BASELINE CORTICAL ACTIVATION TO FOOD PICTURES ASSOCIATED WITH CHANGE IN WEIGHT, HUNGER, COGNITIVE RESTRAINT, AND DISINHIBITION FOLLOWING BARIATRIC SURGERY

A THESIS IN Psychology

Presented to the Faculty of the University of Missouri-Kansas City in partial fulfillment of the requirements for the degree MASTER OF ARTS

by
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ABSTRACT

Introduction: Recent research suggests that bariatric surgery may be associated with functional brain changes. Baseline functional magnetic resonance imaging (fMRI) food motivation paradigms may reveal particular patterns of brain activation, which could indicate successful outcomes in weight and other behavioral outcomes following bariatric surgery. The aim of the present study was to determine if activation to food images during a baseline fMRI food motivation paradigm is associated with post-surgical laparoscopic adjustable gastric banding (LAGB) outcomes. We hypothesized that areas previously implicated in food motivation and reward, as well as, cognitive control (inferior, middle, medial superior prefrontal cortex (PFC)) would be associated with changes in weight, hunger, cognitive restraint, and disinhibition.

Methods: 18 participants viewed food and non-food pictures from a well-established food motivation paradigm during an fMRI scanning session prior to LAGB surgery. Weight and three factor eating questionnaire (TFEQ) scores on cognitive restraint, disinhibition, and hunger were assessed pre-surgery and three and six months post-surgery. fMRI data were analyzed using BrainVoyager QX statistical package.

Results: Whole brain analyses, corrected for multiple comparisons, were performed to analyze the relationship between pre-surgical brain activation and subsequent weight loss. Increased activity in frontal regions associated with cognitive control (medial, middle, superior frontal
gyrus), with the exception of inferior frontal gyrus, was associated with more weight loss following LAGB. Increased activity in posterior cingulate cortex (PCC) was also associated with greater weight loss post-LAGB. In contrast, decreased brain activity to food cues in frontal areas related to control (inferior, middle, medial, and superior frontal gyri) and increased activity in areas related to reward and motivation (PCC) at baseline was associated with greater improvement in hunger, cognitive restraint, and disinhibition following surgery.

Discussion: This is the first study to use fMRI to predict LAGB outcomes. We found that neural activity in previously established regions associated with food motivation, visual attention, and higher order processing predict weight loss following bariatric surgery. These preliminary findings highlight the role of neural circuitry in the success and maintenance of weight loss and suggest a possible future use of fMRI in screening LAGB surgery candidates.
The faculty listed below, appointed by the Dean of the College of Arts and Sciences have examined a thesis titled “Baseline Cortical Activation to Food Pictures Associated with Weight Change following Bariatric Surgery,” presented by Abigail R. Ness, candidate for the Master of Arts degree, and certify that in their opinion it is worthy of acceptance.

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LIST OF ABBREVIATIONS

Functional Magnetic Resonance Imaging = fMRI

Body Mass Index = BMI

Three Factor Eating Questionnaire = TFEQ

Roux-en-Y gastric bypass = RYGB

Laparoscopic adjustable gastric banding = LAGB

Inferior Frontal Gyrus = IFG

Superior Frontal Gyrus = SFG

Prefrontal Cortex = PFC

Inferior Parietal Lobule = IPL

Posterior Cingulate Cortex = PCC

Middle Temporal Gyrus = MTG

Region of Interest = ROI

General Linear Model = GLM

Analysis of Variance = ANOVA
CHAPTER 1

REVIEW OF THE LITERATURE

Obesity in the United States has been labeled an epidemic, crisis, and most recently, a disease (Carmona, 2003; Hensrud & Klein, 2006). Obese patients are diagnosed more frequently than healthy-weight individuals with type II diabetes, hypertension, heart disease, stroke, cancer, gout, sleep apnea, asthma, gallbladder problems, osteoarthritis, stress fractures, depression, and anxiety (National Institutes of Health, 2010). Nearly two-thirds of all adults in the US are overweight or obese and one-third of children are overweight or obese (Wang & Beydoun, 2007). Due to the widespread prevalence of obesity and the negative physical, economic, and social costs, obesity is a problem that is imperative to address in both research and practice.

