction

Addiction is chronic state characterized by loss of control and excessive intake of a rewarding substance regardless of the detrimental health or life consequences. Addiction is typically associated with substance abuse and is often defined by excessive energy invested in seeking the addictive substance, intense craving for, tolerance, and withdrawal symptoms that accompany absence of the substance. A model of obesity as an addiction similar to substance addiction has been proposed (Volkow, Wang, Fowler, & Telang, 2008) and the striking similarities between drug addiction and obesity have been previously noted (for review Volkow, Wang, Tomasi et al., 2012).

Evolution equipped humans with mechanisms to desire and seek out rewards. Participating in natural rewards such as eating and sex elicits pleasurable responses that initiate processes that aim to increase the likelihood that the behaviors will be repeated. In the case of illicit substances, such as heroin or cocaine, these substances hijack the natural reward circuitry and thus, induce the same reinforcement mechanisms that have evolved to accommodate beneficial food and mating behaviors. Obesity has long been referred to as the consequence of an addiction to food—a distorted adaption of the consumption of a natural reward. An addiction to food is a highly complex phenomenon that involves many brain areas including sensory (insula), emotion and memory (amygdala and hippocampus), homeostatic (hypothalamus), and reinforcement/reward (ventral striatum/nucleus accumbens) processes.

Dopamine (DA) is the primary neurotransmitter involved in reinforcement mechanisms. The primary reinforcement circuit, sometimes referred to as reward circuit, involves dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) (Wise, 2006). With exposure to food, a naturally reinforcing substance, activity of this circuit increases, releasing greater levels of dopamine in the NAc (Norgren, Hajnal & Mungarndee, 2006). After repeated exposure to a specific food reward, the DA system becomes less responsive as tolerance to that food reward develops (Epstein, Temple, Roemmich et al., 2009). In other words, habitual food exposure dampens the DA response and a once highly rewarding food is not as rewarding as it was at first exposure. This is the same tolerance phenomenon that is widely observed in substance addiction as addicts must consume greater amounts of drug to experience the same level of euphoria. Another critical component of addiction is the establishment and heightened salience of reward-anticipation cues. Because of the evolutionary advantage of repeatedly obtaining rewarding substances, cues in the environment that are associated with successfully obtaining rewards are preferentially processed with high reactivity (Drummond, 2001). In other words, food associated cues (e.g. the smell of the food or an advertisement for a restaurant) induce craving (Robinson & Berridge, 1993) even in the absence of the actual food. While obese individuals demonstrate greater activation in reward circuitry when viewing high-calorie foods (Stoeckel, Weller, Cook et al., 2008; Rothemund, Preuschhof, Bohner et al., 2007), interestingly, these individuals experience a decrease in activation of reward centers when actually consuming the high-calorie foods and increase in activity in somatosensory regions that specifically process palatability (Stice, Spoor, Bohon et al., 2008). These results together have been

suggested to explain the compensatory, reward-driven overeating that is characteristic of obesity (Stice, Spoor, Bohon & Small, 2008).

Impulsivity & Cognitive Restraint

In addition to the reward-driven craving that characterizes addiction there is also a disinhibition or loss of control that contributes to the continued use and abuse of substances (in drug addiction) or the continued eating beyond satiety in obesity. Thus, cognitive restraint and inhibitory control are crucial to overcoming addiction and avoiding relapse. As shown in animal models, up-regulation of striatal dopamine D_2 receptors (DR2) reduces impulsive drug consumption (Thanos, Volkow, Freimuth et al., 2001) whereas DR2 down-regulation enhances the sensitization of the drug effects (Ferguson, Eskenazi, Ishikawa et al., 2011) inducing greater impulsive intake. In humans, this reduction of striatal dopamine directly reduces activity in the orbital frontal cortex (OFC), anterior cingulate cortex (ACC), and dorsal later prefrontal cortex (dlPFC). Given the aforementioned brain regions and their crucial role in inhibitory control, reward anticipation, and decision making, it is theorized that this mechanism underlies the loss of self-control associated with addiction and impulsive drug-seeking in states of craving and withdrawal (Goldstein & Volkow, 2002; Volkow & Fowler, 2000). Crucially, for our current discussion, this reduction in striatal DR2 has been documented in obese individuals (de Weijer, van de Giessen, van Amelsvoort et al., 2011) indicating a possible reduction in the ability to exhibit appropriate levels of cognitive control in obese individuals.

Impulsivity, a trait heavily associated with cognitive control, has been identified as a multi-faceted construct, comprising many different derivatives and manifestations (Evenden, 1999). In general, impulsivity can be defined as acting quickly with lack of forethought which may or may not be appropriate for the situation. Impulsivity has been synonymous with a lack of self-control or a break-down of inhibitory control. However, impulsivity has been repeatedly associated with psychiatric disorders including, most notably, substance abuse and attention deficient hyperactivity disorder as well as bipolar disorder and personality disorders (Moeller, Barratt, Dougherty et al., 2001). Recently, behavioral addictions such as gambling, binge eating, excessive shopping, and internet use have also been recognized as highly impulsive phenomenon (Grant, Potenza, Weinstein et al., 2010). Ironically, the role of cognitive restraint in weight loss and weight loss maintenance is equivocal. Counter-intuitively, a recent meta-analysis revealed that out of 40 total studies neither dieting nor restrained eating significantly predictor weight loss (Lowe, Dashi, Katterman et al., 2013). In fact, 75% of the dieting-based studies and 5% of the restrained eating studies significantly predicted *weight gain*. More research in needed to fully understand the role of cognitive restraint in weight loss and weight loss maintenance.

Weight Loss Maintenance

With so many mechanisms (salient reward and low impulse control) are evolutionarily hard-wired to drive humans to seek-out and consume large amounts of food, it's no wonder that weight loss in general is difficult to achieve. In fact, most individuals who successfully managed to lose an average of 10% of their initial body weight have

demonstrated a return to baseline (relapse) in a mere 2-5 years, some in as little as six months (Kouvelioti, Vagenas, Langley-Evans, 2014; Carnell, Gibson, Benson et al., 2012; Wadden, Sternberg, Letizia et al., 1989; Wadden, Stunkard & Liebschutz, 1988). Countless weight loss programs and methods exist in society and their success can be attributed to a combination of calorie restriction, behavioral modification techniques, pharmacological interventions, and physical activity/exercise (Kraschnewski, Boan, Esposito et al., 2010; Anderson, Konz, Frederich et al., 2001). However, despite their prevalence and initial weight-loss success, a disappointing minority of individuals successfully maintain weight loss years later thus indicating that a better understanding of the neurobiological factors that contribute to weight loss maintenance success is necessary.

It has been hypothesized that failure to maintain weight loss can be attributed to a combination of hyperactive reward centers and hypoactive cognitive control abilities (Blomain, Dirhan, Valentino et al., 2013; Carnell, Gibson, Benson et al., 2012; Volkow, Wang, Fowler, Tomasi & Telang, 2011; Volkow, Wang, Fowler & Tomasi, 2012; Tataranni & Delparigi, 2003). Neuroimaging evidence reveals that post-obese individuals fail to demonstrate a compensatory attenuation of reward anticipation to food cues after being subjected to overfeeding. In other words, compared to thin individuals, post-obese individuals demonstrated significant brain activation in the insula, inferior visual cortex, and hypothalamus after experiencing overfeeding. Authors concluded that this was evidence of greater attentional resources being allocated to food despite sufficient energy balance in post-obese individuals, indicating their vulnerability to excessive energy intake (Cornier, Salzberg, Endly et al., 2009). Another study conducted

in 2009, compared successful weight losers to obese and normal weight controls on their responses to food pictures. Results indicated greater activation in the left superior frontal and right middle temporal regions in successful weight losers compared to the normal weight and obese individuals. Authors posit that greater cognitive restraint as evidenced by the superior frontal regions and conscientious food monitoring, via the middle temporal activation, provide support for their successful weight loss maintenance (McCaffery, Haley, Sweet, et al., 2009). More recently, Sweet and colleagues reported similar findings with an investigation into the temporal nature of recruitment of inhibitory control areas and orosensory information (Sweet, Hassenstab, McCaffery, et al., 2012). In this study, successful weight maintainers demonstrated greater reward activation to an oral food stimulus than either obese or normal weight individuals. However, despite the greater reward activation in the left putamen, successful weight maintainers recruited greater inhibitory control processes—via activation in the left inferior frontal gyrus—compared to the other groups following food presentation (Sweet et al., 2012). In addition, a PET imaging study revealed a significant correlation between dietary restraint and recruitment of inhibitory control areas such as the dorsal prefrontal cortex (dPFC) after exposure to oral-food stimuli in successful dieters (Delparigi, Chen, Salbe et al., 2007). The aforementioned studies implicate activation in the prefrontal areas (e.g. superior and inferior frontal regions) as the key to successful weight loss maintenance via cognitive control abilities. Additionally, increased reward anticipation (putamen) and visual processing evidence (e.g. middle temporal region) support this idea with the notion that individuals that have maintained weight loss are more likely to be sensitive reward

but simultaneously more likely to engage in compensatory actions such as cognitive restraint.

