NEURAL MECHANISMS OF AFFECTIVE PROCESSING IN OBESITY AND ASSOCIATIONS WITH WEIGHT LOSS

by

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To my mother, who taught me to always ask, “Why?” through math and science;
To my father, who taught me persistence and attention to detail through music.

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Obesity affects over one-third of the American population and is associated with a myriad of physiological and psychological health concerns. While obesity has a number of contributing factors, the most prevalent is consumption of food beyond caloric need. Thus, valuation of salient external stimuli is implicated, as well as approach and avoidance behavior. These occur through affective processing, which drives an individual's valuation and orientation toward valenced stimuli.

Affective processing abnormalities in individuals with obesity have been shown in the context of food, as well as other stimuli, including facial expression of emotion. However, to date, a direct comparison between facial affective processing in individuals with obesity and lean controls, as well as in individuals with obesity before and after weight loss, has not been examined. To that end, we used a facial affective processing task in a functional magnetic resonance imaging experiment to identify differences in affective processing between lean participants and

participants with obesity, as well as participants with obesity before and after significant weight loss.

We found that lean individuals demonstrated greater bilateral insula activation when viewing neutral faces compared to affective faces, while participants with obesity demonstrated greater dorsolateral prefrontal cortex activity when viewing neutral faces compared to affective faces. Additionally, participants with obesity demonstrated increased functional connectivity within the affective network while viewing affective faces. However, there was no difference in affective processing in participants with obesity after weight loss. These results indicate that lean controls may demonstrate increased uncertainty and attention to neutral faces in an attempt to decipher unexpressed emotion, while participants with obesity may demonstrate greater executive control, perhaps in the maintenance of attention to faces without emotion expression.

In conclusion, these results suggest differences in affective processing between participants with obesity and lean controls, and a lack of change in affective processing after weight loss. These results may help guide future treatment options for obesity, particularly incorporating affective processing.

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CHAPTER ONE

INTRODUCTION

1.1. Obesity

Obesity, defined as having a body mass index ≥ 30, affects 37.9% of the American population (Flegal, Kruszon-Moran, Carroll, Fryar, & Ogden, 2016) and 13% of the global population (World Health Organization, 2016). In turn, the obesity epidemic continues to be the single greatest financial burden on America's health care system, with costs of $140 billion for treatment of related diseases (Centers for Disease Control and Prevention, 2017). These include diabetes and cardiovascular complications (Cawley, Frisvold, & Meyerhoefer, 2012; Mokdad AH, Ford ES, Bowman BA, et al, 2003), as well as mental illnesses such as depression and impulse control disorders (Mobbs, Crépin, Thiéry, Golay, & Van der Linden, 2010).

While obesity has a variety of contributing factors, including sedentary lifestyle, genetics, and hormonal conditions (Chaput, Pérusse, Després, Tremblay, & Bouchard, 2014), the most prevalent cause is consistent over-consumption of palatable foods regardless of homeostatic need (Taubes, 2013). The behavior of eating despite a positive caloric balance has roots in the hypothalamic control of appetite, as well as the cortico-limbic circuit (Shin, Zheng, & Berthoud, 2009; Soczynska et al., 2011). The cortico-limbic circuit is responsible for assigning positive or negative valence to stimuli such as food, so they may be approached or avoided, respectively. This valuation of stimuli is affective processing and has been shown to be blunted in individuals with obesity, which may play a role in food consumption and adiposity (Brewer, Cook, Cardi, Treasure, & Bird, 2015). While there are psychological factors that contribute to compulsive overeating, including affective processing abnormalities, the neural mechanisms that underlie

affective processing as it relates to obesity have not yet been determined (Davis et al., 2011; Lowe & Fisher Jr, 1983) (Pelchat, 2002).

1.2 Affective processing in individuals with obesity

Affective processing is a key factor contributing to self-control, decision-making, and thus, food overconsumption. This is not surprising because valuation of a stimulus and its effect on internal sensation is a component of eating. The literature widely supports a model of decreased affective processing in individuals with eating disorders in general (Brewer et al., 2015; Harrison, Sullivan, Tchanturia, & Treasure, 2010), and particularly, in obesity (Cserjési, 2009). The relationship between impaired affective processing and the continued eating after satiety that causes obesity was first described in the 1970s: "... the very organization of awareness of hunger and of other bodily needs is the outcome of reciprocal transactional processes within the interpersonal field" (Bruch, 1973). Since then, evidence suggests that obesity itself can be linked to impaired awareness of hunger and emotion (Fassino, Pierò, Gramaglia, & Abbate-Daga, 2004).

In one study of emotional awareness, Rommel and colleagues used the Level of Emotional Awareness Scale to show that women with obesity demonstrated impaired awareness of emotion in themselves and others, compared to controls. Additionally, women with obesity were more likely to partake in emotional eating than controls, and were more likely to report overprotective parents who denied emotional autonomy during childhood (Rommel et al., 2012). Etiologically, individuals with reduced response to affective stimuli may be at risk for obesity because they do not derive the same motivation to stop overeating if weight gain is less aversively salient to them, and weight loss is less positively salient (Wegener et al., 2008).

Weight loss is impeded by comorbid emotion-related disorders, indicating another mechanism by which affective processing may be a contributor to obesity (Kalarchian et al., 2008). Depression has been shown to impede weight loss after gastric band surgery (Rydén, Hedenbro, & Frederiksen, 1996); and attachment behavior, which is rooted in impaired affect regulation, has similarly been linked to less successful weight loss (Kiesewetter, 2016). In sum, these studies suggest that obesity may be a byproduct of impaired hunger and affective processing.

However, there is also evidence for changes in affective processing after weight loss. One group showed that, while pre-weight-loss depression resulted in less weight lost over all, depression, but not anxiety, improved 6–12 months after weight loss, and was maintained 24 to 36 months later (de Zwaan et al., 2011). Another study examining depression and anxiety in conjunction with weight loss after bariatric surgery found increased interoceptive awareness and impulse regulation two years after surgery (Beck, Mehlsen, & Støving, 2012). Furthermore, learning emotion-regulation techniques in a weight loss study helped participants overcome binge eating (Telch, Agras, & Linehan, 2001). However, to date, no one has examined the neural response to affective stimuli directly in individuals before and after significant weight loss, such as that conferred by bariatric surgery.

Other work has shown that participants who have undergone bariatric surgery exhibit changes in neural response to food cues, which incorporates salience and reward networks (A. Bruce et al., 2014; Ochner et al., 2011; Scholtz et al., 2014). One meta-analysis of neural response to food cues in individuals pre- and post-weight loss showed consistent changes in the cingulate gyrus, lentiform nucleus, and precuneus. In another study, when participants were

instructed to “crave” or “resist craving” during a food cue task, the dorsolateral prefrontal cortex was activated in the “resist” condition and activity correlated with weight loss success (Goldman et al., 2013). Thus, similar differences may occur in response to affective stimuli. In fact, changes in amygdala activity have been associated with recovery from affective disorders (Canli et al., 2005). Similarly, orbitofrontal cortex (OFC) activity is greater in individuals with obesity when evaluating salient stimuli than in controls (Scharmüller, Übel, Ebner, & Schienle, 2012). Thus, after weight loss, bottom-up affective processing (amygdala-to-OFC) may be increased, or strength of top-down processing (OFC-to-amygdala) may contribute to subcortical emotional processing. These studies demonstrate that executive control increases in individuals post-weight loss, and that changes in affective processing may also occur.

To that end, we will examine whether the neural mechanisms underlying affective processing are altered in individuals with obesity compared to individuals with a healthy weight (BMI <25), and whether these alterations are specific to changes in body weight (vs. pre-morbid condition). We will analyze existing functional magnetic resonance imaging (fMRI) data on obese individuals collected before and after weight loss via bariatric surgery, and compare neural activation during the Faces Task between obese patients and healthy-weight controls. We will then examine functional connectivity between regions of interest and the experimental construct of affect to evaluate functional connectivity within the affective salience network. To examine whether changes in the affective salience network are specific to weight change (vs. pre-morbid risk factors), we will compare the difference in neural activation before and after weight loss. To our knowledge, this is the first examination of affective processing in individuals with obesity

compared to lean controls, as well as after weight loss. While our small sample size might result in insufficient power, the unique nature of this data set warrants its examination.

1.3 Defining the construct of affective processing

Affect is defined as "valenced responses to external stimuli and/or internal mental representations," and affective processing describes the neural mechanisms underlying these responses (Ochsner & Gross, 2005). Individuals vary in the degree to which they process affective stimuli and this variability has been linked to psychiatric disorders. For obesity, differences in inherent affective processing between individuals may play a role in food consumption and adiposity (Brewer et al., 2015; Kemps & Tiggemann, 2015). Thus, alterations in the integration of stimuli (e.g. food) and salience (e.g. positive, desirable) can influence behavior, and examining how a brain processes salient stimuli can help us understand the health concerns related to the subsequent behaviors.

Affective neuroscience, or the study of brain mechanisms that underlie affective processes, has evolved over the past century from its initial focus on the limbic system and its challenges in the quantification of subjective emotion. fMRI has improved the measurement of affective processing through experimental paradigms that elicit an individual's response to emotionally salient stimuli and its effects on cognition (Armony & Vuilleumier, 2013). Visual stimuli most often consist of either appetitive images (e.g. food, babies, attractive faces) or aversive images (e.g. spiders, pictures of violence). These fMRI experiments have helped define the construct of affective processing as the salience and valuation elicited by a perceived

stimulus (Aftanas, Varlamov, Pavlov, Makhnev, & Reva, 2001). Furthermore, they demonstrate that emotionally salient stimuli vary across individual factors including the presence of underlying psychopathologies such as psychopathy and substance use disorders (Eder, Hommel, & Houwer, 2007).

1.3.1. Neural mechanisms of affective processing

Neural processing of affective stimuli incorporates regions of perception, arousal, and salience evaluation, which facilitate everyday responses to and interaction with relevant stimuli in a healthy individual. The perception of faces is a complex cognitive process incorporating the integration of many cortical areas (Wechsler, Phillips, Bruce, Soulie, & Huang, 2012). The neural mechanisms of face perception have been extensively studied, revealing parallel processes for the subcomponents of faces as parsed by the brain including structure, gaze, facial expression, and motion (Haxby, Hoffman, & Gobbini, 2000). Early perception of facial features occurs in the inferior occipital gyri and is then parsed into two primary pathways: facial features and structure are processed primarily through the ventral pathway along the inferior temporal lobe, while facial motion and socially relevant cues (e.g. averted gaze) are processed by the dorsal stream, which projects to the superior temporal sulcus (STS) (Breen, Caine, & Coltheart, 2000; Haxby, Hoffman, & Gobbini, 2002). The posterior STS integrates socially relevant and affective facial stimuli, and thus has robust connectivity to the amygdala and OFC (Allison, Puce, & McCarthy, 2000).

Both the amygdala and the OFC are involved in processing emotions expressed on faces, as well as other visual, emotionally salient information (Cserjési, Vermeulen, Lénárd, & Luminet, 2011; Goodkind et al., 2012; Grynberg et al., 2012; LoPresti et al., 2008). Previous

work has shown bidirectional functional and effective connectivity between the OFC and amygdala during affective processing (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Sladky et al., 2015). Bidirectional signaling may play a role in linking sub-cortical to cortical ("bottom-up") as well as cortical to sub-cortical ("top-down") processing (Luiz Pessoa & Adolphs, 2010), with implications for alterations in behavior. One study of effective connectivity analyses in healthy individuals assumed the OFC-to-amygdala pathway as part of their base model to look at other, less-relevant connections during neural processing of fearful stimuli — matching faces expressing fear, anger, or disgust (Stein et al., 2007). This is consistent with affective processing as the valuation of valence, which is thought to be assigned by the OFC (Rolls, 2008). However, other work has shown that response to facial emotion is initiated by the amygdala, which is directly connected to preliminary visual processing in general (Frick, Howner, Fischer, Kristiansson, & Furmark, 2013; Liao et al., 2010; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). The amygdala is thought to be the primary detector of emotional stimuli, and thus might be a gating mechanism for OFC evaluation (Costafreda, Brammer, David, & Fu, 2008).