Despite severe consequences related to physical, emotional, social, and economic well-being, most obese individuals report failure to lose and maintain weight loss using behavioral means alone; thus, a growing number of individuals turn to surgery in an attempt to lose their excess weight (Fisher & Schauer, 2002; Picot et al., 2009). Laparoscopic adjustable gastric banding (LAGB) is an increasingly popular surgical intervention for weight loss (Picot et al., 2009). LAGB is an effective method to induce and sustain weight loss for many people who have not succeeded using diet and exercise (Chapman et al., 2004; Dixon, Dixon, & O’Brien, 2001). In addition to excess weight loss, LAGB surgery also has many other health-related benefits associated with a reduction in mortality risk (Pontiroli & Morabito, 2011). Patients who undergo the surgery and lose weight often experience improvements in, or resolution of, comorbid health conditions. Buchwald and colleagues (2004) conducted a meta-analysis and found that 47.8% of LAGB patients experience resolution of their diabetes and 94.6% of patients experience a complete resolution of their obstructive sleep apnea (Buchwald et al., 2004). As well, 80.2% of...
LAGB patients with diabetes, 71.1% with hyperlipidemia, and 71.5% with hypertension experience improvement and/or resolution of their respective conditions (Buchwald et al., 2004). Although LAGB surgery is an expensive procedure, with average estimates ranging from $11,598 to $19,330 (Campbell et al., 2010), it has been shown to be cost-effective among patients with a body mass index (BMI) of 35 kg/m² or more. (Campbell et al., 2010; Keating et al., 2009; Picot et al., 2009; Pollock et al., 2013; Salem, Jensen & Flum, 2005). Given the cost effectiveness and overall improvements associated with bariatric surgery, some authors have asserted that bariatric surgery should be universally available (Chang et al., 2011).

In part due to these promising outcomes, LAGB was championed in the late 1990s to mid-2000s as the surgery of choice for weight loss (Suter et al., 2006). More recent research reveals that long-term outcomes of LAGB may be mixed (Livingston, 2010). Suter and colleagues (2006) found that seven years after LAGB surgery, approximately 40 percent of individuals had failed to lose at least 25 percent of their excess weight— an amount considered the minimum criterion for success post LAGB (Suter et al., 2006). Their research also revealed that approximately one-third of individuals experienced late complications related to their LAGB surgery (Suter et al., 2006). Common complications include: band erosion, pouch dilation/slippage, and other catheter/port- related problems (Singhal et al., 2010; Suter et al., 2006). These complications highlight a need for improved pre-surgical methods to identify which patients are most likely to have successful outcomes following LAGB.

Researchers have recently begun to implement functional magnetic resonance imaging (fMRI) techniques to better understand the neural mechanisms of food motivation and obesity (Bruce, Martin, & Savage, 2011; Bruce et al., 2012; Martin et al., 2010, Ochner et al., 2012; Rothemund et al., 2007). When presented with food-related stimuli, overweight individuals show different levels of neural activity in areas of the brain related to food motivation compared to their healthy-weight counterparts (Carnell et al., 2012; Martin et al., 2010). Specifically, such
individuals have shown greater activation in medial prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex, insula, striatum, and somatosensory processing areas including the hippocampus and parahippocampal regions (Carnell et al., 2012; Martin et al., 2010; Rothemund et al., 2007, Stoeckel et al., 2008).

Recent research also suggests that weight loss from bariatric surgery may be associated with specific functional brain changes. Ochner and colleagues (2012) found that patients who underwent Roux-en-Y gastric bypass (RYGB) surgery displayed decreased activation in the striatal area, which they interpreted as patients’ decreased food motivation following weight loss. In another study conducted by our group (Bruce et al., 2012), patients’ brains were scanned both at baseline (i.e. before) and 12 weeks after LAGB surgery. Post-surgery, patients exhibited less brain activation to food pictures in parahippocampus, medial prefrontal cortex, insula, and inferior frontal gyrus, all of which are associated with food motivation and inhibitory control. Moreover, patients exhibited increased brain activation pre- to post- surgery in right middle frontal gyrus and superior frontal gyrus which is a known inhibition and cognitive control region.

Research groups have begun to identify behavioral predictors of success following bariatric surgery (Crowley et al., 2012; Dixon et al., 2001; Livhits et al., 2012; Sarwer et al., 2008; Thalheimer et al., 2009). A study by Sarwer and colleagues (2008) found gender and pre-operative cognitive restraint each to be individually significant predictors of weight loss following surgery. In a mixed model analysis, they found that males lost more weight than females, and those with higher reported cognitive restraint prior to surgery lost more weight than their counterparts (Sarwer et al., 2008). Another study found that individuals with more food cravings and less post-consumption guilt lost more weight; together these factors accounted for 25% of the variance in weight lost at six months following baseline assessment (Crowley et al., 2012). Despite these emerging predictors, more research is needed before they can reliably be used in clinical practice to indicate which candidates are most suitable for LAGB (Crowley et al., 2012).
fMRI food motivation paradigms offer a potentially powerful way to predict outcomes following LAGB. The goal of the current study was to determine if baseline brain activation to a food motivation fMRI paradigm could be used to predict post-surgical LAGB outcomes. Previous research has demonstrated that obese individuals show increased brain activity to images of food in limbic and paralimbic regions, inferior frontal cortex, orbito-frontal cortex, hippocampal formation, striatum, and insula (Martin et al., 2010). Moreover, a recent study by Murdaugh and colleagues (2012) found that obese patients who exhibited increased activation in regions associated with reward were less successful following a weight loss intervention. Thus, we anticipated that increased activation in areas associated with food motivation and reward would be associated with less weight loss and a smaller decrease in hunger and disinhibition ratings from baseline to post-surgery (Rothemund et al., 2007; Stoeckel et al., 2008; Zheng & Berthoud, 2007). In addition, we hypothesized that greater activation in known areas of cognitive control at baseline (superior, middle, and medial frontal gyri, anterior cingulate) would be associated with greater weight loss, increases in cognitive restraint, and decreases in hunger and disinhibition from baseline to post-surgery.
CHAPTER 2