A common neuroimaging paradigm for measuring inhibitory control/cognitive restraint is the Go/No-Go task. Participants engage cognitive control areas in order to countermand a prepotent motor response. Past studies implementing fMRI Go/No-Go tasks have demonstrating robust activation in the dlPFC, ACC, insula, and inferior parietal areas (Garavan, Hester, Murphy et al., 2006) as well as inferior frontal and superior frontal gyri (Nakata, Sakamoto, Ferretti, et al., 2008). In addition to the cognitive control regions mentioned above, a recent study characterized the neural networks of successful and unsuccessful response inhibition during a task of inhibitory control with over 1,800 participants. Whelan and colleagues reported the networks most active during successful motor inhibition are: bilateral basal ganglia structures (putamen, caudate, pallidum, and thalami), the right inferior frontal gyrus, right insula, right anterior cingulate, bilateral substantia nigra and subthalamic nuclei, bilateral superior and middle orbital gyri, bilateral superior, middle, and medial orbital gyri, bilateral inferior and superior parietal lobules, and bilateral pre-SMA and precentral gyri (Whelan, Conrod, Poline et al., 2012). Brain regions that are involved when a participant fails to inhibit include: bilateral anterior cingulate, insula, and inferior frontal gyrus, bilateral substantia nigra and subthalamic nuclei, bilateral putamen, caudate, and pallidum, bilateral posterior cingulate, and bilateral superior, middle, and medial orbital gyri (Whelan et al., 2012). With regards to obesity, an elegant fMRI study performed by Batterink and colleagues (2010) successfully correlated greater BMI with hypo-functioning of frontal inhibitory brain regions (e.g. mPFC, orbital frontal cortex, superior and middle frontal gyri) as well

as greater activation in food-reward centers in response to a food-based Go/No-Go task (Batterink, Yokum & Stice, 2010). Additionally, individuals with higher BMIs committed significantly more errors of commission than those with lower BMIs (Batterink et al., 2010). A Go/No-Go task using food-associated words and neutral-object words was recently tested in obese and normal weight individuals (Loeber, Grosshans, Korucuoglu, et al., 2012). Surprisingly, results indicated greater inhibitory control impairment was related to neutral stimuli (i.e. greater number of errors of commission). More importantly, the number of errors nor the reaction time were related to BMI, even though authors predicted that obese individuals would be more impaired in this situation due to their preoccupation with food cues. In contrast, another recent study found impairments in inhibitory control abilities (increased reaction time and greater number of errors of commission) in obese/overweight individuals with binge-eating disorder in both food and neutral stimuli conditions, though poor performance was exacerbated in the food condition compared to non-binge eating disorder individuals (Svaldi, Naumann, Trentowska, et al., 2014). Though the authors posit binge-eating disorder could explain the discrepancy between the two aforementioned studies, this demonstrates the importance of much needed research in the context of obesity, related topics such as weight loss, and inhibitory control.

Given the similarities between drug addiction and obesity it is important to note important findings in the drug-abstinence literature. During a Go/No-Go task, no significant differences in inhibitory brain activation nor the number of errors of commission were revealed between abstinent cocaine users and healthy controls (Bell, Foxe, Ross, et al., 2014). In addition, it was revealed that activation in the insula was

related to the length of abstinence which the authors suggest could indicate a mechanism which facilitated the continued abstinence (Bell et al., 2014). These results are in contrast to the literature that inhibitory control is impaired in current cocaine users (Garavan, Kaufman & Hester, 2008; Kaufman, Ross, Stein et al., 2003). To add support for a recoverable inhibitory control circuit in former addicts, a complimentary study also found no significant deficits in inhibitory control—both electrophysiologically and behaviorally—in abstinent drug users compared to healthy controls (Morie, Garavan, Bell et al., 2014). Thus, for the purpose of the current study, individuals that lose weight and maintain the weight loss (or continue to lose weight) can be considered 'abstinent' and therefore may demonstrate appropriate levels of inhibitory control. Further it is possible that individuals that fail to maintain weight loss could represent current drug abusers and thus their inhibitory control performance and brain activity may be compromised.

While recruitment of inhibitory control regions has been investigated in successful weight losers, much research is needed on their specific role in weight loss and weight loss maintenance. To date there are no studies that attempt to characterize response inhibition brain activation patterns in individuals who have experienced a range of initial weight loss success and a subsequent range of longitudinal individual weight loss outcomes (i.e. weight regain, continued weight loss, or maintenance of original weight loss). The current study takes a spectrum approach (i.e. using continuous variables) to weight loss and weight loss maintenance success in a group of older adult women. It is expected that the more weight an individual is able to initially lose and subsequently maintain or continue to lose, the greater recruitment of inhibitory control

brain regions they will demonstrate. Additionally, better task performance (i.e. fewer errors of commission) will also be demonstrated by these indidividuals.

Resting State Functional Connectivity

In addition to investigating response inhibition activation, the current study includes an analysis of seed-based resting state functional connectivity (FC) with inhibitory control regions. Much like traditional task-based fMRI, resting state analysis attempts to directly assess the functional connectivity between brain regions by measuring synchronous changes in BOLD signal. However, rather than engaging in a cognitive task, the participants are scanned while in a resting, but not sleeping, state. The first resting state study was conducted in 1995 investigating the FC of the sensorimotor cortex (Biswal, Kylen, Hyde., 1997). It was in this study that the low frequency (e.g. 0.01 to 0.1Hz) fluctuations in activation were established as the dominant frequency of resting state connectivity. Temporal correlations from structurally independent regions that express these low frequency periodic changes are thought to represent the brain's functional organization—a variety of networks that have been shown to be remarkably abnormal or altered in diseases such as Alzheimer's (Li, Wu, Chen et al., 2012), Parkinson's (Tessitore, Amboni, Esposito et al., 2012), and epilepsy (Wurina, Zang & Zhao, 2012) as well as many mental disorders including obsessive compulsive disorder (Li, Li, Dong et al., 2012), schizophrenia (Venkataraman, Whitford, Westin, et al., 2012, and attention deficit hyperactivity disorder (Uddin, Kelly, Biswal et al., 2008).

Combining task-activation connectivity and resting state is an effective method for strengthening conclusions about the functional relationships between brain areas. An

early study in 2002 was able to validate FC results from task-related activation with resting state connectivity (Hampson, Peterson, Skudlarski et al., 2002). The authors successfully identified a network from a listening task that was subsequently revealed to be active in the resting state with the same subjects (Hampson et al., 2002). Condensing brain imaging data from over 30,000 individuals, another more recent study was able to confirm that functional task networks and sub-networks are still dynamically active even in the resting state (Smith, Fox, Miller et al., 2009). By using a seed region selected from response inhibition activation, functional connectivity can be mapped across the brain to understand cognitive networks that are associated with inhibitory control regions during resting state. This is turn could provide insight into functional networks that could help explain the role of cognitive restraint in weight loss and weight loss maintenance.

A recent study investigated the resting state functional connectivity of lean and obese individuals during a fasting state and following a meal (Lips, Wijngaarden, van der Grond et al., 2014). After feeding, only lean individuals demonstrated a decrease in FC between the hypothalamus and insula which the authors interpreted to indicate that lean participants could intrinsically evaluate the satiation of food intake and attenuate food-wanting signals. Additionally, FC in reward areas did not diminish as a result of food intake in the obese individuals. In sum, the authors suggest that obese individuals could not affectively differentiate between hunger and satiety (Lips et al., 2014). Another study involving obese and normal weight children revealed a greater FC between the middle frontal gyrus and the orbital frontal cortex (Black, Lepping, Bruce et al., 2014). Authors concluded that this was indicative of a greater influence of reward on inhibitory control

areas potentially contributing to the obese individuals' susceptibility to environmental food-cues.

To date there have been no resting state functional connectivity studies that specifically target response inhibition seed-regions in an attempt to understand the functional connectivity patterns in weight loss participants. Based on previous obesity research, it is anticipated that individuals who successfully managed to lose a percentage of initial body weight and then subsequently experienced a weight relapse will demonstrate greater functional connectivity between areas of inhibitory control regions (i.e. response inhibition task-activation) and reward areas. This greater tonic input from reward-regions during instances of low-cognitive strain is hypothesized to explain the inability to inhibit inappropriate behaviors such as over-eating or eating unhealthy foods in an everyday environment, thus facilitating weight regain.

Materials & Methods

iReach Weight Management Program

The Department of Nutrition and Food Sciences at the University of Vermont conducted an 18-month weight loss program for men and women (Harvey et al., *in preparation*). All relevant materials and methods have been previously documented (Harvey-Berino, Pintauro, Buzzell et al., 2004). In sum, the authors were interested in the effects of motivational interviewing on a fixed schedule versus a contingent schedule in conjunction with internet-based weight loss intervention techniques on weight loss. Weight measurements for this study were collected at baseline, six months, 12 months, and 18 months. The current study focused on women who experienced weight loss by six months and then subsequent weight relapse, maintenance, or continued weight loss 12 months after the initial six months. All of the current study participants lost between 4.47 and 25.2% of their baseline body weight in the first six months. Whether participants regained, continued to lose, or maintained initial weight loss they were required to have participated in the weight management program until its 18-month completion.

Participants

A total of 31 women (1 left-handed, 1 African American, 1 Hispanic, mean age 55.4 years; range 31-72) participated in this study. All participants had normal or corrected to normal vision with no prior history of psychiatric illness or severe medical condition including but not limited to substance abuse, schizophrenia, panic disorder, seizure disorders, traumatic brain injury, cardio-pulmonary concerns, and/or kidney or liver failure. Participants were also screened for possible pregnancy and for any MRI

contraindications such as piercings, medication patches, IUDs, pacemakers, aneurism clips, hearing implants, pins, plates, and/or screws. All participants had a high-school education or higher. Relevant demographic information is summarized in Table 1. Despite being screened prior to data collection, one subject did not complete the study because she experienced claustrophobia upon entering the scanner.

Table 1. Age and BMI participant descriptive statistics

	Minimum	Maximum	Average	Std. Deviation
Age	31	72	55.35	10.91
BMI				
Baseline	26.86	48.25	33.82	5.04
Six months	21.25	45.28	29.95	5.25
Scan	20.77	49.24	30.15	6.30

Age is expressed in years at the time of scan. BMI (kg/m^2) was calculated using self-report height and weight. Baseline and six month weight were measured with a standardized scale as part of the procedures in the iReach Weight Management study and scan weight was self-reported.

Experimental Procedure

All data for the current study were collected in a single visit per subject over a 10 month period. Participants arrived at the University of Vermont Health Center two hours before their scheduled MRI scan. In a quiet room, all participants completed informed consent, MRI safety and health questionnaires, as well as assessments measuring subjective trait impulsivity, eating behaviors, exercise/physical activity levels, and a hunger scale (detailed descriptions below). Participants then practiced the response inhibition task as well as two other tasks that will not be discussed in this current study.

Participants were briefed on the MRI procedures. All metal objects were removed from person and clothing before entering the scanner. Plastic framed glasses

were also provided for participants who needed corrected vision but did not wear contact lenses. Earplugs and a blanket were given for comfort as well as a pillow placed under the knees for lower back support. All task stimuli were projected on to screen which was viewed through the back of the MRI bore via a mirror that was placed on the head-coil. Participants were instructed on proper use of the response triggers as well as instructed to use the emergency call button in the event of an emergency. Upon completion of the scan, all participants received $50 compensation. A clinical radiologist reviewed all anatomical scans for physical abnormalities.