Functional brain network analytical techniques have been used to subdivide facial processing into a "core network" — comprising the inferior occipital gyrus, STS, and fusiform face area (FFA) — and an "extended network" including the OFC and amygdala (Ishai, 2008). The salience of visual stimuli are evaluated by the amygdala and OFC (Andrews & Ewbank, 2004; Haxby et al., 2002), which both have strong functional connectivity with the STS (Fairhall & Ishai, 2007; Morecraft, Geula, & Mesulam, 1992). Alterations in the strength of connections between these regions can result in pathological affective processing, as evidenced in the increase in negative processing in depression, or the inability to experience positive stimuli in

anhedonia (Davidson, 2002; Horn et al., 2010; Lee et al., 2008; Zeng et al., 2012). Similarly, affective processing abnormalities can contribute to addiction and other diseases with a component of valuation of stimuli and resulting action (e.g. impulsivity, obsessive compulsive disorder) (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Diekhof, Falkai, & Gruber, 2008; Remijnse et al., 2006). Thus, the connectivity of these regions may play a role in pathologies such as obesity, and changes in connectivity after treatment remains undetermined (Rolls, 2008).

1.3.2 An affective processing paradigm: The Faces Task

One of the most prevalent paradigms used to measure affective processing is perception of faces, such as in the Faces Task (Baron, 1979; Desimone, 1991). The Faces Task has been used to examine primarily two cognitive constructs with discrete neural networks: facial expression and facial identity (V. Bruce & Young, 1986). Using this paradigm, lesion studies and animal studies have demonstrated that facial expression of emotion activates the salience network including the OFC and amygdala (Vuilleumier & Pourtois, 2007). Imaging studies have further shown that activation of brain regions involved in facial processing is more prominent for negatively valenced stimuli (e.g. fear, disgust) than positively valenced stimuli (e.g. happy), which may promote survival (Surguladze et al., 2003).

Facial expression is particularly useful for understanding emotion, and can indicate deficits in affective processing. Abnormal processing of stimuli during the Faces Task has been robustly demonstrated and validated (Brewer et al., 2015; Cserjési, 2009; Grynberg et al., 2012; Hariri et al., 2002; Kilts, Egan, Gideon, Ely, & Hoffman, 2003; Tessitore et al., 2002). Faces are generally free from semantic connotation and are therefore a universally recognizable elicitor of emotion (McRae, Misra, Prasad, Pereira, & Gross, 2012). Additionally, facial emotion

recognition allows for identification of an individual's automatic, unfiltered, uncontrolled response, minimizing the potential for response bias (Cserjési et al., 2011). Finally, negative facial expression (e.g. anger, disgust, sadness) elicits a more robust neural response than positive facial expression (e.g. happy) (Olofsson, Nordin, Sequeira, & Polich, 2008), and differentiation between these negatively expressive faces is largely nonexistent (Koch & Pollatos, 2015). Variability in brain regions activated when processing facial emotion (reward circuitry, amygdala, and OFC) demonstrates deficits in functioning in patients with anhedonia, the inability to experience pleasure (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Mitterschiffthaler et al., 2003). The Faces Task is a validated measure of facial emotional processing that can identify both normal and dysfunctional affective processing.

1.3.3 Conclusions

While there is sufficient evidence for impaired affective processing in individuals with obesity, the neural mechanisms underlying this impairment remain unknown. We propose that when viewing affective stimuli, processing of emotional stimuli will elicit activation in the OFC and amygdala. We expect that activity in these regions will be attenuated in participants with obesity compared to controls. Finally, we propose that in the obese individuals, neural activation during the emotional stimuli will be greater after weight loss compared to before weight loss. These studies will demonstrate that affective processing is impaired in individuals with obesity, and attenuated after weight loss. This will bring to bear the need to address affective processing in obese individuals.

2. Specific aims

Affective responsivity by the amygdala is necessary for the valuation of stimuli in the OFC, which can then contribute to the reward response. Thus, affective processing is directly implicated in overeating (Elfhag & Morey, 2008), and is an important factor to consider for the etiology and treatment of obesity (Lowe & Fisher Jr, 1983). Previous work has similarly shown that obese individuals have impaired affective response to emotionally relevant stimuli compared to lean controls. Thus, understanding differences in affective processing in these individuals may advance our knowledge of how emotion contributes to obesity and weight loss.

Our review of the literature shows that affective processing is an important factor to consider in obesity research and that, to date, no one has applied a within-subjects design to determine how this response to affective stimuli may change after weight loss intervention. To test the neural processes of affective processing in obesity, we used existing data collected as part of a larger study by Puzziferri and colleagues (Puzziferri et al., 2016). In this study, 32 bariatric surgery candidates and 14 lean controls underwent the Faces Task while in the scanner. Of these initial participants, 26 participants with obesity repeated the task approximately one year after surgery, and 13 lean controls were re-scanned as a time point control. Nine participants with obesity and six lean controls were excluded from analyses due to missing data. Thus, for this study, pre- and post-surgery data will be used from 23 participants with obesity, and eight time point-matched lean controls at time point 1. Twenty participants with obesity and nine lean controls were included at time point 2.

During the Faces Task, participants viewed images of different faces expressing anger, fear, disgust, and neutral expressions to determine neural mechanisms of affective processing (Mette Posamentier and Dan Krawczyk, unpublished).

Aim 1: Determine whether brain patterns during affective processing are different in obese individuals relative to lean controls.

Hypothesis 1: Because behavioral studies have demonstrated impaired affective processing in those with obesity, we expect similar functional alterations in brain areas related to affective processing. Specifically, we predict that the OFC and amygdala will show greater activation in lean controls compared to participants with obesity.

Hypothesis 2: Functional connectivity analyses will show greater contribution of the interaction of affect with OFC and amygdala activity to neural activity in other regions involved in affective processing (e.g. the hippocampus and the insula) in lean individuals compared to individuals with obesity.

Hypothesis 3: Weight and BMI will correlate with the peak signal from these regions of interest.

Aim 2: Determine whether changes in brain activity during affective processing are associated with changes in body weight.

Hypothesis 1: Because impaired affective processing in individuals with obesity has been shown to improve with change in BMI, we hypothesize that the amygdala and OFC will show greater activity in participants with obesity at time point 2 compared to time point 1.

Hypothesis 2: Functional connectivity analyses will show greater contribution of the amygdala and OFC to the activity of other regions involved in affective processing, in the context of affective stimuli, after weight loss.

Hypothesis 3: We expect the degree of this signal change for each individual will correlate with the amount of weight lost, and change in BMI.

Significance: This project will advance our understanding of the role of affective processing in individuals with obesity. This study is the first to directly examine whether and how the brain response to emotionally charged stimuli is related to changes in body weight. This work will advance the field in the development of obesity treatment strategies. Understanding of the effect of weight loss on affective processing could provide understanding of the complex neural patterns involved in obesity and weight loss.

CHAPTER 2

METHODS

2.1. Bariatric surgery study dataset

This study used an existing dataset from a study conducted by Dr. Nancy Puzziferri investigating how reward and affective processing in participants with obesity change after weight loss.

Participants were recruited from the population of patients eligible and scheduled for bariatric surgery at The University of Texas Southwestern Medical Center bariatric surgery clinic. Only female participants between 18 and 65 years of age were recruited for this study to minimize effects of sex on affect, as emotional reactivity is more prevalent in obese women than obese men (Mulhans 2009). Additionally, females comprise 86% of bariatric surgery candidates, and thus our preliminary focus on this sex is most representative of the population (Kennedy-Dalby, Adam, Ammori, & Syed, 2014). To participate, individuals had to meet criteria for, and consent to undergo, sleeve gastrectomy, gastric bypass, or gastric banding as set by the National Institutes of Health (National Institutes of Health, 2017).

Exclusion criteria included an untreated Axis 1 disorder, vegetarian diet (for diet homogeneity between subjects), and diagnosis of diabetes mellitus, as this condition may be associated with GLP-1 resistance, which may have confounding effects on appetite (Herzberg-Schäfer, Heni, Stefan, Häring, & Fritsche, 2012). Participants with MRI contraindications were also excluded, including traumatic head injury, left-handedness, metal in the body, eyesight corrected to 20/40 or better, claustrophobia, and weight greater than 350 pounds (scanner limit).

2.1.1 Study procedure

Participants were asked to attend two sessions: one before their surgery, and one session approximately one year after their surgery. During both sessions, participants were asked to arrive in a fasted state (not having eaten since the previous evening). Height and weight were acquired at each session. They then entered the scanner and underwent the Faces Task (Figure 1).

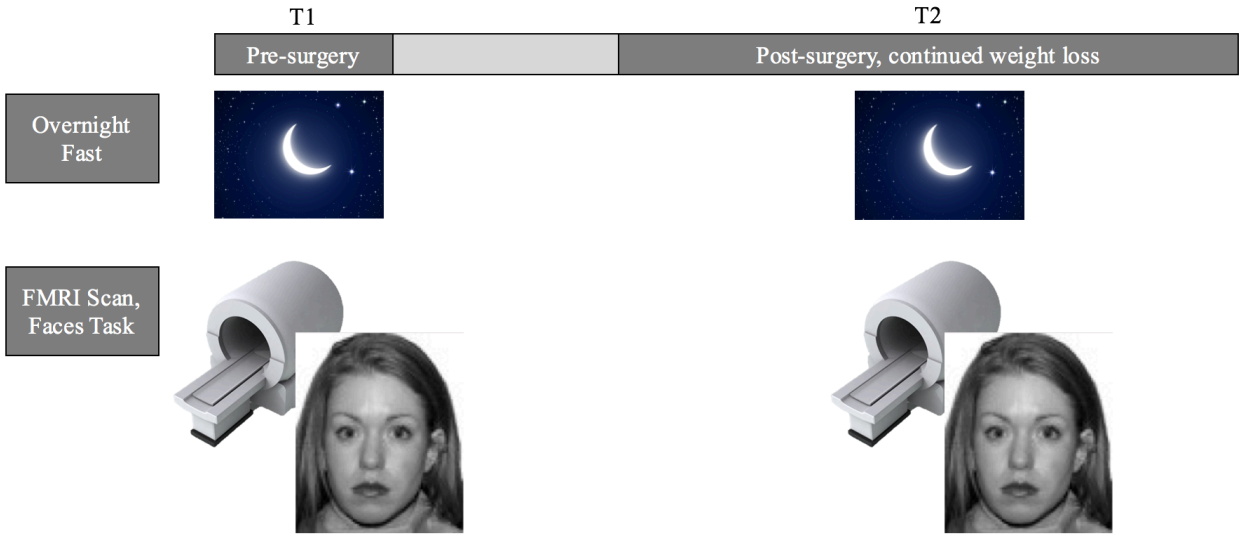


Figure 1. Timeline of experiment.

2.1.2 Assessments

BMI was calculated from participant height and weight, according to the NIH guidelines (National Heart, Lung, and Blood Institute, NIH). Demographic information was collected, including age, ethnicity, race, and metabolic rate.

The Quick Interview for Depressive Symptomatology (QIDS-SR_{16}) was administered to identify measures of depression. This assessment comprises the nine dimensions of depression as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV), including psychomotor agitation or retardation, sad mood, fatigue, sleep disturbance, increase or decrease in appetite or weight, difficulty with concentration, self-criticism, suicidal ideation, and interest in people or activities (Rush et al., 2003) with scores that range from 0-27.

2.1.3 MRI acquisition

fMRI data were acquired on a 3T Philips Achieva MRI (Philips Medical Systems, Netherlands). The echoplanar imaging fMRI sequence parameters were: repetition time (TR)/echo time (TE)/flip angle (FA) = 1500ms/27 ms/60^{o}, field of view (FOV) = 220x220 mm^2, matrix = 64x64, voxel dimension 3.4375 mm 3.4375 mm x 5 mm, 31 slices, thickness = 4 mm, gap = 1 mm. Per each 3.5-minute run, 140 blood oxygen level dependent (BOLD) images were obtained.

Faces Task: This task was based on the original Faces Task by Ekman et al. (Ekman, Friesen, & Tomkins, 1971) and modified by Dr. Dan Krawczyk and Dr. Mette Posamentier at The University of Texas at Dallas. In a series of three runs, participants are presented with images in pairs including objects (e.g. shoes, bags); faces expressing either angry, fearful, disgusted, or neutral expressions; and butterflies. Each image is presented for two seconds. When a pair of butterflies appears, participants are instructed to press two buttons simultaneously on a button box to maintain attention. When the two faces are presented, they are of different people, but equal expression (e.g. both angry, both neutral). Each run contains 10 images of each

emotion. Neural activity during each cue presentation is measured with a stimulus duration of 0 to capture the initial and most robust neural response to each stimulus (Lindquist, Loh, Atlas, & Wager, 2009).