METHODOLOGY

Procedure

Participants in this study were scanned as part of a larger study examining neural changes associated with LAGB surgery (Bruce et al., 2012). Nineteen obese participants were scanned prior to LAGB surgery (i.e. at baseline) using an established food motivation fMRI paradigm. Participants were scanned twice, once while hungry following a fast of ≥4-hours, and again, after eating a small meal. Weight and height were recorded on the day of surgery, three months post-surgery, and six months post-surgery. These data were obtained from medical records at the respective recruitment sites for each individual and were used to calculate BMI at each time point via simple subtraction.

Participants

Participants were identified at two surgical sites in the Kansas City Metropolitan Area. Obese participants (BMI 35-45; age 25-60) with approval for laparoscopic adjustable gastric banding weight loss surgery (LapBand®) were recruited. Individuals with BMI ≥ 46 kg/m² were not included due to MRI scanner size constraints. Individuals were ineligible if they reported use of appetite suppressants or stimulants. Additional exclusion criteria included: current eating disorder, current major depression, history of central nervous system disease, cancer, and a recent cardiac event. Individuals with internal metal objects and those planning a pregnancy or who had been pregnant within the past 12 months were excluded. As the majority of participants seeking bariatric surgery have a history of diabetes, patients who had well-controlled diabetes and were not taking insulin (most recent hemoglobin A1C < 7) were included.

Measures

The Three Factor Eating Questionnaire (TFEQ) is a 51-item self-report scale that assesses behavior associated with food intake. It measures three factors: perceived hunger (14 items),
cognitive restraint (21 items), and disinhibition (16 items) (Stunkard & Messick, 1985). The TFEQ is composed of 36 true-false statements and 15 questions with Likert-scale response options (Stunkard & Messick, 1985). For this study, we examined the differences in patients’ scores from baseline to post-surgery by subtracting post-surgical scores from scores at baseline. Baseline BMI and TFEQ values were subtracted from time 2 and time 3 values separately and individually put into BrainVoyager QX software.

**fMRI Cognitive Activation Paradigm**

The experimental paradigm was based closely on LaBar et al. (2001) and is described in detail elsewhere (Martin et al., 2010). Participants viewed pictures of food, animals, and Gaussian-blurred low-level baseline control images (see figure 1) during two scanning sessions: (1) after fasting for at least four hours (pre-meal) and (2) immediately after eating a small uniform meal (post-meal) that was standardized for energy [Kcal = 500] and micronutrient content (e.g., a weighed lean meat [turkey or ham] sandwich wrap, carrot sticks, a piece of fruit, and skim milk). The order of sessions (pre-meal, post-meal) was counterbalanced across subjects so that approximately half the group started with the pre-meal session and half started with the post-meal session.
fMRI Cognitive activation paradigm (block design) of visual stimuli: food, animals, and blurred baseline

All images for the animal category were obtained from professional stock CD-ROMs and matched to food and blurred control images on brightness, resolution, and size. In addition, by applying a Gaussian kernel to a subset of the animal images (so that the objects are not identifiable); approximately 150 new blurred baseline control images were obtained. To the greatest degree possible, animals that were reminiscent of food (i.e., fish) were removed from the stimuli pool to prevent the possible confusion between animal/food categorizations. Blurred objects were included as a low-level baseline comparison. All images were presented one time only to each subject.

Each functional scan involved three repetitions of each block of each stimulus condition type (i.e., food, animal), alternated between blocks of blurred images. Visual stimuli were projected from the stimuli-generating computer program (NeuroSTIM, Neuroscan, El Paso, TX) onto a screen. Stimulus presentation time was 2.5 seconds, with an interstimulus interval (ISI) of
0.5 seconds. Within each of the two functional scans there was a total of 13 blocks of stimuli presentation; within each block, 10 images were presented. The order of category presentation was counterbalanced across subjects.

To ensure that participants were paying attention to the images presented in the scanner, memory testing followed each scanning session. From each of the food and animal groups, approximately 50% of the images used in the scanning session (30 images) were presented for recall (old) and interspersed with 15 novel distracter images from the same category (new). Participants completed a recognition memory task outside the scanner immediately following each scanning session. Participants were instructed to press one key if they had seen the image in the scanner (old), and another button if they had not seen the image (new). All participants showed memory performance superior to chance (all obtained scores at or above 62%) and none were excluded due to inattention or sleeping during scan time.