Paper Assessments

Barratt Impulsivity Scale (BIS-11)

This scale assesses trait impulsivity and was used to behaviorally assess individual impulsive tendencies. In particular, it provides a subjective rating of impulsivity to compare to the objective task impulsivity that can be measured by the response inhibition task. A 30-item scale, the BIS was designed to measure both personality traits and behaviors characteristic of impulsivity. The BIS has been used in psychological and psychiatric research for over 50 years (Barratt, 1959; Stanford, Mathias, Dougherty et al., 2009) and the latest addition, BIS-11, (Patton, Stanford, & Barratt, 1995) has accumulated over 500 citations since its development in 1995. The scale is designed on a Likert scale from 'Rarely/Never', 'Occasionally', 'Often', to 'Always/Almost Always' and includes statements such as "*I can only think about one thing at a time*", "*I am future oriented*", and "*I say things without thinking.*" Scoring for this scale results in three categories of impulsivity: attentional, motor, and nonplanning.

Three-Factor Eating Questionnaire-Revised 21 (TFEQR21)

This questionnaire measures three facets of eating behavior: emotional eating (EE), uncontrolled eating (UE), and cognitive restraint (CR). Much like the BIS provides a subjective measure of impulsive behaviors, the TFEQR21 provides a subjective assessment of an individual's eating behaviors. This assessment was used to correlate eating behaviors with brain activation patterns.

Emotional eating is broadly described as experiencing greater hunger and less self-control over eating behavior when in a state of emotional distress. Uncontrolled eating is the feeling of not being able to stop once eating has been initiated especially beyond the point of satiety. Lastly, the cognitive restraint factor is the degree to which individuals consciously monitor their food intake in order to maintain a certain weight or diet. Originally, the TFEQ was a 51-item inventory that measured cognitive restraint, disinhibition, and hunger (Stunkard & Messick, 1985). Several studies have noted the success of the original measure to describe the eating behaviors of both overweight/obese individuals as well as normal weight individuals (Lindroos, Lissner, Mathiassen et al., 1997; Annunziato, Lee & Lowe 2007; Svendsen, Rissanen, Richelsen et al., 2008). Importantly, it was found that disinhibition had the strongest connection to obesity and high-calorie food intake (Lindroos et al., 1997). Similarly, reduction of disinhibition and amplification of cognitive restraint were crucial factors in sustained weight loss maintenance (Svendsen et al., 2008). A shorter-18-item version was subsequently designed. Not only was it more efficient, but it also incorporated the EE factor, replacing the hunger factor (Karlsson, Persson, Sjöström, et al., 2000) and was successful at describing the eating behaviors of both obese and normal weight individuals (de Lauzon,

Romon, Deschamps et al., 2004). An additional three items were added to avoid floor and ceiling effects and thus, the most recent version is the TFEQR21 was established and to date has been documented to be stable and valid (Tholin, Rasmussen, Tynelius et al., 2005).

The Aerobic Center Longitudinal Study Physical Activities Questionnaire (ACLSPAQ)

By measuring exercise and physical activity we can investigate whether differences in brain function are due to difference in exercise levels rather than increased inhibitory control or cognitive restraint. This detailed survey asks participants to identify and elaborate on physical activities that they have done on a regular basis within the last three months. For most activities, the subject indicates (and/or describes in more detail if needed) the type of activity, how long each activity is performed on average (minutes), and how many days a week they engage in each activity. For items such as walking, a speed (mph) and distance (miles) are also included and for stair-climbing an average speed of ascent is included as well as a standardized 1 flight = 10 steps. Space was available for participants to elaborate on an activity that was not included in the standard list. The ACLSPAQ's ability to predict fitness levels has been previously validated (Kohl, Blair, Paffenbarger et al., 1988). All grading was completed using activity designated codes and metabolic equivalent of task (MET) levels (Ainsworth, et al., 1993) and values are reported as average METs/wk.

Hunger Scale

Adapted from *You Count, Calories Don't*, this is a simple 1-10 scale that assesses a participants' current hunger state (Omichinski, 1992). Each number is associated with a statement that ranges from a 1 = "*Beyond hungry: You may have a headache. You cannot concentrate and feel dizzy. You may have trouble with coordination. You are totally out of energy and very likely have a low blood sugar level. This often happens when meals are skipped or very little food or protein is eaten*" to a 10 = "*Beyond full: This is a typical Thanksgiving Dinner feeling. You are physically miserable, do not want to or cannot move, and feel like you never want to look at food again*." This form was included to ensure that subjects would not be distracted by hunger pains nor that they would feel nauseated upon beginning the scan because they had eaten too much prior to the initiation of the study visit. To complete the form, participants need only circle the number that best applies to their current state as well as to include a brief explanation of the last thing that they ate/drank and when this occurred. Participants were not allowed to continue if they circled a 1 or a 10 on the hunger indicating that they are famished or extremely full, respectively.

Go/No-Go Task

To assess inhibitory control, two runs of a neutral stimuli Go/No-Go task were used. Using the letters 'X' and 'Y' the participant were presented with a continuous stream of alternating letters. When the letters successfully alternated 'XYXYXY' the participants were told to press a response button every time a letter appeared on the screen. On 10% of the trials the pattern was disrupted via a repeated letter, 'XYXYYX' or 'XYXXY', and during this instance, the participants had to withhold their response. The stimuli were presented at 1 Hz. Each run was 264 seconds and there were 225 'Go' trials and 25 'No-Go' trials. By having a greater number of Go trials than No-Go trials the prepotent action of button-pressing is established. The two separate runs of the task were concatenated together for analysis. The behavioral variable of interest was the number of errors of commission which was used to assess task performance and help understand the relationship between weight loss and brain activations.

Go/No-Go Task Image Acquisition

All structural and functional MRI acquisitions were performed with a 3T Phillips-Achieva d-Stream scanner with a 32-channel birdcage brain coil. Additional padding was used to restrict participant head movement. Disregarding functional tasks that are not pertinent to this paper, five-hundred and twenty-eight T2*-weighted transversal echo-planar images (repetition time = 2000 ms, echo = 35 ms, flip angle = 90°, 32 slices, slice thickness 4 mm, .4 mm gap, voxel dimensions 3.75 x 3.75 x 4.0 mm, field of view 240 x 240 mm, 64 x 64 in-plane resolution covering the whole brain were acquired.

Resting State Image Acquisition

One-hundred and eighty T2*-weighted transversal echo-planar images of the whole brain were acquired while the participant rested with their eyes open. The parameters for the resting state scan were: repetition time = 2000 ms, echo = 35 ms, flip angle = 90°, 33 slices, slice thickness 4 mm, .4 mm gap, voxel dimensions 3.4 x 3.4 4.0 mm^3, field of view 240 x 240 mm^2, and 64 x 64 in-plane resolution.

Anatomical Scan Acquisition

A standard high resolution sagittal anatomical scan was acquired using an inverse recovery T1-weighted sequence TFE (MP-RAGE) in the same orientation as the functional scan to provide detailed anatomy to align the functional data with. The structural sequence was .8 mm^3 isotropic (repetition time = 10 ms, echo = TE of 4.5 ms, flip angle = 8°, 320 slices, slice thickness 4 mm, no gap, field of view 256 x 256 mm^2, 64 x 64 in-plane resolution).

Go/No-Go fMRI Preprocessing

Preprocessing and statistical analysis of brain imaging data were performed using AFNI (Analysis of Functional NeuroImages, Cox, 1996). Anatomical data were deobliqued, skull-stripped, and warped into Talairach space (Talairach & Tournoux, 1998). Functional data were deobliqued, slice time corrected, and motion corrected across the six motion parameters. Once aligned to the anatomical data, edge detection was used to remove activation outside the brain and the two task runs were concatenated together. Lastly, a final motion correction was performed to account for movements between the

two runs. Three participant maps were excluded from the error-related activity map due to a limited number (less than 10) of errors across both runs resulting in n = 28. No participant data was removed for the successful inhibition map analysis, n = 31.

Statistical analysis of the preprocessed fMRI data on the individual level was performed by estimating activation measures for specific task time points using the general linear model. Specifically, the time points of interest were when individuals successfully inhibited a response (stops) and when they did not (error of commission). A hemodynamic response was deconvolved at a 2 second temporal resolution and then subsequently modeled voxel-wise with a gamma-variate function using non-linear regression techniques (Murphy & Garavan, 2005). The final activation measure for this event-related design was calculated with the hemodynamic model area-under-the curve estimation which was expressed as a percentage of the tonic baseline activity. Activation maps were warped into Talairach space (Talairach & Tournoux, 1998) and spatially smoothed with a 4.2 mm full-width half-maximum isotropic Gaussian kernel.

Resting State Functional Connectivity (RSFC) Preprocessing

The preprocessing for resting state was performed using a combination of AFNI and FMRIB Software Library (FSL) and was based on the processing pipeline of the 1000 Functional Connectomes Project (Biswal, Mennes, Zuo, et al., 2010). Preprocessing consisted of deobliquing, skull-stripping, edge detection, slice time correction, head motion correction (across the six motion parameters), and despiking (i.e. removing time series outliers; instances of extreme signal change). Spatial smoothing of resting state

data used a 6 mm full-width half-maximum Gaussian kernel followed by mean-based intensity normalization, band-pass temporal filtering for frequencies in the range of 0.01 – 0.1 Hz, and removal of linear and quadratic trends. The participant's high-resolution T1 anatomical scan described earlier was normalized to a 2 x 2 x 2 mm Montreal Neurological Institute (Quebec, Canada) template (ICBM152, based on an average 152 normal MRI scans) using a linear transformation (FLIRT) (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, et al., 2002) and then a non-linear transformation (FNIRT) (Anderson, Jenkinson & Smith, 2007). The nuisance regressors for this analysis included the six motion parameters and the average signal from white matter and cerebrospinal fluid to control for biological fluctuations not of interest (Kelly, Uddin, Biswal, et al., 2008). Each seed-region from the response inhibition task was applied to each participant's native space and an average time-series was extracted and this value was regressed against all other voxel time-series. This produced a whole brain correlation map that was transformed to a z-score map that was then warped into standard MNI space.