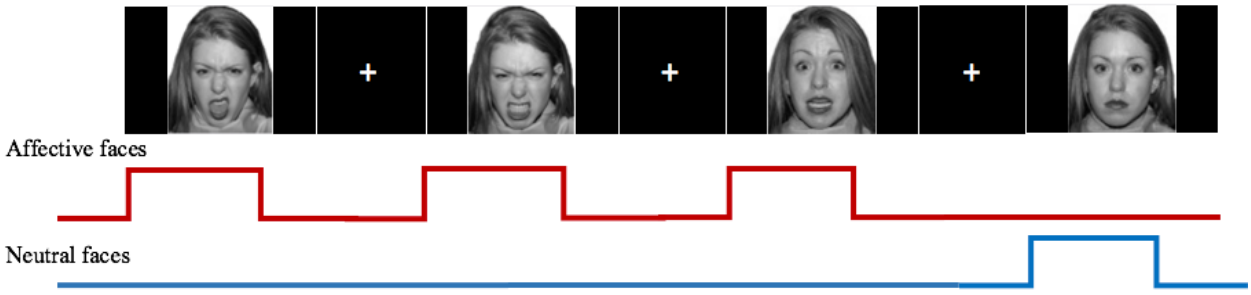


Figure 2. Presentation of negatively valenced (in order: disgust, anger, fear) and neutral faces are modeled with respective regressors to create the affective faces > neutral faces contrast.

2.2 Data analyses

2.2.1 Sample size and power analyses

Data were collected for 32 participants with obesity and 14 lean controls at time point 1. Nine participants with obesity and three lean controls were missing data for time point 1, resulting in final numbers of 24 obese and 11 lean controls. Twenty participants with obesity returned for time point 2, approximately one year after surgery (Figure 3).

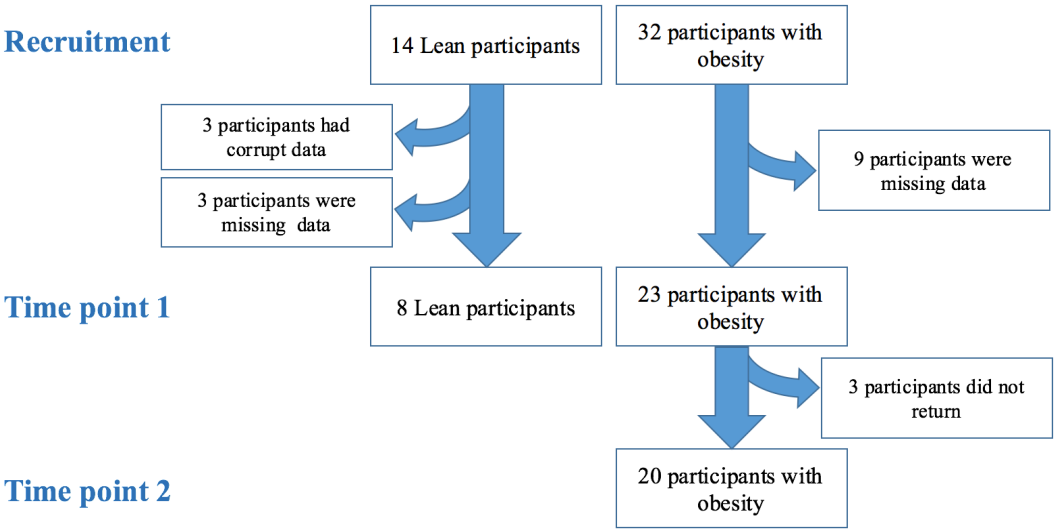


Figure 3. Participants' data at each time point.

Previous work has determined that permutation testing is more sensitive for determining power than parametric testing, especially for functional neuroimaging data (Goulden et al., 2010). In a study similar to our own, nonparametric power analyses were conducted using bootstrap with replacement. With an a priori large effect size (0.8) and a sample size of N=20, they established a power of 0.74 (Goulden et al., 2012).

2.2.2 Functional MRI data analyses

Neural responses to emotional stimuli were measured by the BOLD responses in each experimental condition (emotionally salient vs. emotionally neutral stimuli), at time point 1 for participants with obesity and lean controls for Aim 1, and in participants with obesity before and after weight loss for Aim 2. All data were analyzed using Statistical Parametric Mapping version 12 (SPM12) (UCL, UK: www.fil.ion.ucl.ac.uk/spm) running on MATLAB version R2014a

(MathWorks, Natick, MA, USA). fMRI data underwent a standard pre-processing pipeline including realignment, slice-time correction, co-registration of the structural image to the average functional image, segmentation, normalization of the functional (resolution: 3x3x3 mm^3) and structural (1x1x1 mm^3) images to standard MNI space, and spatial smoothing (with a Gaussian smoothing kernel of 8 mm at FWHM). All images were visually inspected to ensure proper alignment. Stimulus presentation timing was convolved with imaging data by using the double gamma hemodynamic response function (HRF). This allowed for the creation of regressors for each desired condition (viewing affective faces, viewing neutral faces). Application of the task time-series in the first level analysis created two regressors of interest: all faces (angry, fearful, disgusted, neutral) and affective faces (angry, fearful, disgusted), as well as the six motion regressors for each individual subject. These two regressors were then used to create a contrast of affective faces > neutral faces for each participant. These contrasts were then combined in a one-sample t-test in the second level analysis.

At the individual level, a general linear model (GLM) combined these regressors with motion parameters. We then created a contrast of conditions by subtracting the condition of neutral faces from the condition of affective faces, such that neural activity specific to the viewing of affect alone could be identified. At the group-level analysis, these contrasts were combined for each individual in a flexible factorial analysis for the comparison between groups for each aim. After contrast analysis, regions of interest were then included for a psychophysiological interaction (PPI) analysis to examine any co-activation changes between regions as a function of task, as described in (Friston et al., 1997; The FIL Methods Group, 2016). PPI analyses allowed for the examination of how activity in one brain region, in

conjunction with the experimental construct, affects activity in other brain regions. We extracted the time series from within the volume of interest defined in the initial group level analysis. To determine if there was a contribution of affect and region of interest (ROI) activation with other brain regions, these were then included in a PPI analysis with the Affective Stimuli contrast to create an ROI x condition interaction term for each individual. This interaction term was then modeled in each individual's GLM, and all participants were again combined in a flexible factorial analysis to determine if: (1) the interaction term was greater in lean controls compared to participants with obesity, and (2) if the interaction term was greater in participants with obesity at time point 2 compared to time point 1.

We applied a family-wise error (FWE) correction of 0.001, as well as a cluster threshold determined by the most recent iteration of 3dClustSim in AFNI, which has been adjusted to account for inflated false-positives documented by Eklund et al. (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Eklund, Nichols, & Knutsson, 2016). 3dClustSim calculates the non-Gaussian spatial autocorrelation function to estimate the probability of false positives based on smoothness of the voxel map and clustering threshold. According to these parameters, a cluster threshold of 97 voxels was established at a p value of 0.01 and an FWE correction of 0.001.

Finally, to determine if these changes in neural activity are proportional to weight loss and change in BMI in participants with obesity, we found each individual's peak voxel within the volume of interest from the group level. We then correlated this value with each individual's weight lost between time point 1 and time point 2, as well as their change in BMI between time point 1 and time point 2. In sum, these methods allow us to assess how much the original regions of interest contribute to the activity in other brain regions specifically in the experimental context

of perception and valuation of emotionally relevant stimuli brain regions in participants with obesity compared to lean controls. Comparison of neural activity, as well as the interaction between neural activity and affective processing before and after weight loss intervention will allow us to determine potentially altered connectivity through analysis of intrinsic coupling of brain regions after the perception of emotional stimuli.

CHAPTER 3

RESULTS

3.1 Preliminary tests

We performed preliminary analyses to examine the amount of weight lost, and change in BMI, between each group. Because weight loss is continuous over time, and T2 occurred at varying intervals for each individual, we calculated each participant's change in weight and BMI as T1-T2/number of months post-surgery, or comparative time point for controls (Table 1).

Table 1. Normalized weight lost per group, as calculated by total pounds lost divided by months post-surgery.

Group	**ΔWeight/month (lbs.) mean (SD)**	**ΔBMI/month mean (SD)**
Lean	0.07 (0.57)	0.23 (0.62)
Obese	7.09 (4.41)	10.13(3.66)

To ensure that depression was not a driving factor between groups, we examined differences in depression scores on the QIDS-SR_{16} (Rush et al., 2003). All groups scored low on the QIDS-SR_{16} and there was no difference in depression scores between groups or within each group between T1 and T2 (Table 2).

Table 2. Scores on the Quick Inventory of Depression Symptomatology do not differ between each group, or within each group between time points.

Group	**T1 mean (SD)**	**T2 mean (SD)**	**Between time point differences**
Lean	5.75 (3.57)	5.36 (3.18)	t(28)=0.32, p=0.75
Obese	4.51 (2.10)	3.53 (2.61)	t(33)=1.39, p = 0.17
Between group differences	t(21)=1.27, p=0.22	t(25) = 1.76, p=0.09	

Some participants had two post-surgery scans. However, the majority of time point 2 scans occurred around one year after surgery. For participants with obesity, time point 2 occurred an average of 430.81 (SD=383.80) days after time point 1 (Figure 4).

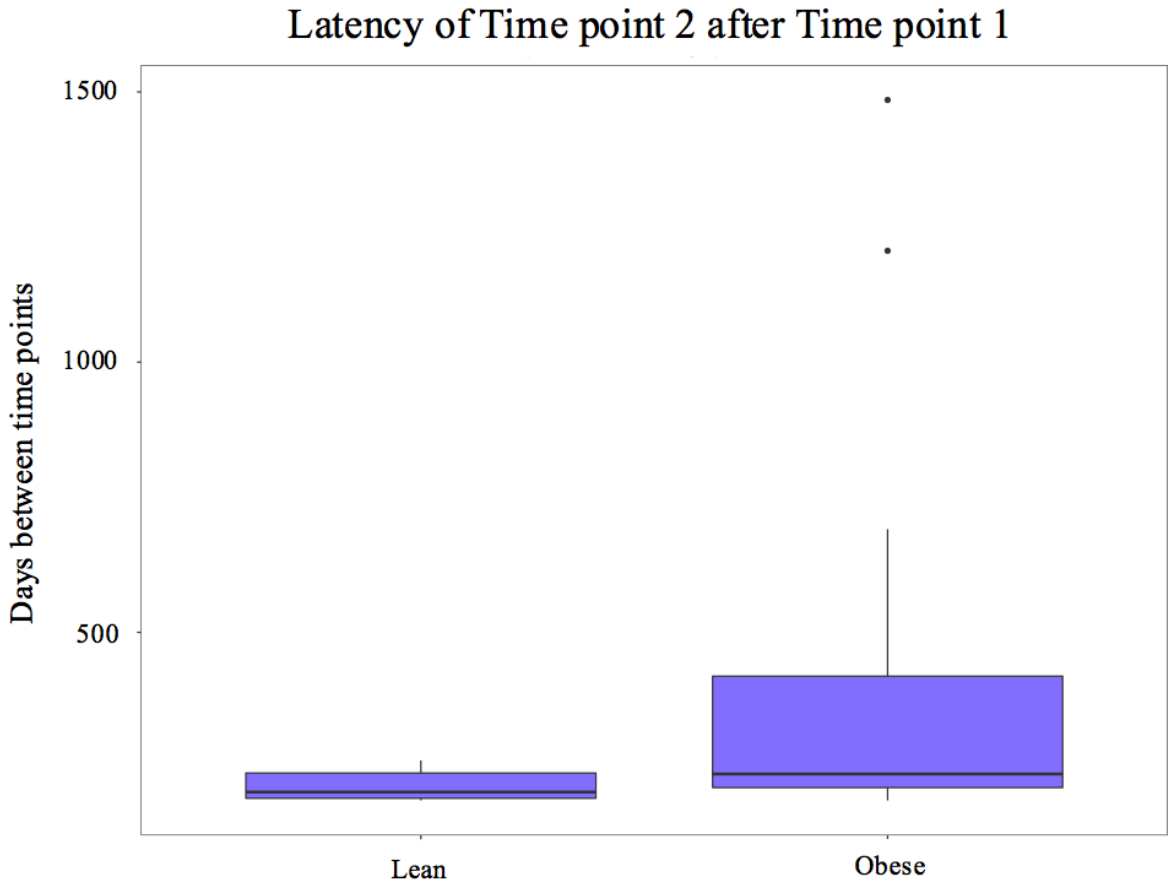


Figure 4. Latency of post-surgery fMRI session. For the sake of homogeneity between groups and between participants, the time point closest to this average was chosen. If this time point was not available (N_{obese} = 1, N_{lean}=1) we chose the latter time point.