**Image Acquisition**

Scanning was performed at the University of Kansas Medical Center Hoglund Brain Imaging Center on a 3 Tesla head-only Siemens Allegra scanner (Siemens, Erlangen, Germany) fitted with a quadrature head coil. Participants’ heads were immobilized with head cushions. Following automated scout image acquisition and shimming procedures performed to optimize field homogeneity, a structural scan was completed. T1-weighted anatomic images were acquired with a 3D SPGR sequence (TR/TE = 23/4 ms, flip angle = 8°, FOV = 256 mm, matrix = 256 x 192, slice thickness = 1 mm) used for slice localization for the functional scans, Talairach transformation, and coregistration with fMRI data. Following structural scans, two gradient echo BOLD scans were acquired in 43 contiguous oblique axial slices at a 40° angle (repetition time/echo time [TR/TE] = 3000/30 ms, flip angle = 90°, field of view [FOV] = 220 mm, matrix = 64x64, slice thickness = 3 mm, .5 skip, in-plane resolution = 3x3 mm, 130 data pts).
Statistical Analysis

fMRI data were analyzed using the BrainVoyager QX statistical package and random effects (Brain Innovation, Maastricht, Netherlands, 2004). Preprocessing steps included trilinear 3D motion correction, sinc-interpolated slice scan time correction, 2D spatial smoothing with 4-mm Gaussian filter, and high pass filter temporal smoothing. Functional images were realigned to the anatomic images obtained within each session and normalized to Talairach and Tournoux’s (1988) stereotaxic atlas. Motion during any run of more than 4 mm along any axis (x, y, or z) resulted in the discard of that run.

Whole Brain Statistical Analyses

Activation maps were analyzed using statistical parametric methods contained within the BrainVoyager QX software (Friston et al., 1995). Regressors representing the experimental conditions of interest were modeled with a hemodynamic response filter and entered into the multiple-regression analysis using a random-effects general linear model (GLM) accounting for individual participant differences. The resulting GLM was overlaid with a contrast of food images greater than nonfood images (F > NF). Separate beta maps for this contrast were created and saved for each of the 19 participants. BMI data was available for all participants at every time point, however, one participant was excluded in each condition (one premeal, one postmeal) due to excess motion. Thus, 18 participants were included in each of the analyses for BMI. Four participants did not provide data for the TFEQ at three months, one subject was excluded for excess motion (postmeal condition only), and one participant was excluded from the analyses of cognitive restraint and disinhibition at three months in the postmeal condition for outlying fit to the regression line (Cook’s Distance > 1). Thus, at three months for TFEQ analyses, 13 participants were included in the postmeal analyses for cognitive restraint and disinhibition. 14 subjects were included in the three month postmeal hunger analysis. 15 subjects were included in the premeal three-month TFEQ analyses. Three participants did not provide data for the TFEQ at
six months, one subject was excluded for excess motion (postmeal condition only). Thus, at six months, 16 subjects were included in premeal TFEQ analyses and 15 subjects were included in postmeal TFEQ analyses. This multi-subject beta map set, containing beta values for the difference between activation to food and nonfood images (F−NF), was then entered into BrainVoyager’s ANCOVA function. Changes in BMI and changes in TFEQ subtest scores for hunger, cognitive restraint, and disinhibition were entered separately for each correlation analysis, with zero between-subjects factors and one within-subjects factor. Resulting correlation maps were overlaid on a three-dimensional rendering of an averaged group brain. To correct for multiple comparisons, a Family wise cluster-level threshold was applied as determined by MonteCarlo simulation on Brain Voyager (Groebel, Esposito, Formisano, 2006; Lieberman & Cunningham, 2009). Voxel values were considered significant if the activation survived a statistical threshold of $\alpha = .05 \ (p < .01; k = 7$ contiguous voxels). This procedure was performed for pre-meal and post-meal analyses separately.
CHAPTER 3

RESULTS

Descriptive Statistics

16 of the 19 participants (84%) were female. The mean age of participants was 38.37 ± 11.24 years (range 21 – 56). Six individuals completed high school, seven completed some college, five completed a 4-year college degree, and one obtained a graduate degree. On average, the baseline fMRI evaluation was conducted 9.05 ± 5.99 days prior to surgery (range 1-19). Average time between the baseline and 3 months evaluation was 91.89 days (SD= 13.10) and average time between the baseline and 6 months evaluation was 179.95 days (SD= 23.89).

Descriptive repeated measures analysis of variance (ANOVA) for BMI and TFEQ values at each time point are listed in Table 1. As expected, participants’ BMI, hunger, and disinhibition significantly decreased from pre surgery to post-surgery and cognitive restraint increased from pre to post-surgery.
Table 1

Repeated Measures ANOVA Representing Change in BMI and TFEQ subtest scores over time.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3months</th>
<th>6months</th>
<th>F</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>F(df)</td>
</tr>
<tr>
<td>BMI</td>
<td>41.98</td>
<td>3.08</td>
<td>37.87</td>
<td>3.01</td>
<td>35.94</td>
</tr>
<tr>
<td>Hunger</td>
<td>9.47</td>
<td>2.56</td>
<td>4.27</td>
<td>2.66</td>
<td>3.20</td>
</tr>
<tr>
<td>Cognitive Restraint</td>
<td>6.80</td>
<td>4.26</td>
<td>13.87</td>
<td>3.93</td>
<td>14.73</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>11.33</td>
<td>3.13</td>
<td>6.80</td>
<td>4.23</td>
<td>5.13</td>
</tr>
</tbody>
</table>

Note: Data were obtained from participant responses to the Three Factor Eating Inventory. Weight was obtained from medical records with authorized consent of participants. Different letter subscripts indicate significant difference between time points using post-hoc paired samples t-tests (p < .01).
fMRI Results

Predicting Change in BMI from Baseline fMRI Scan

Table 2 shows baseline brain activations to food versus nonfood (F > NF) images that were significantly associated with participants’ subtracted BMI difference between baseline and three months and six months.