Go/No-Go Statistical Analysis

Total weight loss (TWL) was calculated for each subject as a percent of their baseline weight expressed as negative numbers indicating that the subject obtained a net *loss* of weight and positive values indicating a net *gain* of weight, (TWL = [(Scan weight – Baseline weight)/Baseline weight] x 100). Using 3dRegAna in AFNI, a whole brain regression was performed with age as a covariate and TWL as the variable of interest

using both the error activation and stop activation maps. To correct for multiple voxel-wise comparisons, a cluster-size criterion was calculated using 3dClustSim—a Monte Carlo simulation within AFNI. An uncorrected $\alpha = .005$ and a cluster-size criterion of 291μl for a corrected $\alpha = .05$ revealed no surviving significant clusters in the stop activation map. Significant clusters at this threshold in the error activation map were revealed to be located in white matter or cerebrospinal fluid and were, therefore, deemed unreliable. Thus, to understand the relationship between TWL and specific task-activated brain regions, a region of interest (ROI) approach was taken. A one-sample t-test was used to select regions of interest for error activation and successful inhibition (stop) activation. An uncorrected threshold of $\alpha = 0.0001$ (Errors $t = 4.59$; Stops $t = 4.51$) was selected to define regions of activation. A cluster size minimum of 200 μl was selected for clusters (approximately a corrected $\alpha < 0.001$). Eighteen regions (8 error activations and 10 stop activations) exhibited significant activation at this threshold (Table 2) (Table 3). Activation scores were extracted from these discrete clusters in each of the activation maps for each subject and then exported to Statistical Package for the Social Sciences version 21 for Macintosh (SPSS, Chicago, IL, USA) for multiple hierarchal regression analysis.

The first step in testing whether TWL was significantly related to any of the ROIs mentioned above required a curve estimation in order to test for a linear and/or quadratic relationship between TWL and the extracted activation scores. Only two regions in the stop activation map revealed a significant relationship to TWL: the right inferior frontal gyrus and the right superior frontal gyrus. Prior to conducting hierarchal multiple regressions, the relevant assumptions of this statistical analysis were tested. The

collinearity statistics (i.e. Tolerance and VIF) were all within acceptable limits (Coakes & Steed, 2003; Hair, Black, Babin et al., 1998) for all analyses. If a significant relationship was predicted with curve estimation, a hierarchal regression was performed with age as covariate and TWL in the second step. To quantify the contribution of the quadratic relationship we included a quadratic term into a linear regression by added a constant of 10 to eliminate the negative values present and then squaring the new values.

The role of these two regions was probed further by testing whether initial weight loss (IWL) or long-term weight loss (LTWL) were significant predictors of brain activity in a multiple regression. IWL was calculated by: ((6 month weight – Baseline weight)/Baseline weight) x 100. More negative values indicated more weight loss. Every participant achieved some percentage of weight loss in the first six months (Figure 2). The range of IWL was from 4.47 to 25.2% of initial body weight. LTWL was calculated by the equation: ((Scan weight – 6 month weight)/6 month weight) x 100). In other words, the variable represented the net fluctuation in weight in the 12 months following initial weight loss. A negative value was associated with continued *weight loss* beyond their initial six month weight loss, a value of zero or near zero meant that the individual achieved a zero net change from their initial six month weight loss, and a positive value meant that the individual gained weight after their initial six month weight loss. IWL and LTWL were not significantly correlated, $r(31) = .24$, $p = .190$. After age, IWL and LTWL were entered in the same step of the linear regression. Task performance and exercise were the two predictors that were initially explored in relation to brain activation and weight loss. Lastly, the three subscales of the BIS-11 and the TFEQR21 were also explored as predictors of brain activation in the rIFG and the rSFG.

RSFC Statistical Analysis

The goal of investigating resting state functional connectivity is to reveal if there are coherent activation patterns that are systematically related to total weight loss or more specifically, initial weight loss and/or long term weight loss status. The following seed-based resting state analysis focused on the two areas that were highlighted in the response inhibition task described previously—rIFG and rSFG.

Like the Go/No-Go task, whole-brain regression analysis was supplemented for a region of interest (ROI) approach when coherent whole brain regression results were not revealed. A one-sample t-test tested the resting state activation against the null hypothesis that there was zero activation change. Because only areas of positive correlation were revealed in the one-sample t-test, the top 1% of positive activation (i.e. greater functional connectivity) voxels were used as a uncorrected threshold ($t = 10.42$, $p = 2.55x10^{-11}$). A cluster size criterion of 100 µl was selected as a means of filtering for meaningful activation patterns. The results of this t-test identified the resting functional connectivity ROIs for both rIFG and rSFG activation. Next, each ROI was tested for a correlation with TWL, IWL, or LTWL. Additionally we tested for correlations between performance (i.e. errors of commission), exercise, impulsivity, and eating behaviors.

Results

Go/No-Go Task

Table 2 summaries task performance for the Go/No-Go task and the summary statistics for the questionnaires. Table 3 displays the correlation matrix for all independent variables described above. Although there were significant correlations between certain variables, especially within impulsivity, only one correlation was above $r = .80$ (TWL and IWL) and these two variables were never included in the same regression and as previously noted all regressions passed appropriate thresholds for Tolerance and VIF which assess collinearity.

Table 2: Task behavior and questionnaire summary statistics

Behavioral Measure	Minimum	Maximum	Average	Std. Deviation
Go/No-Go Task				
Total Errors of Commission	5	38	20.65	8.50
Average RT (ms)	249.22	530.61	358.27	56.94
Exercise (MET/wk)	4.15	87.03	41.33	23.91
Impulsivity				
Attentional	9	22	14.90	2.98
Motor	14	29	20.84	3.61
Nonplanning	11	32	21.90	5.00
Eating				
Emotional	6	24	14.77	5.12
Unrestrained	11	29	19.06	4.57
Cognitive Restraint	10	22	17.39	3.25

Behavioral summaries for Go/No-Go task and questionnaires. RT = reaction time

TWL and errors of commission were significantly correlated, $r(31) = -.33$, $p = .035$. After controlling for age, the number of errors of commission was not significantly related to TWL, $R^2 = .11$, $b = .34$, $t(28) = 1.84$, $p = .076$, even after also controlling for reaction time, $R^2 = .18$, $b = .29$, $t(27) = 1.60$, $p = .120$. Likewise, mean reaction time was

also not significantly related to TWL, R^2 = .11, *b* = -.35, *t*(28) = -1.81, *p* = .081, independent of errors of commission.

Table 3. Independent variables correlation matrix

	TWL	IWL	LTWL	Attentional I.	Motor I.	Nonplanning I.	EE	UE	CR	Ex	Performance
TWL	--										
IWL	.71**	--									
LTWL	.86**	.24	--								
Attentional I	.36*	.41*	.19	--							
Motor I.	.35	.33	.22	.62**	--						
Nonplanning I	.31	.21	.28	.54**	.64**	--					
EE	.45*	.20	.45*	.15	.15	.08	--				
UE	.56**	.34	.51**	.45*	.34	.29	.74**	--			
CR	-.58**	-.25	-.60**	-.26	-.09	-.24	-.56**	-.54**	--		
Ex.	-.37*	-.07	-.45*	-.08	-.31	-.40*	-.41*	-.48**	.19	--	
Performance	.33	.32	.22	-.05	.06	-.08	.15	.07	-.14	-.08	--

I = impulsivity, EE = emotional eating, UE = unrestrained eating, CR = cognitive restraint, Ex = exercise
* = significant at $\alpha = 0.05$
** = significant at $\alpha = 0.01$

Tables 4 and 5 display the regions of significant activation for the errors and the stops, that were revealed with a one-sample voxel-wise t-test and Figure 1 highlights the rIFG and the rSFG which were the only two regions that demonstrated significant correlations with TWL.

Table 4: Error Activations (n = 28)

Structure	Hemisphere	Brodmann Area	*x*	*y*	*z*	Size of cluster (µl)
Frontal						
Ant. Cingulate g.	R	32	-1.7	-24.1	+35.6	3666
Sup. Frontal g.	R	~6	-6.7	-12.9	+60.1	593
Temporal						
Insula	R	13	-40.1	-12.6	+0.2	2156
Insula	L	13	+38.9	-11.3	+3.9	1510
Occipital						
Lingual g.	R	~19	-27.5	+72.2	-6.1	1249
Parietal						
Inf. Parietal l.	R	~40	-49.9	+47.6	+43.0	1216
Striatum						
Lentiform n.	L	--	+24.6	-5.9	+8.9	541

Regions-of-interest (ROIs) were created from a one-sample t-test of the ERROR activation condition against the null hypothesis of zero activation. Talairach coordinates for x, y, and z identify the center of mass. g = gyrus; l = lobule; n = nucleus.

Table 5: Response Inhibition Activations (n = 31)

Structure	Hemisphere	Brodmann Area	*x*	*y*	*z*	Size of cluster (µl)
Frontal						
Inf. Frontal g.	R	46	-40.2	-42.1	+10.2	1029
Sup. Frontal g.	R	~6	-16.9	-23.0	+54.4	724
Sup. Frontal g.	R	9	-20.6	-43.8	+36.9	502
Cingulate g.	L	24	+0.3	+25.6	+33.9	626
Medial Frontal g.	R	32	-4.3	-39.1	+21.9	221
Temporal						
Insula	R	13	-36.0	-9.9	+1.3	2496
Insula	L	13	+41.2	-12.2	+3.7	1355
Middle Temporal g.	R	22	-49.8	+33.1	+0.3	716
Parietal						
Supramarginal g	R	40	-45.2	+52.2	+38.7	6548
Cerebellum						
Culmen	L	--	+7.4	+57.9	-24.1	219

Regions-of-interest (ROIs) were created from a one-sample t-test of the STOPS activation condition against the null hypothesis of zero activation. Talairach coordinates for x, y, and z identify the center of mass. g = gyrus