3.2 Aim 1 results

For Aim 1, we hypothesized that the OFC and amygdala would show greater activation in lean controls compared to participants with obesity. However, preliminary ROI analyses showed

no significant results. Thus, we examined whole brain analyses to identify other potential activity patterns. This yielded no results at the original cluster threshold of 97 voxels, p=0.01 FWE corrected, which could be due to a small sample size. To accommodate for loss of power, we examined all contrasts between conditions in the whole brain at p=0.05 uncorrected, with a cluster threshold of 120 voxels (Gu et al., 2015, 2016).

We first examined the data for a main effect of all faces (Figure 5), a main effect of affective faces (Figure 6), and main effect of neutral faces (Figure 7) at time point 1 (Table 3). Overall, participants showed greater activation in the bilateral insula when viewing neutral faces compared to affective faces.

We also examined main effects of participant group when viewing all faces. Lean participants demonstrated greater activation in bilateral insula (Figure 8), while participants with obesity demonstrated greater whole-brain activity (Figure 9) (Table 4).

We then examined each group individually, with the contrast between face conditions. In lean participants only viewing affective > neutral faces, there were no suprathreshold clusters, whereas when viewing neutral > affective faces, there was one large cluster with peak activation in the left insula, which spanned the cortex to include the right insula (Figure 10, Table 5). In participants with obesity viewing affective > neutral faces, as well as neutral > affective faces, there were no suprathreshold clusters (Table 5).

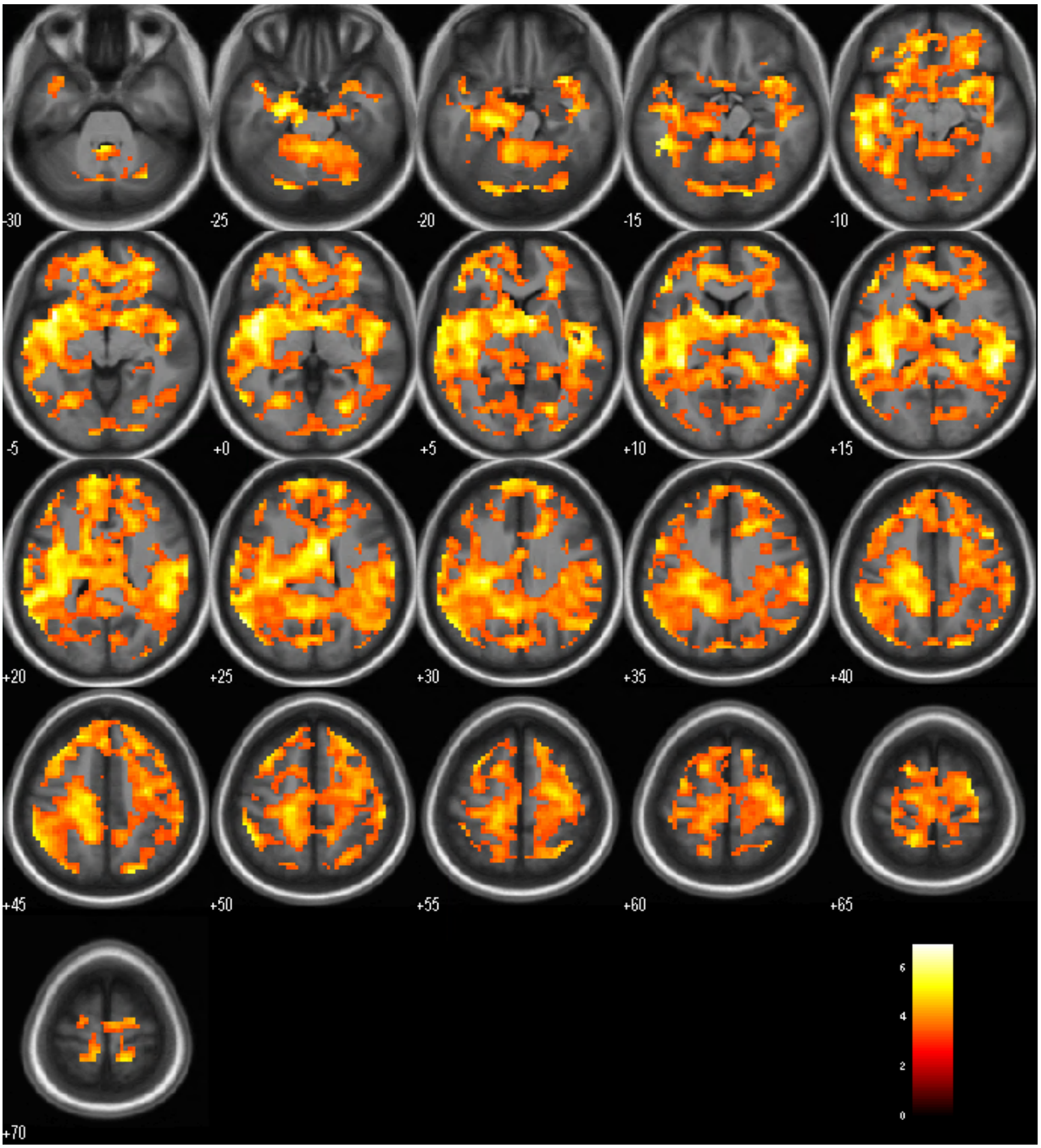


Figure 5. Main effect of faces in lean controls and participants with obesity at time point 1, $p<0.001$ uncorrected, $K>120$.

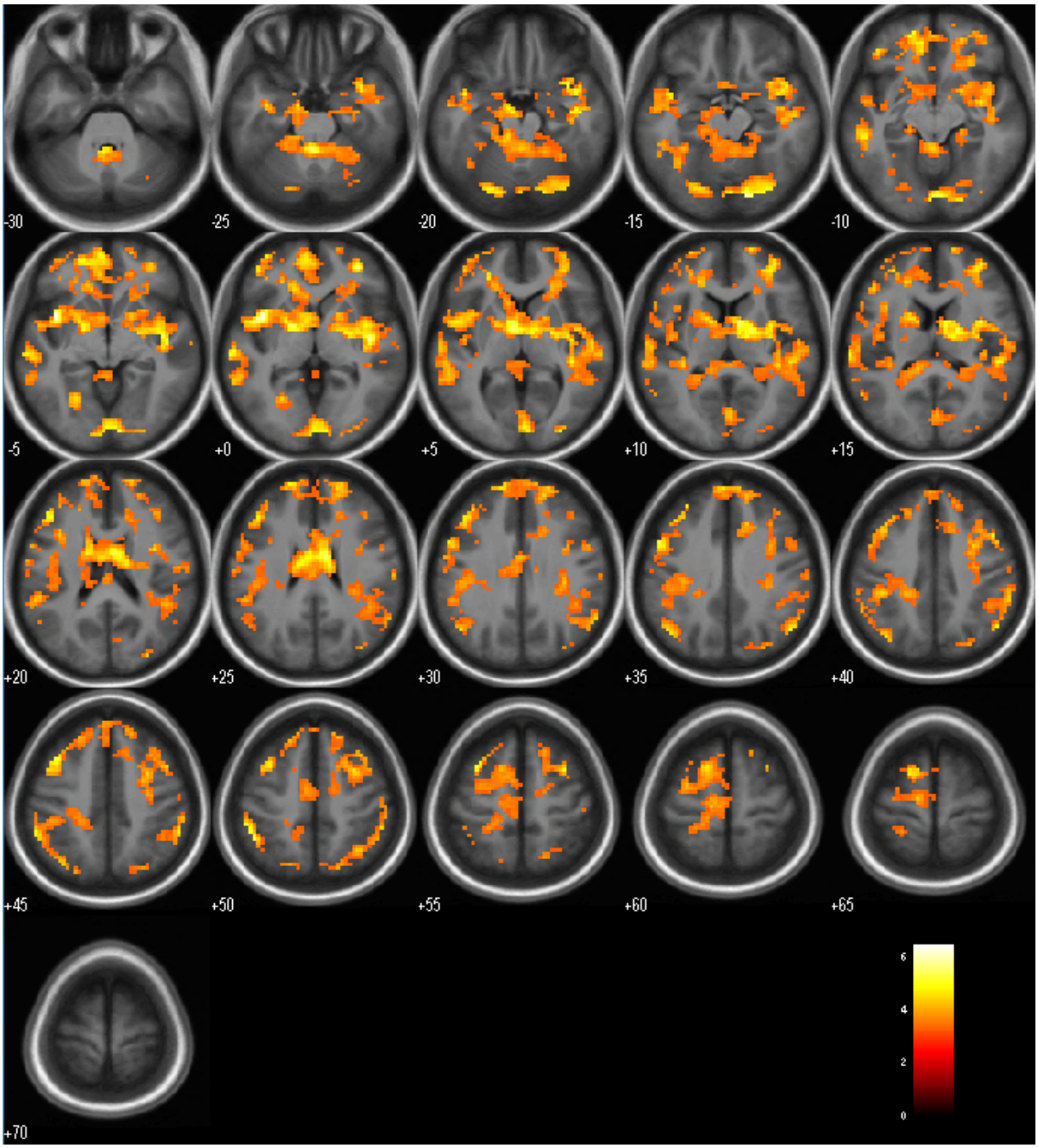


Figure 6. Main effect of affect in lean controls and participants with obesity at time point 1, p<0.001 uncorrected, K>120.

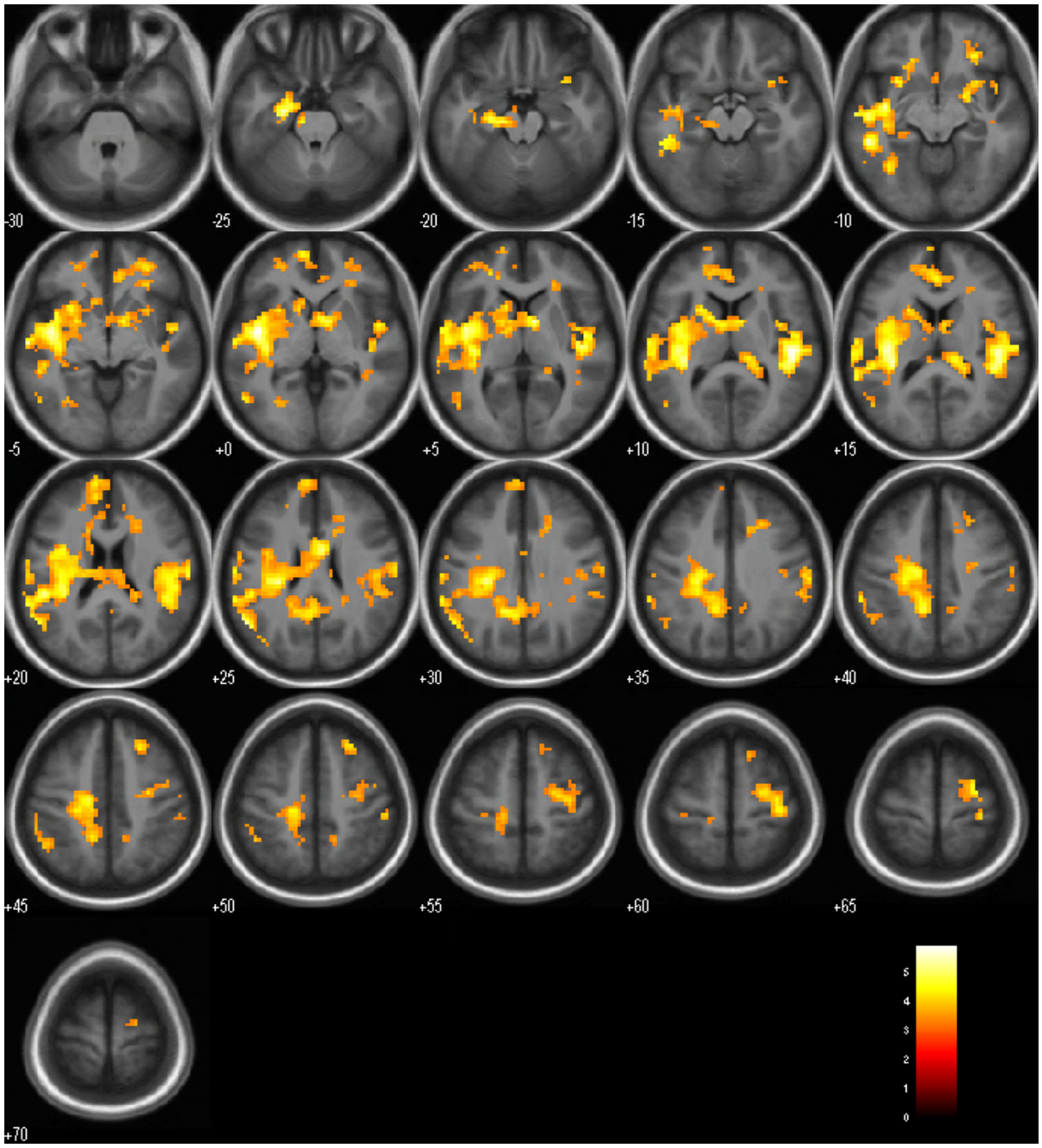


Figure 7. Main effect of neutral faces in lean controls and participants with obesity at time point 1, $p<0.001$ uncorrected, $K>120$.