3 months

*Premeal:* Greater activation to pictures in left middle, superior, and medial frontal gyri, and right paracentral lobule was associated with a greater amount of weight loss from pre-surgery to 3 months post-surgery. *Postmeal:* Greater activation to pictures in bilateral medial frontal gyrus at postmeal was associated with a greater amount of weight loss from pre-surgery to 3 months post-surgery.

6 Months

*Premeal:* Greater activation to in left fusiform gyrus, and two regions of left middle frontal gyrus, was associated with a greater amount of weight loss from pre-surgery to 6 months post-surgery. Decreased activation to pictures in right inferior frontal gyrus was associated with a greater amount of weight loss from pre-surgery to 6 months post-surgery (see figure 2). *Postmeal:* Decreased activation to pictures in right inferior parietal lobule at postmeal was associated with a greater amount of weight loss from pre-surgery to 6 months post-surgery. Greater activation to pictures in right middle temporal gyrus and bilateral posterior cingulate was associated with a greater amount of weight loss from pre-surgery to 6-months post-surgery.
Table 2

*Significant correlations between baseline brain activation to food and nonfood images and BMI at 3 and 6 months post-surgery.*

<table>
<thead>
<tr>
<th>Brain activation associated with 3 month BMI change</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>r</th>
<th>Voxels</th>
<th>Brodmann Area</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postmeal BMI Association</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral Medial Frontal Gyrus</td>
<td>0</td>
<td>-1</td>
<td>55</td>
<td>0.75</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td><strong>Premeal BMI Association</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. Paracentral Lobule</td>
<td>3</td>
<td>-37</td>
<td>58</td>
<td>0.7</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>L. Medial Frontal Gyrus</td>
<td>-6</td>
<td>11</td>
<td>55</td>
<td>0.76</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>L. Superior Frontal Gyrus</td>
<td>-3</td>
<td>-1</td>
<td>64</td>
<td>0.8</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>L. Middle Frontal Gyrus</td>
<td>-27</td>
<td>-1</td>
<td>43</td>
<td>0.78</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brain activation associated with 6 months BMI change</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>r</th>
<th>Voxels</th>
<th>Brodmann Area</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premeal BMI Association</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. Inferior Frontal Gyrus</td>
<td>42</td>
<td>47</td>
<td>1</td>
<td>-0.78</td>
<td>21</td>
<td>47</td>
</tr>
<tr>
<td>L. Middle Frontal Gyrus</td>
<td>-27</td>
<td>-1</td>
<td>40</td>
<td>0.8</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>L. Middle Frontal Gyrus</td>
<td>-42</td>
<td>17</td>
<td>31</td>
<td>0.78</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>L. Fusiform Gyrus</td>
<td>-42</td>
<td>-43</td>
<td>-17</td>
<td>0.71</td>
<td>8</td>
<td>37</td>
</tr>
<tr>
<td><strong>Postmeal BMI Association</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. Inferior Parietal Lobule</td>
<td>51</td>
<td>-43</td>
<td>34</td>
<td>-0.75</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>R. Middle Temporal Gyrus</td>
<td>42</td>
<td>-58</td>
<td>-2</td>
<td>0.74</td>
<td>8</td>
<td>37</td>
</tr>
<tr>
<td>Bilateral Posterior Cingulate</td>
<td>0</td>
<td>-43</td>
<td>4</td>
<td>0.79</td>
<td>9</td>
<td>31</td>
</tr>
</tbody>
</table>

*Note:* Positive maximum voxel r-values indicate increased activity to F>NF pictures associated with greater weight loss at three and six months. Negative r-values indicate reduced activity to F>NF pictures associated with greater weight loss at three and six months. X, Y, and Z are maximum/peak voxel values.
Predicting Change in Three Factor Eating Inventory from Baseline fMRI Scan

We examined baseline activation to F > NF images and associations with future behavioral outcomes. Table 2 shows baseline brain activations that were significantly associated with participants’ subtracted TFEQ subscale scores between baseline and three months post-surgery. Table 3 shows baseline brain activations to F > NF images that were significantly associated with participants’ subtracted TFEQ subscale scores between baseline and six months post-surgery.