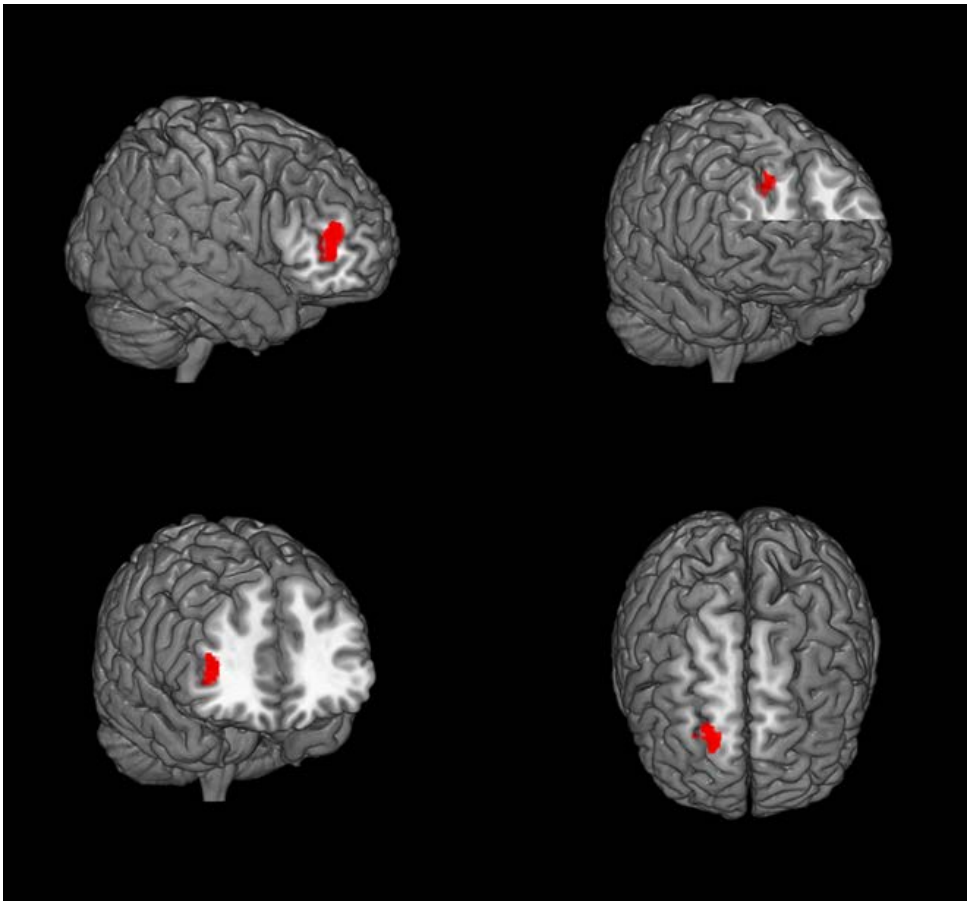


Figure 1. Right inferior frontal gyrus (left) and right superior frontal gyrus (right) ROIs that demonstrated a significant correlation with TWL. Regions were derived from a one-sample t-test that tested the null hypothesis that there was zero activation change in the successful inhibitions activation map (stops).

After adjusting for age, introducing TWL explained a unique 14% of the variance in rIFG activation and this change in R^2 was significant, $R^2 = .14$, $F(1, 28) = 4.61$, $p = .041$, specifically, more activation was associated with less total weight loss (Table 6). Errors of commission were also associated with rIFG activation, $R^2 = .20$, $b = .44$, $t(28) = 2.62$, $p = .014$, indicating fewer errors with less activation. When we controlled for errors in a follow-up analysis, the relationship between TWL and rIFG activation was no longer significant, $b = .26$, $t(27) = 1.47$, $p = .154$.

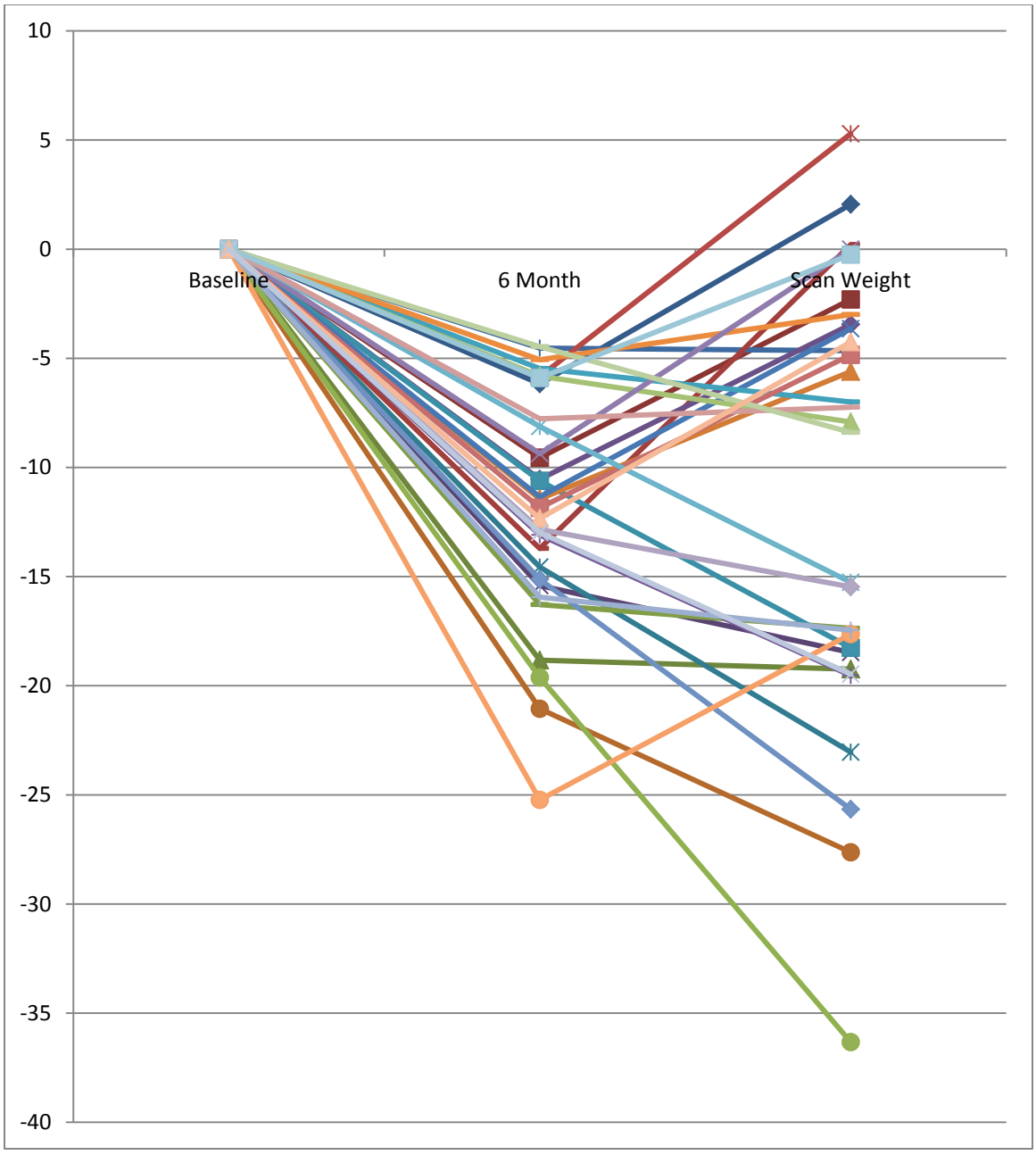


Figure 2: Each line represents a single participant and point zero represents the baseline weight for all participants. Baseline weight is the weight prior to beginning the weight loss program, the six month weight is the weight loss after the initial six months of the program represented as a percent of the baseline and scan weight is the self-report weight of the participants presented as a percent of the baseline weight when they came in for testing. The graph demonstrates that every participant lost some percentage of weight at six months.

A graphical representation of the weight loss achieved by the participants is depicted in Figure 2. Neither IWL, (b = .15, t(27) = 0.77, p = .448) nor LTWL (b = .32, t(27) = 1.72, p = .097) were significant predictors of rIFG activation (Table 6). No quadratic relationships were found for IWL and LTWL with the rIFG.

Table 6: Multiple hierarchal regression results for rIFG

Weight Measure	b value	t-value	p-value
TWL	0.37	2.15	0.041*
IWL	0.15	0.77	0.448
LTWL	0.32	1.72	0.097

* = significant at $\alpha = 0.05$

A single rSFG activation outlier was revealed and upon inspection, the quadratic relationship described below remains significant at $\alpha < 0.05$ whether the case is removed or not, thus, the results below will be presented with the case included. A three-stage hierarchal multiple regression was conducted with activation in the rSFG as the dependent variable, age as a covariate, and TWL +10 and $(\text{TWL} +10)^2$ were added in step two. The $(\text{TWL}+10)^2$ term was a significant predictor of rSFG activation, b = -1.80, t(27) = -2.66, p = .013, and accounted for a unique 17% of the variance in rSFG activation. TWL +10 was also a significant predictor of rSFG activation, b = 1.45, t(27) = 2.5, p = .041. Specifically, as TWL continues to decrease, rSFG activation increases at first and then begins to decrease (Figure 3).

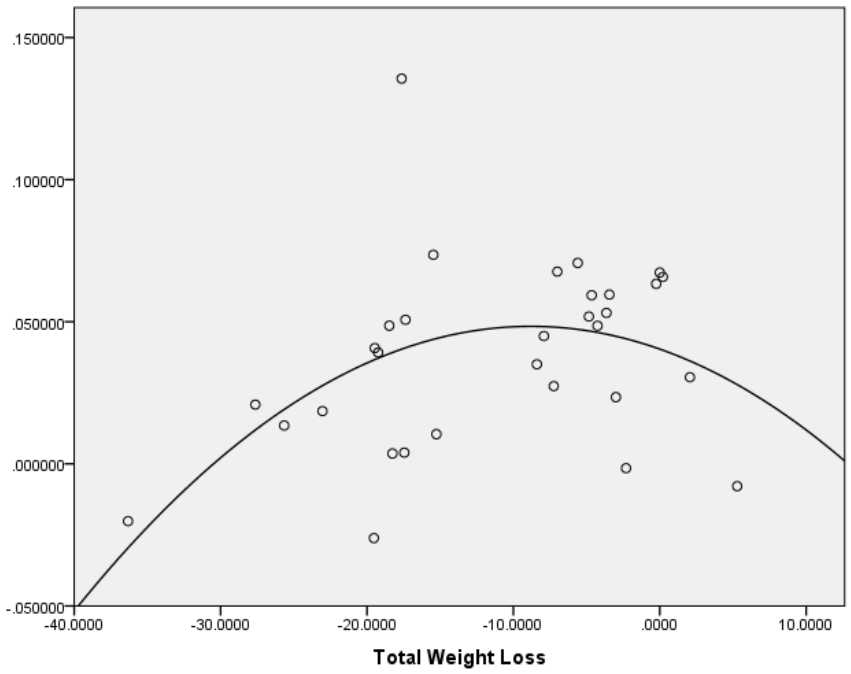


Figure 3: The plot above displays the quadratic relationship between rSFG activation and TWL. Activation is low when TWL is high and when TWL is low. The relationship remains significant at $\alpha < 0.05$ even when an outlier is removed.