Table 3. Main effects of conditions for Aim 1. All results are at a threshold of $p<0.001$, $K>120$ voxels.

A. Main effect of all faces in lean controls and participants with obesity					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
R. Superior Temporal Gyrus	22056	5.89	48	-31	14
B. Main effect of affective faces in lean controls and participants with obesity					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
L. Insula	8541	5.59	-39	8	-4
L. Medial Frontal Gyrus		5.08	-18	53	-7
R. Cerebellum (Declive)	461	5.13	15	-82	-16
C. Main effect of neutral faces in lean controls and participants with obesity					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
R. Transverse Temporal Gyrus	778	5.19	48	-22	11
R. Insula		4.61	48	-10	8
R. Postcentral Gyrus		4.44	60	-19	17
L. Insula	4088	5.19	-45	-7	-1
L. Parahippocampal Gyrus	145	4.93	-24	-13	-25
R. Postcentral Gyrus	265	4.7	39	-28	62
R. Precentral Gyrus		4.38	27	-13	68
R. Superior Frontal Gyrus	292	4.19	27	32	-10

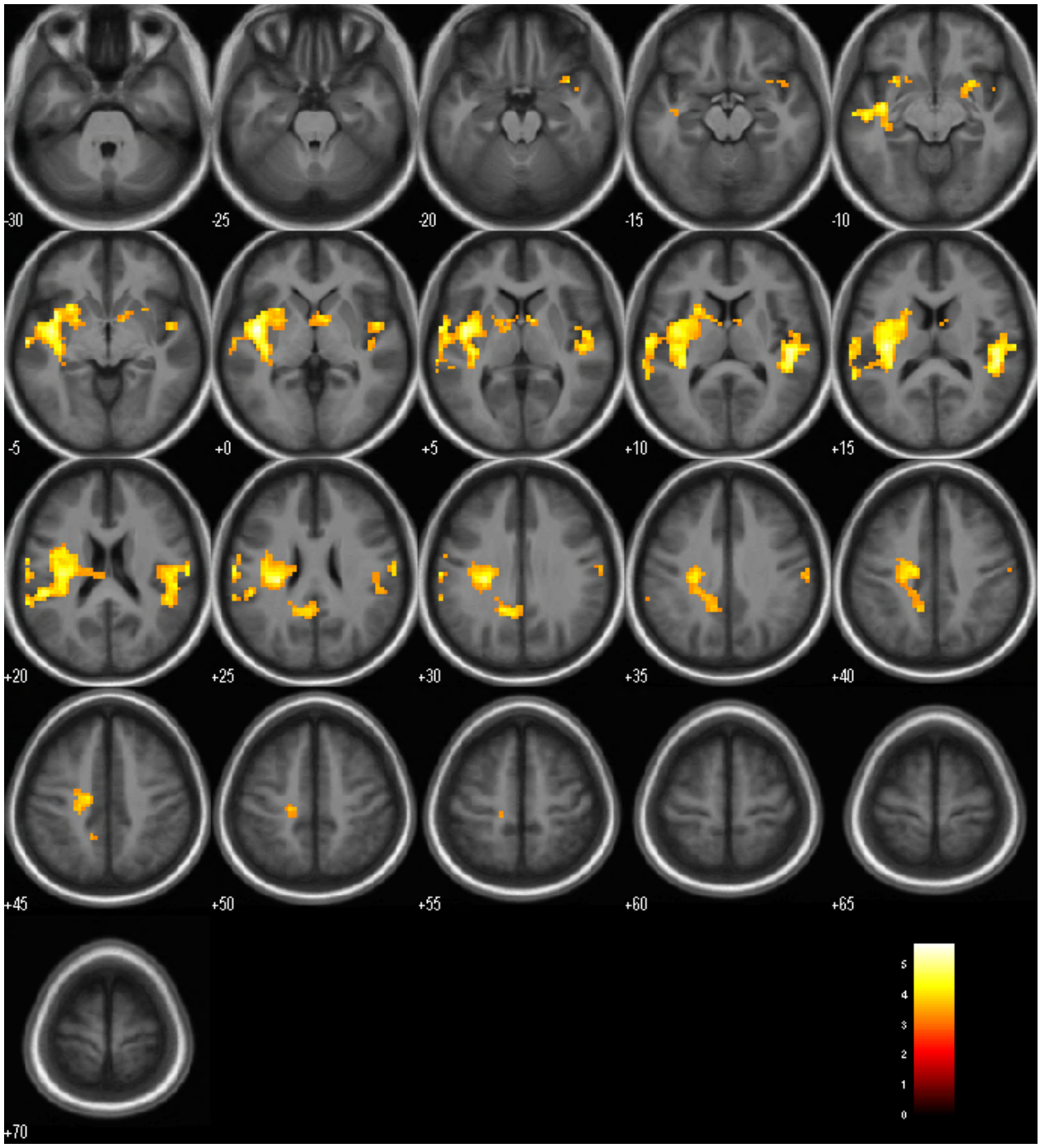


Figure 8. Main effect of all faces in lean controls at time point 1, p<0.001 uncorrected, K>120.

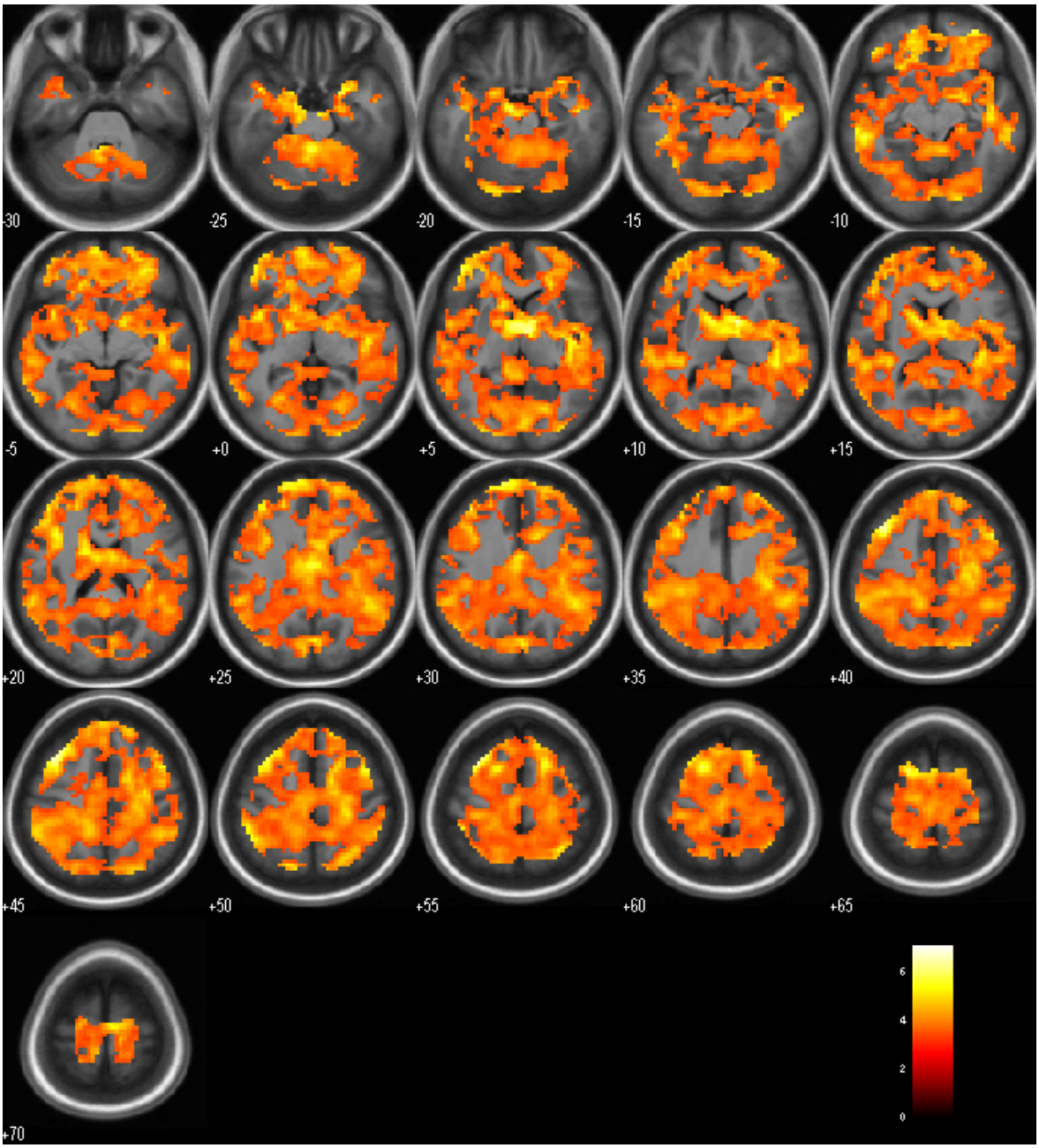
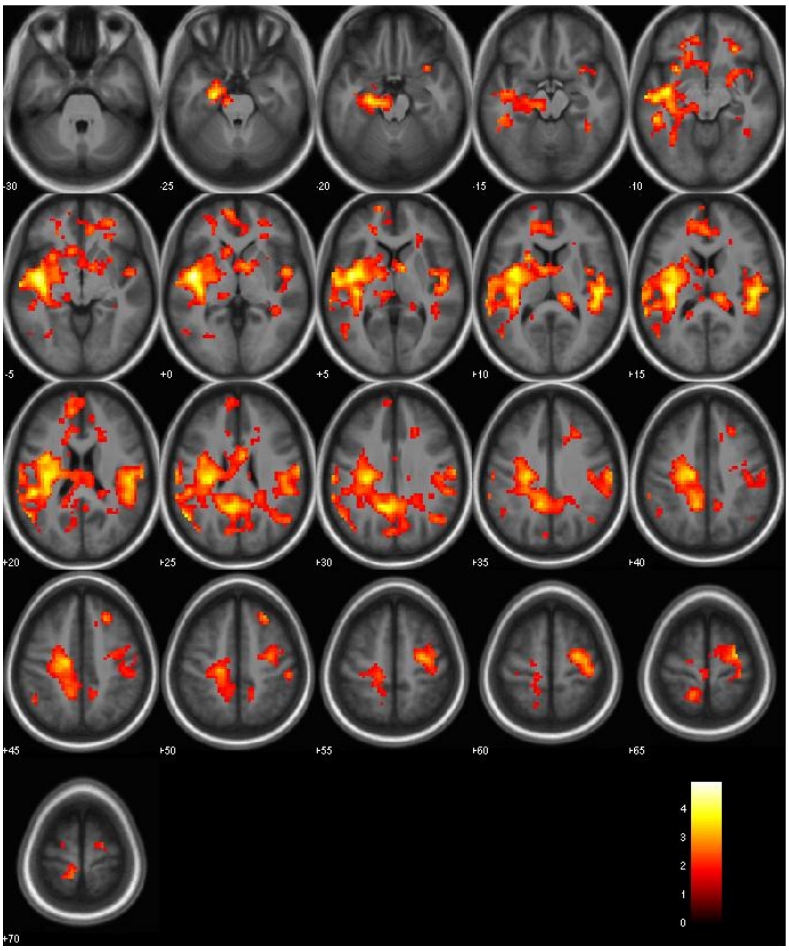


Figure 9. Main effect of all faces in participants with obesity at time point 1, $p<0.001$ uncorrected, $K>120$.

Table 4. Main effects for each group at time point 1. All results are reported at $p<0.001$, $K>120$ voxels.