3 Months Premeal

*Hunger:* Decreased activation in right middle frontal gyrus, right inferior frontal gyrus, left thalamus, and in bilateral superior frontal gyrus was associated with a greater decrease in hunger ratings from pre-surgery to three months following surgery. *Cognitive Restraint:* Decreased activation at baseline in right precentral gyrus/inferior frontal gyrus, right middle frontal gyrus, and left middle temporal gyrus was associated with greater increase in cognitive restraint. Increased activation in the left cerebellum at the baseline scanning session in the left cerebellum was associated with greater change cognitive restraint. *Disinhibition:* Increased activation to images at baseline in right fusiform gyrus, and right middle temporal gyrus was associated with greater decrease in disinhibition from pre- to post-surgery. Decreased activation images during baseline scan in right cingulate and left post-central gyrus was associated with greater decrease in disinhibition from pre- to post-surgery.

3 Months Postmeal

*Hunger:* No significant areas of activation to food and nonfood images were associated with change in hunger from baseline to three months post LAGB surgery. *Cognitive Restraint:* Decreased activation images during the baseline scan in bilateral superior frontal gyrus was associated with greater increase in cognitive restraint following LAGB surgery. *Disinhibition:*
Decreased activation images during the baseline scan in right superior frontal gyrus and right medial frontal gyrus was associated with greater increase in cognitive restraint following LAGB surgery.

6 Months Premeal

*Hunger:* Decreased activation images at baseline in right middle frontal gyrus and right superior frontal gyrus was associated with greater decrease in hunger. *Cognitive Restraint:* Increased activation images at baseline scanning session in the right cerebellum, left posterior cingulate/limbic lobe, and left middle temporal gyrus was associated with greater increase in cognitive restraint. *Disinhibition:* Decreased activation to images at baseline in left cuneus was associated with greater decrease in disinhibition from pre-surgery to six months post-surgery.

6 Months Postmeal

No significant areas of activation to food and nonfood images were associated with change in hunger, cognitive restraint, or disinhibition from baseline to six months post LAGB surgery.
Table 3

*Significant correlations between baseline brain activation to food and nonfood images and TFEQ measures at 3 months post LAGB.*

<table>
<thead>
<tr>
<th>3 month brain activation associated with TFEQ Outcome</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>r</th>
<th>Voxel</th>
<th>Brodmann Area</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premeal Hunger</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>R. Middle Frontal Gyrus</td>
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<td>23</td>
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<td>8</td>
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<tr>
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<td>7</td>
<td>-0.81</td>
<td>15</td>
<td>45</td>
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<tr>
<td>R. Superior Frontal Gyrus</td>
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<td>12</td>
<td>9</td>
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<tr>
<td>R. Superior Frontal Gyrus</td>
<td>9</td>
<td>14</td>
<td>70</td>
<td>-0.84</td>
<td>13</td>
<td>6</td>
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<tr>
<td>L. Superior Frontal Gyrus</td>
<td>-15</td>
<td>44</td>
<td>52</td>
<td>-0.75</td>
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<td>8</td>
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<tr>
<td>L. Thalamus</td>
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<td>-22</td>
<td>13</td>
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<td>10</td>
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<tr>
<td>L. Superior Frontal Gyrus</td>
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<td>53</td>
<td>34</td>
<td>-0.84</td>
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<td>9</td>
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<tr>
<td>R. Precentral Gyrus/Inferior Frontal Gyrus</td>
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<td>8</td>
<td>10</td>
<td>-0.83</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>R. Middle Frontal Gyrus</td>
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<td>35</td>
<td>37</td>
<td>-0.83</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>L. Cerebellum (Posterior Lobe)</td>
<td>-48</td>
<td>-67</td>
<td>-23</td>
<td>0.79</td>
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<tr>
<td>L. Middle Temporal Gyrus</td>
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<tr>
<td>R. Superior Frontal Gyrus</td>
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<td>-0.86</td>
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<td>9</td>
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<td><strong>Premeal Disinhibition</strong></td>
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<td>R. Fusiform Gyrus</td>
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<td>0.73</td>
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<td>37</td>
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<td>-67</td>
<td>4</td>
<td>0.8</td>
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<td>R. Posterior Cingulate</td>
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<td>-0.86</td>
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<tr>
<td>L. Post-Central Gyrus</td>
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<td>-49</td>
<td>70</td>
<td>-0.81</td>
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<tr>
<td><strong>Postmeal Disinhibition</strong></td>
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<td></td>
<td></td>
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<tr>
<td>R. Superior Frontal Gyrus</td>
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<td>R. Medial Frontal Gyrus</td>
<td>3</td>
<td>50</td>
<td>19</td>
<td>-0.89</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

*Note:* Positive maximum voxel r-values indicate increased activity to F>NF pictures associated with greater change in TFEQ values of hunger, cognitive restraint, and disinhibition. Negative r-values indicate reduced activity to F>NF pictures associated with greater change in TFEQ values of hunger, cognitive restraint, and disinhibition. X, Y, and Z are maximum/peak voxel values.
Table 4

*Significant correlations between baseline brain activation to food and nonfood images and TFEQ Measures at 6 months post LAGB.*