To probe the relationship between rSFG activation and weight loss further, TWL was broken down into IWL and LTWL. Entered in the same step (after adjusting for age), IWL was not a significant predictor of rSFG activation, $b = -.20$, $t(27) = -1.23$, $p = .229$ and LTWL was a significant predictor of rSFG activation, $R^2 = .26$, $b = .54$, $t(27) = 3.31$, $p = .003$, indicating that the more weight participants continued to lose the less activation in the rSFG (Table 7).

Table 7: Multiple hierarchal regression results for rSFG

Weight Measure	b value	t-value	p-value
Total weight loss			
Linear	1.45	2.15	0.041*
Quadratic	-1.80	-2.66	0.013*
Initial weight loss	-0.20	-1.23	0.229
Long term weight loss	0.54	3.31	0.003**

* = significant at $\alpha = 0.05$
** = significant at $\alpha = 0.01$

Exercise, Impulsivity & Eating Behaviors

After adjusting for age, exercise was not a significant predictor of rIFG activation, b = -.20, $t(28)$ = -1.08, p = .292 (Table 8). Exercise was a significant predictor of rSFG activation, R^2 = .19, b = -.44, $t(28)$ = -2.68, p = .012, such that greater exercise was associated with less activation (Table 9). When exercise was accounted for, both the linear term and the quadratic term for TWL remained significant; TWL+10: p = .002; $(TWL+10)^2$: p = .001. LTWL was not significantly related to rSFG after adjusting for exercise, p = .375.

Impulsivity was broken down into three different subscales: attentional, motor, and nonplanning. After adjusting for age (step one), none of the impulsivity subscales (entered at step two) were significant predictors of rIFG activation, attentional: b = -.32, $t(26)$ = -1.25, p = .221; motor: b = .32, $t(26)$ = 1.12, p = .274; nonplanning: b = -.02, $t(26)$ = -.10, p = .925. Likewise, none of the impulsivity subscales were significant predictors of rSFG activation, attentional: b = -.35, $t(26)$ = -1.45, p = .158; motor: b = .21, $t(26)$ = .80, p = .430; nonplanning: b = .22, $t(26)$ = .93, p = .362.

Eating behaviors were also broken down into three different categories: emotional eating (EE), unrestrained eating (UE), and cognitive restraint (CR). After adjusting for

age at step one, none of the eating behaviors (entered at step two) were significant predictors of rIFG activation, EE: b = -.08, $t(26)$ = -.27, p = .787; UE: b = .22, $t(26)$ = .76, p = .454; CR: b = -.15, $t(26)$ = -.64, p = .527.

EE was a significant predictor of rSFG activation, b = -.50, $t(26)$ = -2.06, p = .049, revealing that on average the more emotional eating that was reported the less activation in the rSFG. UE was a significant predictor of rSFG activation, b = .77, $t(26)$ = 3.18, p = .004, indicating that on average the more unrestrained eating that individuals reported the greater the rSFG activation. Lastly, CR was not a significant predictor of rSFG activation, b = .03, $t(26)$ = .13, p = .900. Table 8 and Table 9 summarize the behavioral results above. EE was positively correlated with UE, $r(31)$ = .74, p = .010 and negatively correlated with CR, $r(31)$ = -.56, p = .010. CR was negatively associated with UE, $r(31)$ = -.54, p = .010 (Table 3).

Table 8: Behavioral data results for rIFG

Behavioral Measure	b value	t-value	p-value
Exercise (MET/wk)	-0.20	-1.08	0.292
Impulsivity			
Attentional	-0.32	-1.25	0.221
Motor	0.32	1.12	0.274
Nonplanning	-0.02	-0.10	0.925
Eating			
Emotional	0.08	-0.27	0.787
Unrestrained	0.22	0.76	0.454
Cognitive Restraint	-0.15	-0.64	0.527

Impulsivity measures were from the Barratt Impulsivity Scale (BIS-11) and the eating behaviors were from the Three Factor Eating Questionnaire-Revised 21 (TFEQR21). Neither impulsivity nor eating behaviors were significant predictors of rIFG activation at $\alpha < 0.05$.

Table 9: Behavioral data results for rSFG

Behavioral Measure	b value	t-value	p-value
Exercise (MET/wk)	-0.47	-2.68	0.012*
Impulsivity			
Attentional	-0.35	-1.45	0.158
Motor	0.21	0.80	0.430
Nonplanning	0.22	0.93	0.362
Eating			
Emotional	-0.50	-2.06	0.049*
Unrestrained	0.77	3.18	0.004**
Cognitive Restraint	0.03	0.13	0.900

* = significant at $\alpha = 0.05$
** = significant at $\alpha = 0.01$

RSFC Results

With the rIFG as the seed region, our analysis revealed five regions that demonstrated a positive correlation (Table 10). Of these areas, only the left middle temporal gyrus (lMTG) demonstrated a significant relationship to TWL (Table 11). TWL was a significant predictor of functional connectivity between the rIFG and lMTG, $R^2 = .26$, $b = -.51$, $t(28) = -3.39$, $p = .002$, indicating that a greater correlation between the rIFG and the lMTG was significantly associated with increasing TWL. TWL accounted for a unique 26% of the variance in functional connectivity between rIFG and lMTG (Figure 6). When we controlled for errors of commission, the above relationship remained significant, $R^2 = .28$, $b = -.56$, $t(27) = -3.48$, $p = .002$.

IWL was not a significant predictor of functional connectivity between rIFG and lMTG, $b = -.23$, $t(27) = -1.37$, $p = .181$. LTWL was a significant predictor of functional connectivity between rIFG and lMTG, $R^2 = .15$, $b = -.41$, $t(27) = -2.52$, $p = .018$, meaning that the more weight that participants continued to lose, the greater functional connectivity between rIFG and lMTG (Table 10) (Figure 7). This relationship remained

significant even after we controlled for errors of commission and reaction time, $R^2 = .19$, $b = -.47$, $t(26) = -2.68$, $p = .013$.

Increased functional connectivity between the rIFG and the left inferior frontal gyrus (lIFG) was not a significant predictor of TWL, $b = .06$, $t(28) = .34$, $p = .734$, nor LTWL, $b = -.23$, $t(27) = -1.43$, $p = .165$. However, it was a significant predictor of IWL, $R^2 = .12$, $b = .36$, $t(27) = 2.18$, $p = .038$, indicating that on average as functional connectivity between rIFG and lIFG increased, IWL decreased (i.e. more weight lost) (Table 11) (Figure 5). When we controlled for errors of commission, this relationship was no longer significant, $b = .25$, $t(27) = 1.46$, $p = .156$. Figure 4 displays the two areas of significant greater functional connectivity to the rIFG that show a significant correlation to our weight loss measures.

Table 10: RSFC for rIFG

Structure	Hemisphere	Brodmann Area	*x*	*y*	*z*	Size of cluster (µl)
Frontal						
Middle Frontal g.	R	~9	-46.1	-5.5	+37.7	196
Inf. Frontal g.	L	47	+49.9	-20.5	-0.9	194
Temporal						
Sup. Temporal g.	R	22	-55.9	+47.0	+14.0	710
Middle Temporal g.	L	~22	+52.9	+49.6	+6.0	151
Parietal						
Paracentral l.	L	~5	+0.1	+46.7	+66.5	108

g. = gyrus; l = lobule

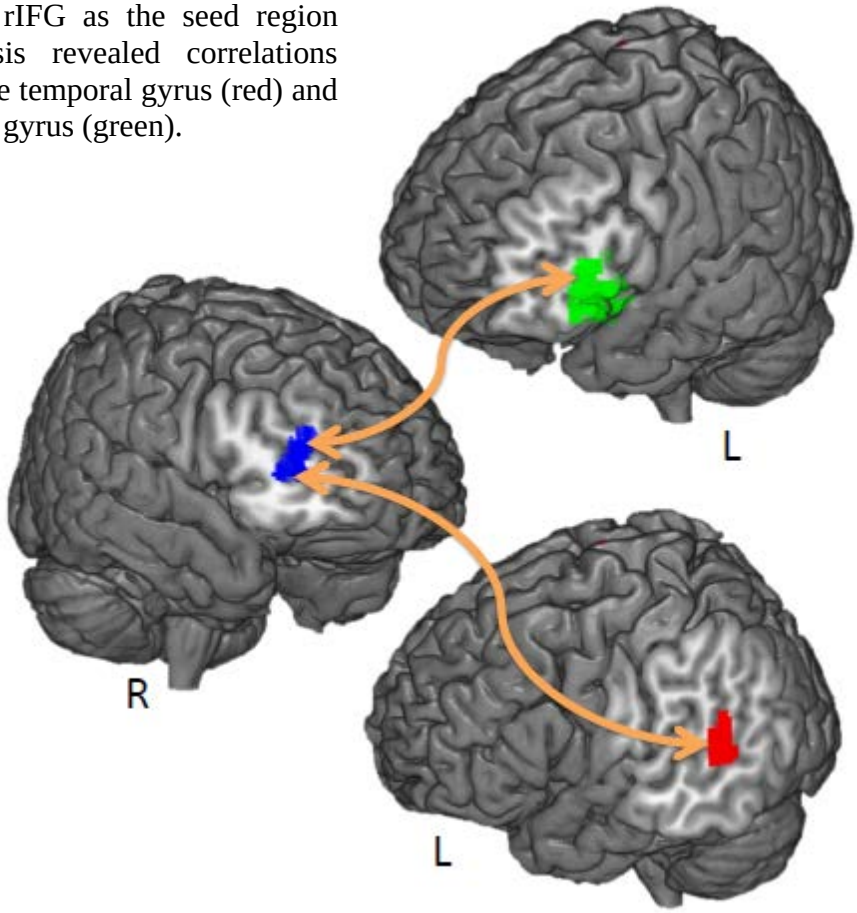
Table 11: Regression results for RSFC for rIFG

Structure	b value	t-value	p-value
Middle Frontal g. (R)			
TWL	0.22	1.19	0.244
IWL	0.04	0.21	0.837
LWTL	0.22	1.14	0.266
Inf. Frontal g. (L)			
TWL	0.06	0.34	0.734
IWL	0.36	2.18	0.038*
LWTL	-0.23	-1.43	0.165
Sup. Temporal g. (R)			
TWL	-0.08	-0.44	0.660
IWL	0.05	0.25	0.808
LWTL	-0.14	-0.72	0.481
Middle Temporal g. (L)			
TWL	-0.51	-3.39	0.002**
IWL	-0.23	-1.37	0.181
LWTL	-0.41	-2.52	0.018*
Paracentral l. (L)			
TWL	0.20	1.18	0.247
IWL	0.11	0.56	0.579
LWTL	0.15	0.81	0.425

* = significant at $\alpha = 0.05$

** = significant at $\alpha = 0.01$

Figure 4: With the rIFG as the seed region (blue), RSFC analysis revealed correlations between the left middle temporal gyrus (red) and the left inferior frontal gyrus (green).