A. Main effect of all faces in lean controls					
Region	**Cluster Size (voxels)**	**Peak Z**	**x**	**y**	**z**
L. Insula	1811	5.05	-42	-7	2
L. Insula		4.83	-36	-19	14
L. White Matter		4.69	-27	-25	26
R. Superior Temporal Gyrus	380	4.82	48	-31	14
R. Transverse Temporal Gyrus		4.69	48	-22	11
R. Postcentral Gyrus		4.15	60	-19	17
B. Main effect of all faces in participants with obesity					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
R. Caudate	25342	5.95	9	2	8
L. Middle Frontal Gyrus		5.68	-36	17	44
L. Frontal White Matter		5.67	-42	44	2

A



B

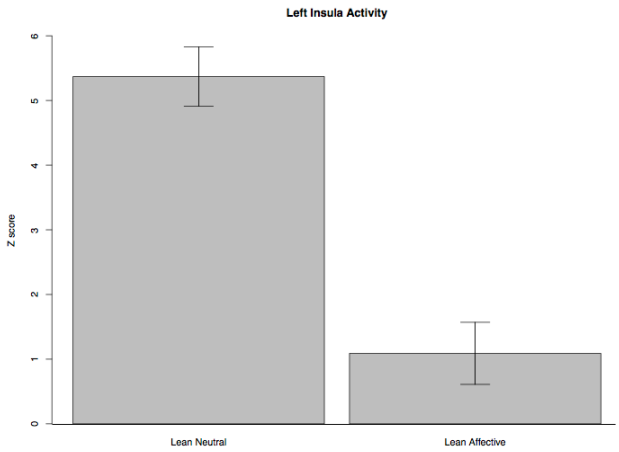


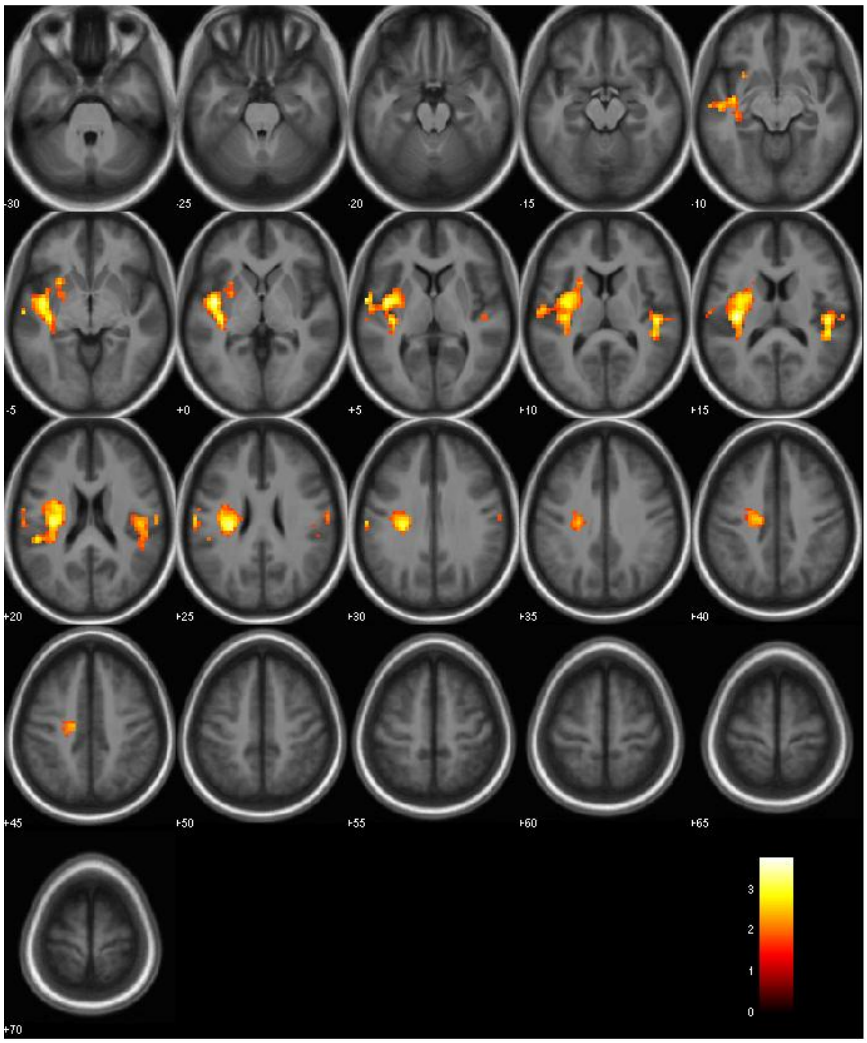
Figure 10. A. Lean participants viewing neutral faces > affective faces, $p<0.05$, $k>120$ voxels. B. Z score for peak voxel in each condition.

Table 5. Condition contrasts within each group individually, p<0.05, k>120 voxels.

Lean only, affective > neutral faces					
No suprathreshold clusters					
Lean only, neutral > affective faces					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
L. Insula	7665	4.51	-45	-7	-1
Obese only, affective > neutral faces					
No suprathreshold clusters					
Obese only, neutral > affective faces					
No suprathreshold clusters					

We then examined the groups in conjunction with each other. In lean participants > participants with obesity for the affective faces > neutral faces condition, there were no suprathreshold clusters at a threshold of p=0.05, uncorrected, k>120 voxels. In lean participants > participants with obesity in the neutral > affective faces condition, at this threshold, there was one cluster of activation centered in the left posterior insula (Figure 11, Table 6). In participants with obesity > lean controls for the affective > neutral faces condition, there were no suprathreshold clusters at p<0.05 K>120 voxels. In participants with obesity for the neutral > affective faces condition, there was one cluster in the left dorsolateral prefrontal cortex (Figure 12, Table 6).

A



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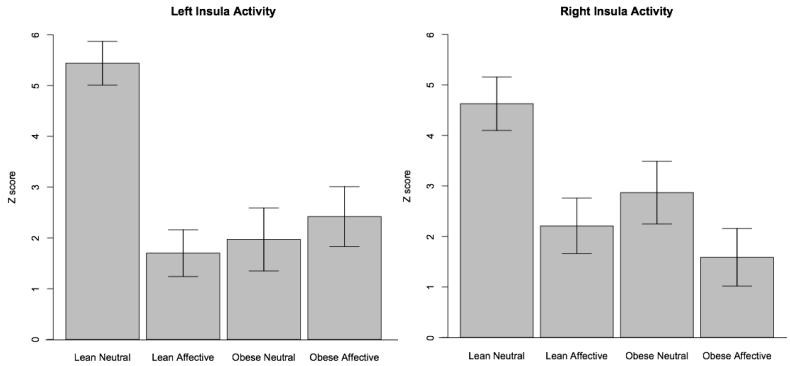
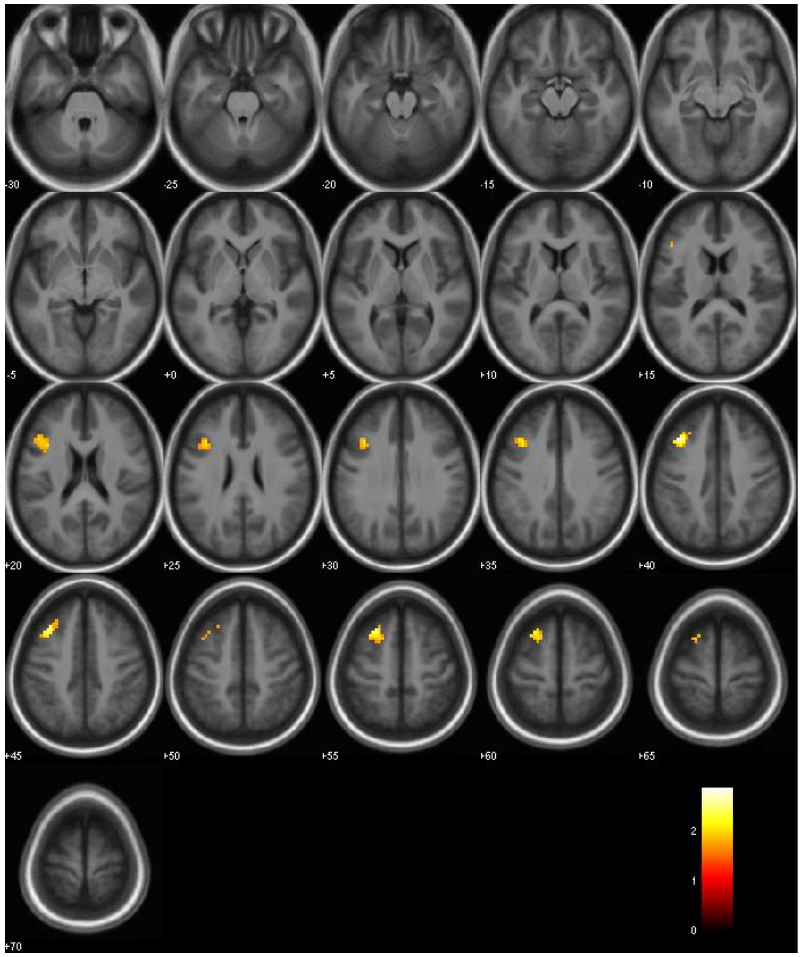


Figure ll. A. Lean participants > participants with obesity, neutral > affective faces, $p<0.05$, $K>120$ voxels. B. Z score for peak voxel in each condition.

A



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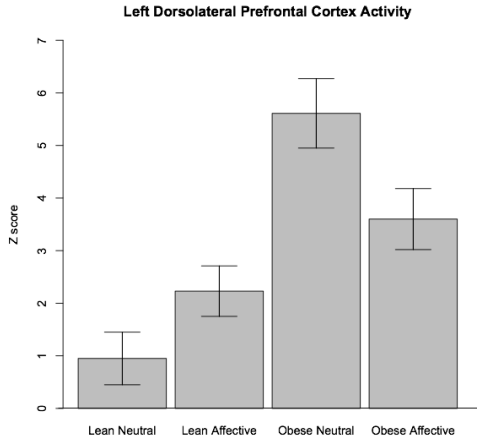


Figure 12. A. T1, Participants with obesity > lean controls, neutral > affective faces, $p<0.05$, $k>120$ voxels. B. Z score for peak voxel in each condition.

Table 6. Cluster coordinates for results of Aim 1. All coordinates are in MNI space.

A. T1, lean > obese, affective > neutral faces					
No suprathreshold clusters					
B. T1, lean > obese, neutral > affective faces					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
L. Posterior Insula	1035	3.55	-42	-7	2
R. Insula	180	3.10	48	-22	14
C. T1, obese > lean, affective > neutral faces					
No suprathreshold clusters					
D. T1, obese > lean, neutral > affective faces					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
L. Dorsolateral Prefrontal Cortex	204	2.78	-39	20	41

To address the second hypothesis — that our regions of interest would demonstrate greater functional connectivity in the context of affect — we initially intended to perform dynamic causal modeling. However, because our a priori regions of interest were not active at the group level, we chose the region of peak activation (the left posterior insula) and used it as a seed for PPI analyses (Figure 13).

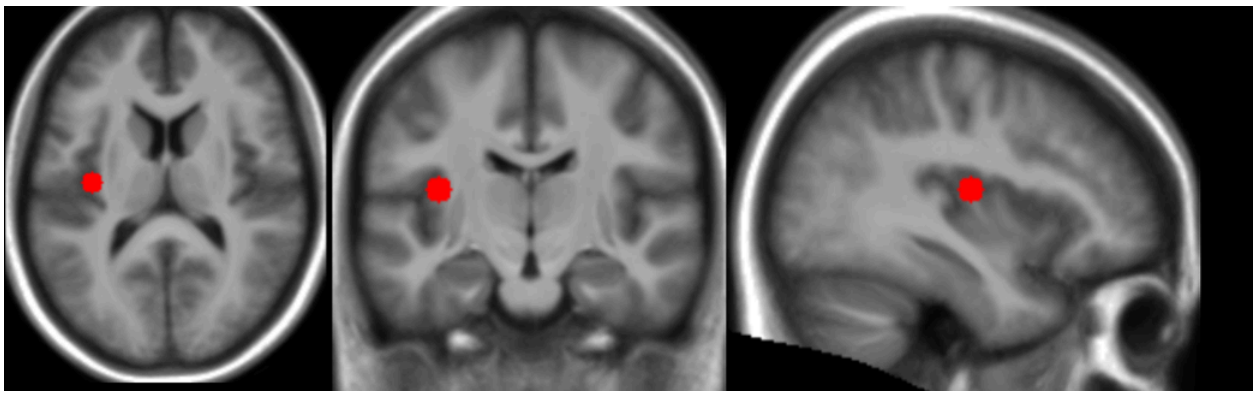


Figure 13. Left posterior insula seed used for PPI analyses, 5 mm radius.

We first examined each group separately. In lean controls, the left insula demonstrated no functional connectivity with other regions in the context of affect (Table 7A). In participants with obesity, there was an interaction between insula and affective > neutral faces including the left superior frontal gyrus, the right precentral gyrus, right postcentral gyrus, right insula, right parahippocampal gyrus, and right cingulate (Figure 14, Table 7B).