<table>
<thead>
<tr>
<th>6 month brain activation associated TFEQ Outcome</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>r</th>
<th>Voxels</th>
<th>Brodmann</th>
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<tr>
<td>Premeal Hunger Association</td>
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<tr>
<td>R. Middle Frontal Gyrus</td>
<td>48</td>
<td>20</td>
<td>46</td>
<td>-0.77</td>
<td>18</td>
<td>8</td>
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<tr>
<td>R. Superior Frontal Gyrus</td>
<td>21</td>
<td>23</td>
<td>61</td>
<td>-0.81</td>
<td>13</td>
<td>6</td>
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<tr>
<td>Premeal Cognitive Restraint Association</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. Cerebellum</td>
<td>9</td>
<td>-55</td>
<td>-23</td>
<td>0.75</td>
<td>8</td>
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<tr>
<td>L. Posterior Cingulate/Limbic Lobe</td>
<td>-27</td>
<td>-70</td>
<td>16</td>
<td>0.76</td>
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<td>23</td>
</tr>
<tr>
<td>L. Middle Temporal Gyrus</td>
<td>-36</td>
<td>-67</td>
<td>19</td>
<td>0.81</td>
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<td>21</td>
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<td>Premeal Disinhibition Association</td>
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<td>L. Cuneus</td>
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<td>-85</td>
<td>31</td>
<td>-0.76</td>
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</tbody>
</table>

*Note:* Positive maximum voxel r-values indicate increased activity to F>NF pictures associated with greater change in TFEQ values of hunger, cognitive restraint, and disinhibition. Negative r-values indicate reduced activity to F>NF pictures associated with greater change in TFEQ values of hunger, cognitive restraint, and disinhibition. X, Y, and Z are maximum/peak voxel values.
CHAPTER 4

DISCUSSION

This study examined differences in baseline brain activation that may serve as indicators of post LAGB weight loss success and improvements in hunger, cognitive restraint, and disinhibition. Brain regions implicated in reward (PCC, IPL) and cognitive control (inferior, medial, middle, superior PFC) were consistently found to be associated with weight loss and constructs measured by the TFEQ. Brain regions identified in the present study were consistent with those identified in previous fMRI studies of obesity, food motivation, and cognitive control. However, results only partially supported our hypotheses. Although areas of activation were consistent with previous research, the direction of the associations was not consistently in line with our expectations.

**Body Mass Index**

Previous research has shown brain regions linked to cognitive control (inferior, medial, middle superior PFC) and motivation (PCC, IPL) are also associated with food motivation and differences in BMI. Our results demonstrated that activation in these regions may also be associated with post-surgical weight loss outcomes. In the premeal condition, we found that increased activity in the left medial, middle, and superior frontal gyri was associated with increased weight loss at each of these time points. This was consistent with our hypothesis that greater activation to food images in areas related to inhibition, decision making, and cognitive control would be associated with increased weight loss.

Further, less activation to food versus nonfood images in the right inferior frontal gyrus (IFG) in the premeal condition was associated with increased weight loss at six months post-LAGB (Figure 2). A number of studies have shown that right IFG is involved in inhibition and
attentional control (Hampshire et al., 2010; Menon et al., 2001; Rubia et al., 2003; Aron et al., 2004). We expected that increased activity in this area at baseline would show an association with increased weight loss; however, the opposite was found. Future research to tease apart differential mechanisms of various frontal regions associated with cognitive control may provide rationale for this discrepant finding.

Figure 2

*Decreased activation to F > NF images in IFG in premeal baseline scan associated with increased weight loss at six months post-surgery.*
In the postmeal condition, increased activity in bilateral posterior cingulate at baseline was associated with greater weight loss at six months. According to a recent meta-analysis, posterior cingulate has been associated with reward processing (Liu et al., 2011). This was also contrary to our predictions; we expected increased activity in areas of motivation, such as posterior cingulate, to be indicative of higher food and reward motivation, and, in turn, poorer outcomes from LAGB surgery. However, it is possible that increased activity could indicate greater awareness of desire for reward and may alert such individuals to certain cues and triggers that precede over-indulgence. Posterior cingulate has also been associated with the default mode network (Greicius & Menon, 2003, 2004; Molner-Szakacs & Uddin, 2013). Greicius and Menon (2003) highlight increased PCC activation during undemanding tasks, for example, the passive viewing of stimuli, and decreased activation during tasks that are cognitively demanding. Some may question the effect of increased default mode network on attention to images, however, we do not believe this is a concern as participants all exhibited satisfactory performance (>62% accuracy) on the test of attention following scanning sessions.