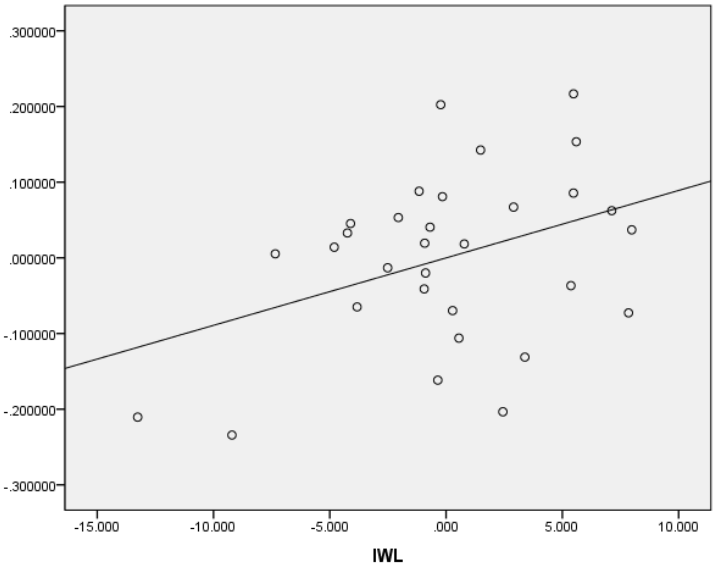


Figure 5: Partial regression scatterplot depicting the positive relationship between IWL and the RSFC correlation between the

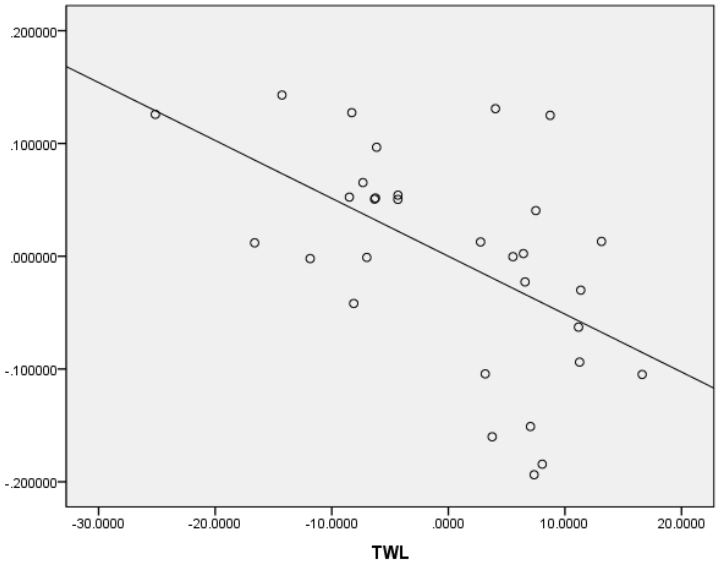


Figure 6. Partial regression scatterplot depicting the positive relationship between TWL and the RSFC correlation between the rIFG with the lMTG.

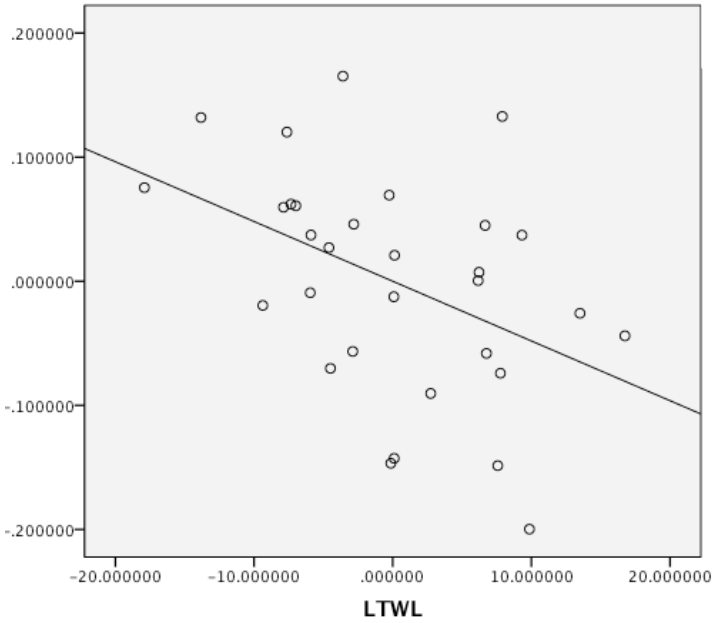


Figure 7. Partial regression scatterplot depicting the negative relationship between LTWL and the increased RSFC correlation of the rIFG with the lMTG.

Unfortunately none of the surviving clusters demonstrated a significant relationship to total weight loss, initial weight loss, or long term weight loss when functional connectivity with the rSFG increased (Table 12) (Table 13).

Table 12: RSFC for rSFG

Structure	Hemisphere	Brodmann Area	*x*	*y*	*z*	Size of cluster (µl)
Middle Frontal g.	L	~9	+32.2	-28.7	+31.8	382
Cingulate g.	R	~32	-2.2	-27.2	+31.8	369

g. = gyrus

Table 13: Regression results for RSFC for rSFG

Structure	b value	t-value	p-value
Middle Frontal g. (L)			
TWL	0.27	1.46	0.155
IWL	-0.02	-0.10	0.919
LWTL	0.34	1.72	0.097
Cingulate g. (R)			
TWL	0.06	0.31	0.762
IWL	0.09	0.44	0.665
LWTL	-0.01	-0.07	0.945

Exercise, Impulsivity & Eating Behavior

Out of the behavioral measures, only the cognitive restraint (CR) score of TFEQR21 was significantly correlated to increased RSFC between the rIFG and lMTG, R^2 = .21, *b* = .57, *t*(26) = 3.22, *p* = .003. After controlling for CR along with age, the relationship between the rIFG and lMTG RSFC and TWL was not significant, *b* = -.25, *t*(27) = -1.47, *p* = .152. Likewise, after controlling for age and CR score, the relationship between rIFG and lMTG RSFC correlation and LTWL was not significant, *b* = -.13, *t*(26) = -.72, *p* = .479. None of the behavioral measures demonstrated a significant relationship to the RSFC between the rIFG and the lIFG.

Discussion

When performing a response inhibition task, individuals who had experienced weight loss via a weight loss program demonstrated significant positive brain activation in the right inferior frontal gyrus and the right superior frontal gyrus. The involvement of the rIFG and rSFG in the response inhibition network has been previously documented (Nakata, Sakamoto, Ferretti, et al., 2008; Aron, Robbins & Poldack, 2014, Aron, Robbins & Poldack, 2014) providing reasonable evidence that the participants were appropriately engaged and completed the response inhibition task. Importantly, these two areas were positively correlated with the total amount of weight loss that was achieved by the participants. Specifically, the rIFG showed a positive linear relationship where-as our results revealed a quadratic relationship between TWL and rSFG activation. In the case of rSFG, individuals who gained weight by the end of 18 months exhibited lower rSFG activation and individuals that achieved the highest TWL also demonstrating lower rSFG activation relative to the individuals who only experience minimal weight loss or maintained the weight loss from the initial six months. Additionally, rSFG was also positively correlated with LTWL such that less activation was revealed in individuals who continued to lose weight beyond six months. Our findings are counter to our hypothesis that greater weight loss would yield the greatest inhibitory control activation. Previous literature has documented greater inhibitory control activation in individuals that have successfully maintained weight loss compared to those that had not experienced significant weight loss (Sweet et al., 2012; McCaffery et al., 2009). Another study with ex-smokers demonstrated greater cognitive control activation in the rIFG during a

Go/No-Go task in ex-smokers as compared to the current smokers and control participants (Nestor, McCabe, Jones et al., 2011). A possible explanation for this decrease in inhibitory control activation with more weight loss could be explained by cognitive efficiency. Cognitive efficiency is the psychological phenomenon that occurs when one has performed a task frequently enough that excessive brain resources are not required to engage in that task and a decrease in functional activity is seen. Specifically, the brain through plasticity changes becomes more efficient and a task that once required significant cognitive engagement no longer requires excessive recruitment of neural processes (Bargh, 1994). In the current study, it can be argued that losing weight during the weight loss program and continuing to lose weight required significant cognitive restraint (e.g. continued exercise and/or making healthy eating choices). Thus, when participants were instructed to perform a task of inhibitory control, the individuals who succeeded in losing weight and continuing to lose weight did not need to recruit excessive cognitive resources in order to exhibit inhibitory control. Neuroimaging has documented this phenomenon of cognitive efficiency in the prefrontal cortex during tasks of executive function (Rypma, Berger, Prabhakaran et al., 2006). In support of cognitive efficiency, task performance was positively correlated with activation in the rIFG meaning fewer errors of commission were associated with less rIFG activity. Once we controlled for age and task performance, TWL was no longer a significant predictor of rIFG activation suggesting task performance is a plausible mechanism through which weight loss can be related to rIFG activation. Unlike our results, a previous study by Batterink and colleagues noted higher BMI was associated with poorer task performance and hypofunctioning in the superior and middle frontal gyri (Batterink et al., 2010).

However, our results did not demonstrate either of the above patterns for rSFG activation, thus, further explanation was needed.