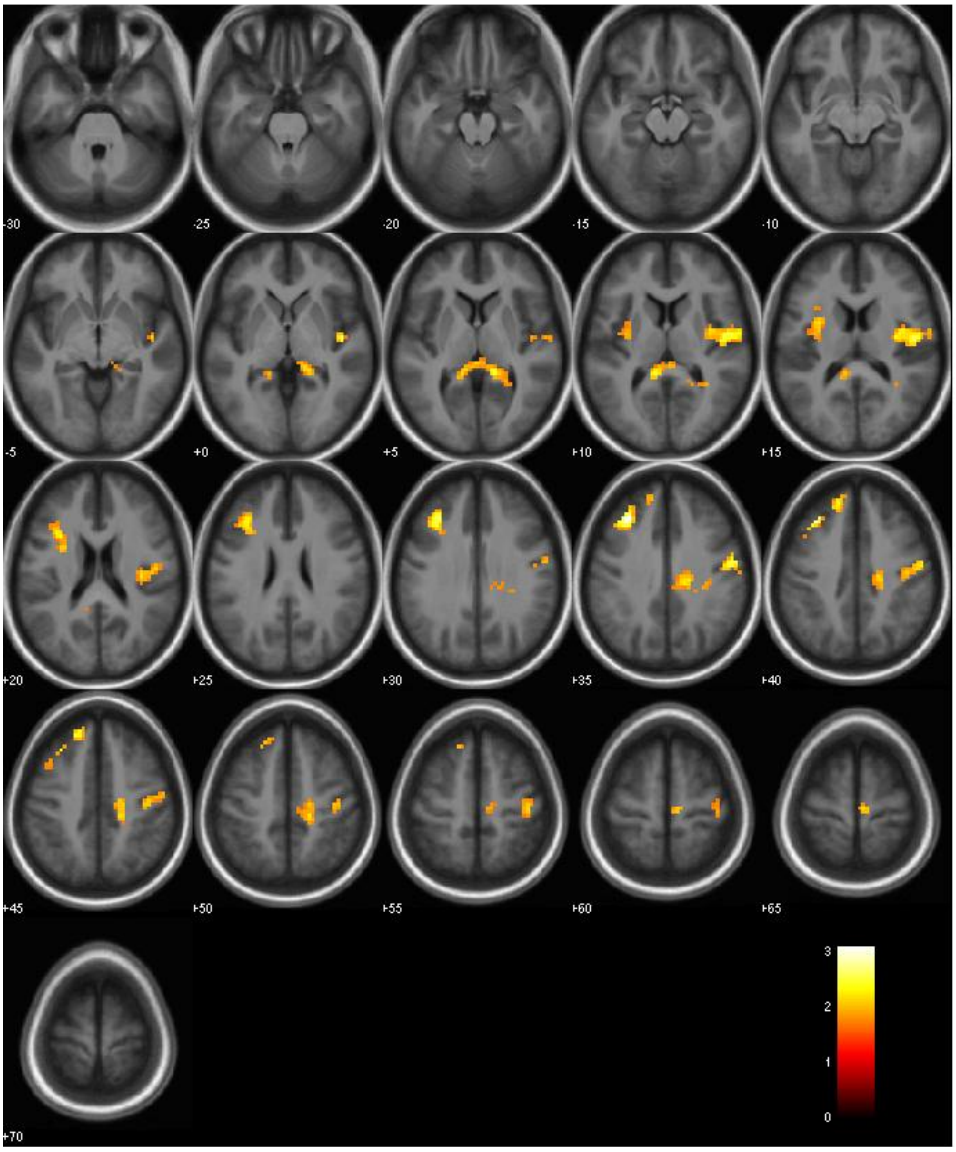


Figure 14. Participants with obesity, Insula x affective > neutral faces.

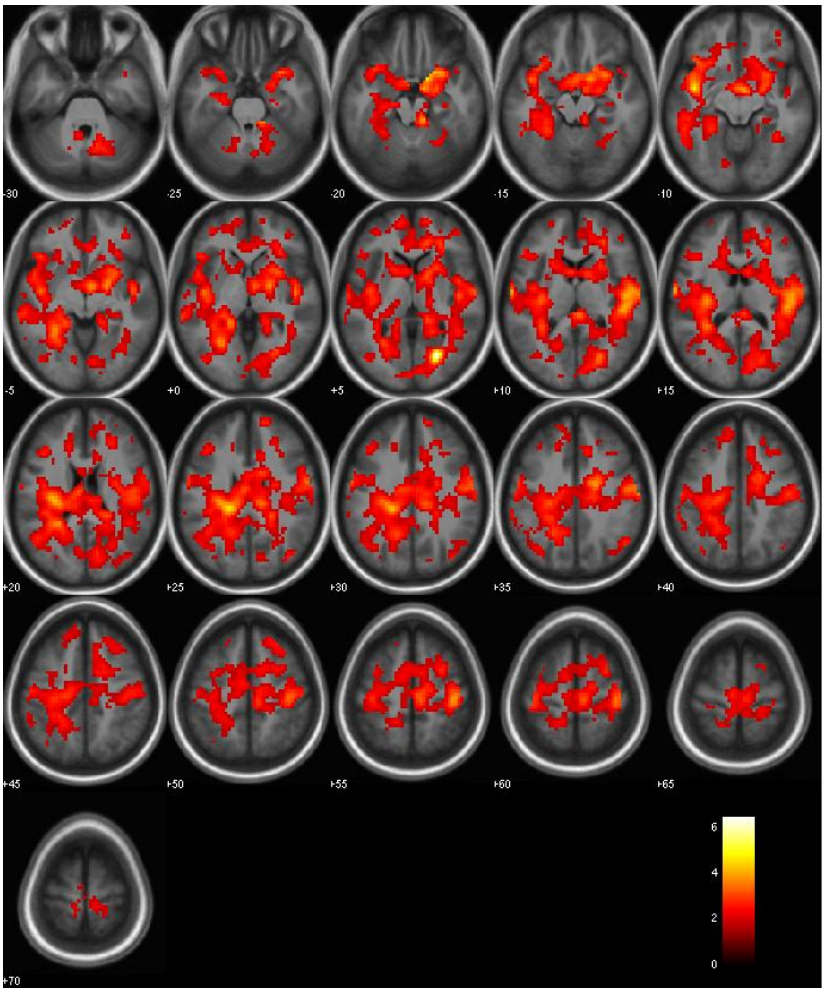
Table 7. PPI analyses in each group individually, $p<0.05$, $k>120$ voxels.

A. T1, lean only, Insula x affective > neutral faces					
No suprathreshold clusters					
B. T1, obese only, Insula x affective > neutral faces					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
L. Superior Frontal Gyrus	292	2.82	-30	29	35
R. Precentral Gyrus	147	2.43	54	-7	38
R. Postcentral Gyrus		2.06	42	-22	56
R. Insula	198	2.42	51	-7	11
R. Parahippocampal Gyrus	154	2.36	15	-37	2
R. Cingulate Gyrus	165	2.2	18	-28	47

We then compared the groups to each other. In lean controls > participants with obesity, no clusters survived the liberal threshold of $p=0.01$, uncorrected (Table 8A). In participants with obesity > lean controls, we found that the left insula is functionally connected to several regions in the context of affect, including the right lingual gyrus and the left insula (Figure 15, table 8B).

Our third hypothesis was that in participants with obesity, both weight (in pounds) and BMI would correlate with peak activation from the OFC and amygdala at time point 1. Since we saw no activation of the OFC and amygdala at the group level, but did see activation of the left posterior insula, we performed correlation analysis between the peak z score in the left posterior insula with weight and BMI instead. There was no correlation between peak insula activity and weight at time point 1 $r(22)=-0.01$, $p=0.95$ (Figure 16), or between peak insula activity and BMI at time point 1 $r(22)=-0.22$, $p=0.30$ (Figure 17).

A



B

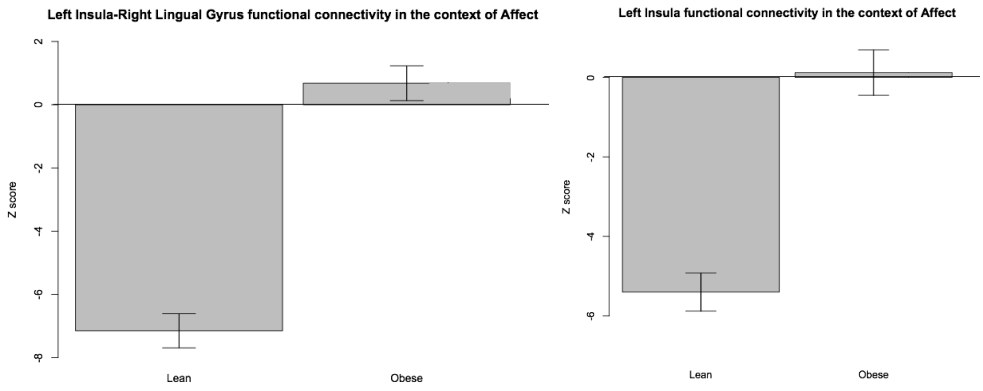


Figure 15. A. Participants with obesity > lean controls, insula x affective > neutral faces, $p<0.05$, $k>120$ voxels. B. Z score for peak voxel in each condition.

Table 8. PPI analyses comparisons between groups, p<0.05, k>120 voxels.

A. T1, lean > obese, Insula x affective > neutral faces					
No suprathreshold clusters					
B. T1, obese > lean, Insula x affective > neutral faces					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
R. Lingual Gyrus	13971	4.91	24	-70	5
Insula		3.93	-42	-4	-10

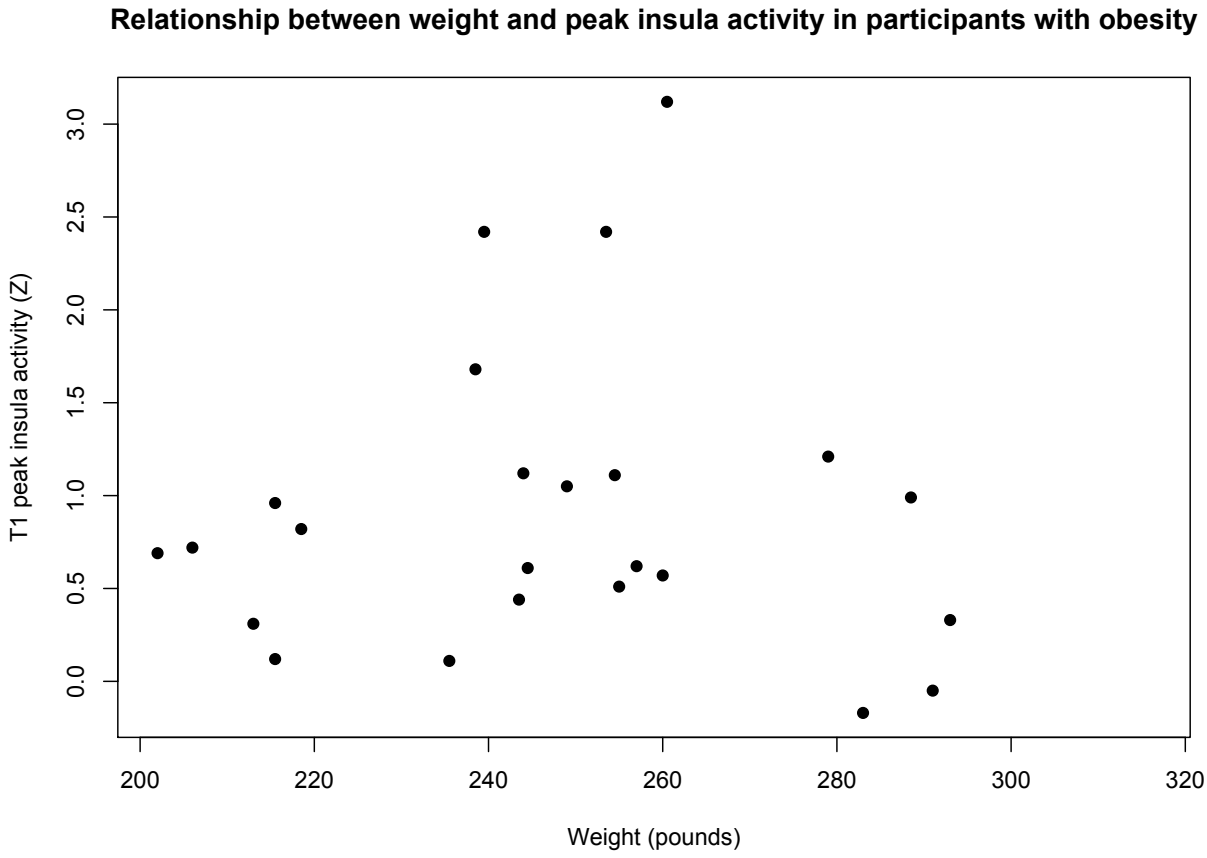


Figure 16. There is no relationship between weight and peak Z in the left posterior insula in participants with obesity, N=23.