Additionally, we found that decreased activation in right inferior parietal lobule and increased activation in right middle temporal gyrus were associated with greater weight loss at six months. Right inferior parietal lobule is known for its role in emotion, body image, attention and processing sensory information (Clower et al., 2001; Wagner et al., 2003). In a meta-analysis by Liu and colleagues (2011), IPL was also implicated in reward anticipation. Decreased activity in right IPL at baseline may indicate that such individuals are less emotionally responsive to food and place a smaller reward value on food than their higher activation counterparts. By possessing the ability to think less emotionally and appraise the mental/physiological reward of food more accurately, individuals could have the capacity to cope with emotional triggers and cravings for rich foods more effectively. Right middle temporal gyrus (MTG) is cited as a region associated with higher order processing and perception of visual and semantic information (DelParigi et al.,
Gearhardt and colleagues (2013) suggested that increased activity in MTG by obese patients is evidence of increased use of strategies to control response while viewing food commercials. Successful post-surgery patients in our study may have possessed stronger control strategies at baseline for inhibiting extreme neural responses to images of food.

**Three Factor Eating Inventory**

Decreased activation to food in areas of cognitive control (inferior, middle, and superior frontal gyri) pre-surgery was associated with increased cognitive restraint, and decreased hunger and disinhibition post-surgery. Conversely, increased activation to food in areas of motivation and reward (posterior cingulate/limbic lobe) was associated with greater changes in TFEQ values. The associations between brain activation at baseline and change in TFEQ variables at three and six months were inconsistent with our hypothesis that greater activation to food pictures in known areas of cognitive control would be associated with greater changes in TFEQ values. Thus, future research is imperative to determine mechanisms which underlie brain activity associated with changes in behavioral outcomes post LAGB.

It is possible that LAGB provides a means to compensate for an inherent lack of control that those who benefit most from LAGB need to lose and maintain weight loss. Moreover, those who display less activation to food images in areas related to control could benefit most from the band because it may act as a surgically induced control mechanism. Conversely, patients with increased activation in areas known to be associated with food motivation and reward showed greater improvement in behavioral outcomes measured by the TFEQ post-surgery; it is possible that such individuals already have functioning reward appraisal systems that benefit them as they work to maintain the lifestyle and dietary changes required by the band.

Contrary to our hypotheses, there were no significant associations between six month TFEQ results or three month hunger ratings and baseline post-meal brain activations. It is unclear why results emerged at three but not six months. It is possible that brain activity in the postmeal
condition is a poorer indicator of outcome overall as evidenced by fewer significant areas of activation in the postmeal condition compared to the premeal condition. It may be that the premeal condition is more indicative of the underlying neural mechanisms for food craving that LAGB patients will need to fight in order to lose weight and maintain necessary lifestyle changes. Previous studies have, however, documented similar results. A study by Ochner and colleagues (2012) found no changes in cognitive restraint or motivation and reward regions in the post meal scan following participant weight loss from RYGB surgery. Another study, by Bruce and colleagues (in press), found no differences between bariatric and diet participants in cognitive restraint or motivation and reward regions in the post meal scan following participant weight loss.

Conclusion

Although brain responses to food stimuli were associated with increased weight loss and with change in hunger, cognitive restraint, and disinhibition, we cannot infer causality. While analyses were corrected for multiple comparisons and a Monte Carlo simulation was conducted to determine the cluster threshold and necessary significance value, the specific r values are inflated due to the selection of the voxel most highly correlated with the covariate of interest (Poldrack and Mumford, 2009). Future studies should conduct focused region of interest (ROI) analyses to normalize inflated r-values and allow for the creation of predictive models. In addition to specific ROI analyses, researchers should examine outcomes further from surgery (i.e. > 6 months) to determine the long-term predictive power of baseline brain activity for weight loss and behavioral outcomes. As well, although the proportion of males to females in the study was consistent with the gender breakdown of bariatric surgery patients (Buchwald, et al., 2007), future studies should include greater sample sizes of men to examine differences in brain activation between men and women. Future studies should also examine individuals with BMIs greater than 46 kg/m² as these subjects were not included in our study due to scanner limitations.
This study substantiates that there are patterns of brain activity, prior to LAGB surgery, which are differentially associated with outcomes following LAGB. Results suggest that there may be neural mechanisms which underlie an individual’s weight loss success following surgery. Certain individuals may have physiological and neural processes that respond to LAGB in such a way that they beneficially adapt in their experience of hunger, cognitive restraint, and disinhibition. Specifically, activation in areas associated with decision making, planning, executive functions, and reward expectancy is differentially associated with weight loss. This is the first fMRI study to examine the brain regions at baseline associated with changes in weight, hunger, cognitive restraint, and disinhibition at three and six-months post-LAGB surgery. Future studies may conduct focused region of interest analyses to determine if baseline brain activation can accurately predict post-LAGB success. Knowledge of differential baseline brain activation may be used to screen candidates for LAGB surgery to prevent unnecessary costs and procedures. Alternatively, people with high risk of LAGB failure, as identified by pre-surgical fMRI screening, may require more intensive post-surgical monitoring and support. Finally, treatments may be developed to alter cognitive control and improve the likelihood for success with LAGB surgery. Ultimately, the goal must be to better understand the neural mechanisms associated with obesity, its maintenance, and potential recovery in order to improve the quality of life, lessen the burden of disease, and improve the economic impact on those sufferers of obesity and society at large.
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doi: 10.1093/scan/nst059


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VITA

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