Greater exercise was significantly associated with less rSFG activation. Acute exercise and healthy lifestyle change has already been shown to improve working memory and reduce resting state activity in the dlPFC in middle-aged adults compared to non-intervention controls (Small, Silverman, Siddarth et al., 2006). The authors of this study posit that this decrease in RSFC represents an increase in cognitive efficiency. The results of the current study could suggest that exercise is a mechanism by which cognitive efficiency is an explanation for the decrease in inhibitory control activation. Exercise has also demonstrated a pivotal role in *maintaining* weight loss (Andersen, Wadden, Bartlett et al., 1999). However, when controlling for exercise, the quadratic relationship between rSFG activation and TWL as well as the positive linear relationship between rSFG and LTWL persists.

An alternative post-hoc explanation for the low activation in the individuals who gained weight (i.e. the individuals to the right of zero in Figure 3) is that these individuals were poor task performers and that the low rSFG activation is a reflection of this. As a group, the three individuals that gained weight back were above average on the number of errors of commission committed (>19errors). When we removed these individuals, the quadratic relationship between TWL and rSFG was no longer significant and a significant positive linear relationship with less activity associated with greater TWL remained. TWL was negatively correlated with exercise (i.e. more weight loss, greater exercise) and when we controlled for it in a follow-analysis, the negative linear relationship between TWL and rSFG was no longer significant. This suggests that once we removed poor

performers from our analysis, greater exercise is a possible mechanism that explains the relationship between greater TWL and less rSFG activation. Once we adjusted for exercise after removing poor task performers, the relationship between rSFG and LTWL was also no longer significant.

Exercise was also negatively associated with emotional and unrestrained eating. In support of a cognitive efficiency explanation for the above results, this could suggest that lower EE and UE represent less emotional dependence and less impulsive reaction tendencies toward eating and food which goes along with the stress reduction and behavioral lifestyle change that Small and colleagues successful related to increased cognitive efficiency (2006). A 2011 review documented the importance of exercise in decreasing impulsive overeating by increasing neurocognitive resources in order to improve cognitive restraint (Joseph, Alonso-Alonso, Bond et al., 2011). Though we didn't find a correlation between cognitive restraint and exercise, we propose that emotional and unrestrained eating share some impulsive eating attributes as evidence by their negative correlation to cognitive restraint and therefore can help support cognitive efficiency. In other words, in addition to exercise, another suitable explanation for the rIFG and rSFG relationship to TWL is that individuals that were able to lose more total weight did not prescribe to negative eating behaviors such as emotional and unrestrained eating and therefore had increased neurocognitive resources to improve cognitive restraint during their everyday lives. Well-practiced cognitive control could explain the cognitive efficiency patterns (i.e. lower) in rIFG and rSFG for those women who were able to achieve greater total weight loss.

While the interrelationship between eating behaviors correlations followed a predictable pattern—greater EE and UE, less CR—their relationship to inhibitory control activation in the rSFG was not as clear. Greater EE was associated with less rSFG activity and the opposite was true for UE. Given the highly positive correlation between EE and UE, this result is puzzling. It is likely the case that age played a role in this relationship because after removing age in a supplementary analysis, only UE was a positive significant predictor of rSFG. The last eating behavior from the TFEQR21, cognitive restraint (CR) did not demonstrate any significant relationship to rSFG. Ironically, the role of cognitive restraint in weight loss and weight loss maintenance is equivocal. Counter-intuitively, a recent meta-analysis revealed that out of 40 total studies neither dieting nor restrained eating significantly predicted weight loss (Lowe, Doshi, Katterman et al., 2013). In fact, 75% of the dieting-based studies and 5% of the restrained eating studies significantly predicted *weight gain*. Thus, it is understandable why the current study did not a find a coherent relationship between more efficient inhibitory control (and greater weight loss) and eating behaviors. Given that over half of the participants managed to maintain initial weight loss or continue to lose weight, it was expected that a greater amount of cognitive restraint would have been reported in these individuals. A recent study documented that more flexibility in dietary restraint was associated with greater weight loss maintenance (Westenhoefer, Engel, Holst et al., 2013). Given that greater total weight loss was associated with less rSFG activation it is possible that the participants in this study prescribed to a more flexible eating regime that ultimately benefitting some with successful weight loss maintenance while others were

unsuccessful. More research is needed to disentangle the relationship between inhibitory control activation and eating behavior patterns.

Strangely, none of the impulsivity measures were significant predictors of either rIFG or rSFG activation despite their widely accepted role in response inhibition networks and—by association—impulsivity. A previous study found a negative correlation between BIS-11 impulsivity and right superior frontal gyrus activation (Horn, Dolan, Elliot, et al., 2003). Of note, is that this study was only interested in total BIS-11 rather than exploring any of the specific subscales of impulsivity. In a supplementary analysis, our study found a significant *positive* relationship between total BIS-11 score and rIFG activation though the effect size was minimal. In addition, Horn and colleagues only recruited healthy adult males (ages 18-50) and given the activation differences across genders and age have already been discussed (Casey, Trainer, Orendi et al., 1997; George, Ketter, Parekh et al., 1995), it is possible our cohort of older adult women (ages 31-72) with a history of obesity may have had dramatically different activation patterns. Another study with men and women (ages 23-30) revealed a significant negative correlation between the Motor subscale of the BIS-11 and right dorsal lateral prefrontal cortex (Asahi, Okamoto, Okada et al., 2004), an area that includes parts of the rIFG and rSFG and is involved in executive function including response inhibition (Mostofsky, Schafer, Abrams et al., 2003). The fact that the Go/No-Go task used in this experiment was a block design that required a 50/50 response/inhibit response rate and their use of younger participants, together, were suggested to be the explanation for the negative correlation (Asahi et al., 2004). Given the specifics of our cohort and the complex nature

of impulsivity it is possible that our Go/No-Go task was insensitive to the three specific subscales (i.e. attentional, motor, nonplanning) of the BIS-11.

Though we didn't find any FC correlations between inhibitory control areas and reward regions, our RSFC analyses revealed greater FC between the rIFG and the lIFG. Greater FC between these two regions was associated with less IWL. A similar cognitive efficiency relationship can be used to explain this. Black and colleagues noted that food-reward anticipation input (i.e. greater FC) between the OFC and the middle frontal gyrus was correlated with obesity (Black et al., 2014). With regards to our study, more tonic activity (i.e. more inhibitory control resources) from the lIFG at rest was demonstrated by those who were not able to lose more initial weight in the first six months of the weight loss program. The lIFG has been implicated in inhibitory control especially when the inhibitory control task is difficult (Swick, Ashley & Turken, 2008). Thus, it appears that more weight loss could be associated with less at rest activity from inhibitory control networks. This finding mirrors the evidence for cognitive efficiency in the Go/No-Go task results which revealed greater weight loss was correlated with less inhibitory control brain activation. A counter argument to cognitive efficiency is that one previous study quantified efficiency as the ability to respond quickly and accurately during a Go/No-Go task and then subsequently demonstrated that highly efficient task performers preferentially engaged the left prefrontal cortex as opposed to the right which has been well documented in inhibitory control research (Hirose, Chikazoe, Watanabe et al., 2012). More research is needed in order to clarify this FC relationship in regards to inhibitory control and weight loss.

Our results also revealed increased FC between the rIFG and the lMTG for both total weight loss and long term weight loss status (i.e. for those participants that continued to lose more weight past the initial six months). To date, the only other resting state analysis that probed FC in the IFG found decreased FC between the left IFG and the lMTG in individuals who were dyslexic providing evidence of reduced language comprehension (Schurz, Wimmer, Richlan et al., 2014). Another study looked at internet gaming addiction found bilateral hypoactivation in the middle temporal gyri during a Go/No-Go task. The authors posit that the hypoactivation was a consequence of overexposure to loud auditory noise from excessive game play (Ding, Sun, Sun et al., 2014). Based on its connections to audition, in our study, the increased FC in the lMTG is likely do to the participants engaging in listening to the noise of the MRI scanner. Another explanation for this FC pattern is increased inner dialogue (i.e. internal language comprehension) during the resting state scan acquisition. Another study looking at adults versus adolescents during a Go/No-Go task found that prolonged recruitment of the right middle temporal gyrus was related to adolescence (Vara, Pang, Vidal et al., 2014). The authors speculated that the recruitment of this area suggests immature inhibitory control systems via recruitment of supplementary inhibitory regions such as the middle temporal gyrus. In a resting state, functional connectivity patterns can provide insight into behavior and brain activation patterns that were present during a cognitive task. Given our support for cognitive efficiency, it is unlikely that subjects with greater cognitive efficiency would express RSFC that suggests the rIFG is receiving tonic input from an immature inhibitory control network region such as the lMTG. Additionally, there was a positive correlation between increased FC between the rIFG and lMTG and the cognitive

restraint measure of the TFEQR21. Taken together, a possible explanation is that cognitive restraint is a mechanism is which this cross-hemisphere relationship between the rIFG and lMTG can account for increased weight loss. However, further research is needed to understand these unclear FC results in weight loss participants.

A limitation of this study is that functional MRI data was only collected at a single time point—after the weight loss program had been completed by participants. Thus, the results and conclusions discussed above are retrospective. Especially when considering initial weight loss, it is clear that multiple fMRI acquisitions would have provided a more definitive profile of response inhibition and RSFC. Had fMRI data been collected immediately following the six months of initial weight loss, perhaps a better understanding of the role of rIFG and rSFG as well as RSFC in initial weight loss would have been possible. Further, a scan session acquired prior to weight loss program recruitment, in addition to scans acquired after six months and after 18 months, would have provided the most elegant and complete profile of inhibitory control and RSFC by allowing for temporal comparison of functional changes.

Although the goal of this study was to analyze initial weight loss across a wide spectrum and various long term weight loss outcomes, the wide range of initial weight loss may have proven to be insensitive to our response inhibition task. While there were some participants that experienced >10% weight loss from baseline, a few participants managed only half of that figure. That being said, it's entirely possible that the relationship between weight loss and activation in the rIFG and/or rSFG was only detectable when weight loss was substantial. In this case effects would have been masked by a limited range of weight loss. Future studies should aim to recruit a larger

sample of weight loss participants in order to sufficiently power for small effects. Along the same lines, our long term weight loss status variable may have been misrepresented. In other words because of limited sample size, rather than having three groups of individuals (i.e. those that regained weight, those that continued to lose weight and those that maintained their initial weight loss) our regression analysis attempted to include all experiences in a single continuous variable. While this proved to be a logical statistical method, a larger sample size would not only help increase statistical power and detection of small effects but also provide a clearer response inhibition and RSFC profile for different weight loss outcomes.

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