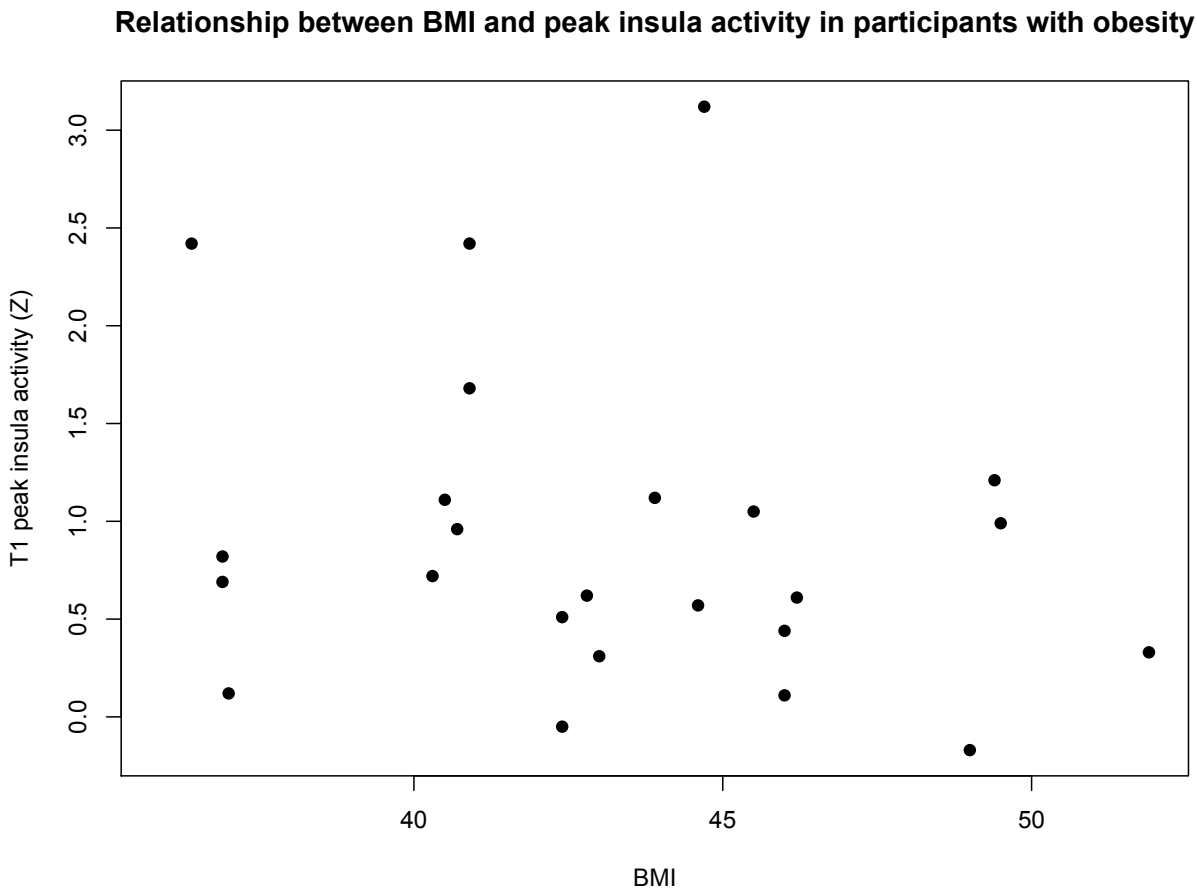


Figure 17. There is no relationship between BMI and peak Z in the left posterior insula in participants with obesity, N=23.

3.3 Aim 2 results

For hypothesis 1, we postulated that the OFC and amygdala would show greater activation in participants after weight loss compared to before weight loss. However, preliminary ROI analyses showed no significant results. Thus, we examined whole brain analyses to identify other potential activity patterns. This yielded no results at our a priori threshold of p=0.01 FWE corrected, which could be due to the small sample size in this study. Thus, to accommodate for loss of power, we examined the whole brain at p=0.01 uncorrected.

We first examined the data for a main effect of faces across time points, which revealed substantial global activation (Figure 18). A main effect of affective faces (Figure 19) revealed substantial global activation as well, but slightly less than the main effect of neutral faces (Figure 20).

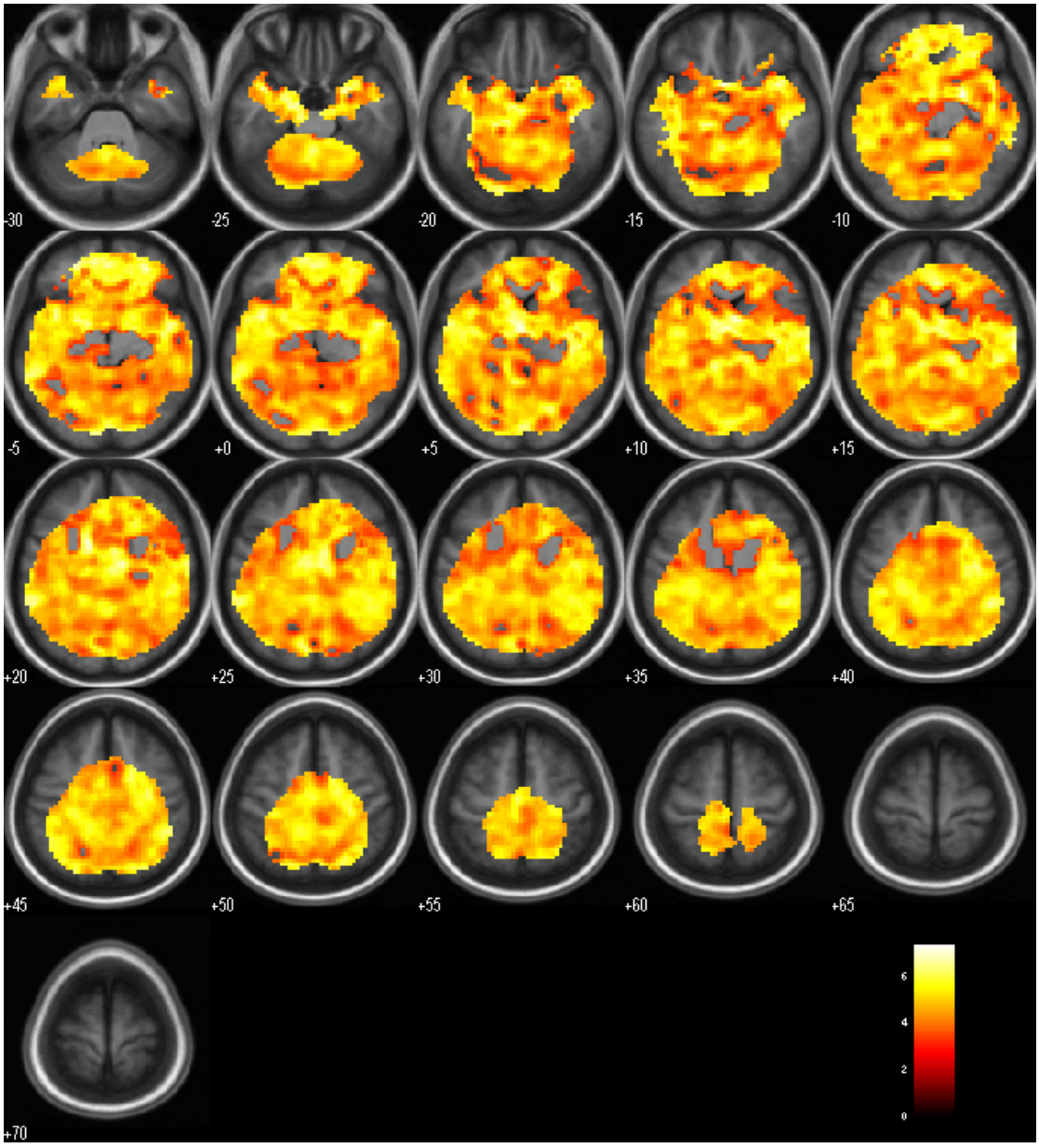


Figure 18. Main effect of all faces in participants with obesity at time point 1 and time point 2, $p<0.001$ uncorrected, $K>120$.

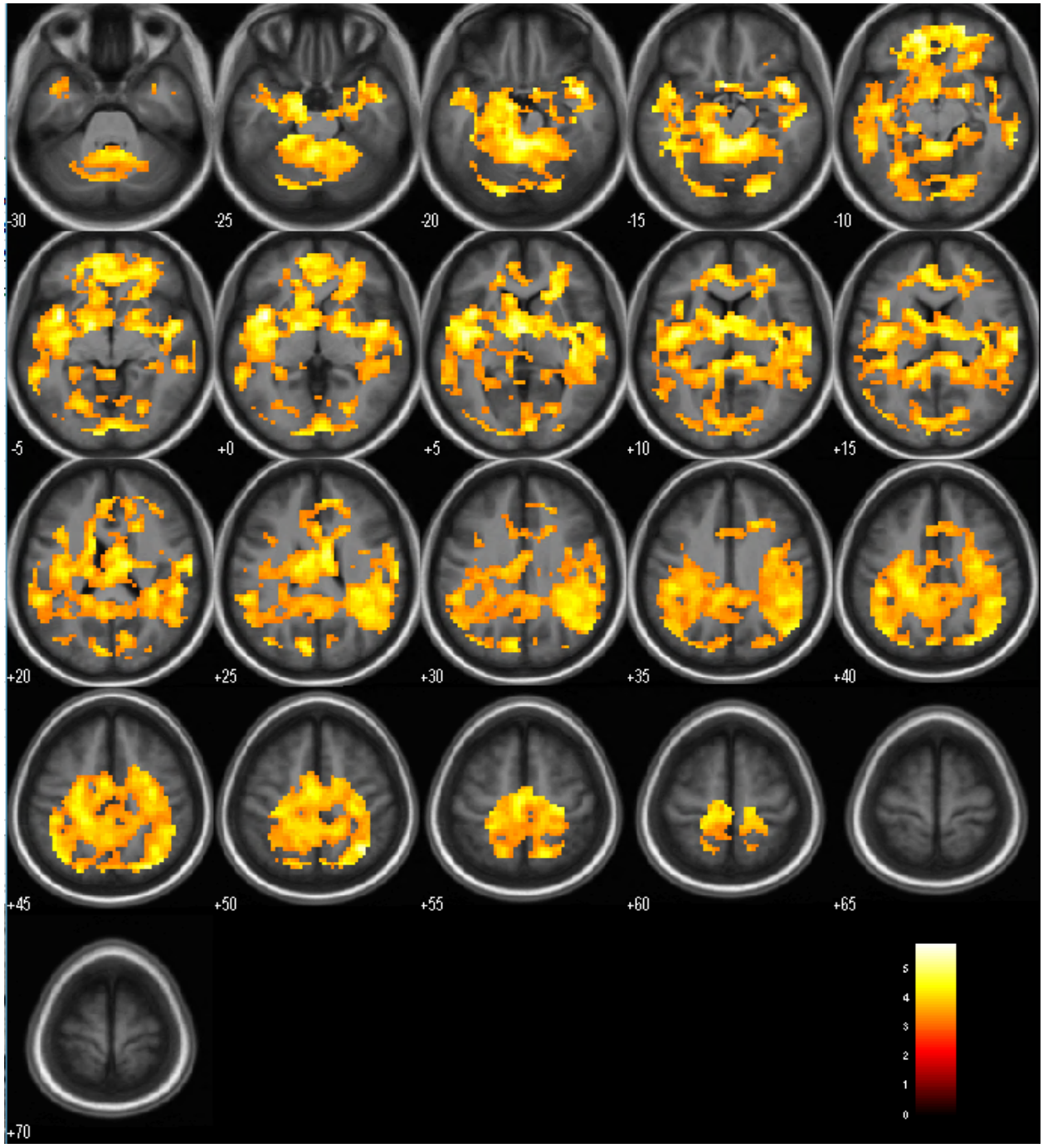


Figure 19. Main effect of affective faces in participants with obesity at time point 1 and time point 2, $p<0.001$ uncorrected, $K>120$.

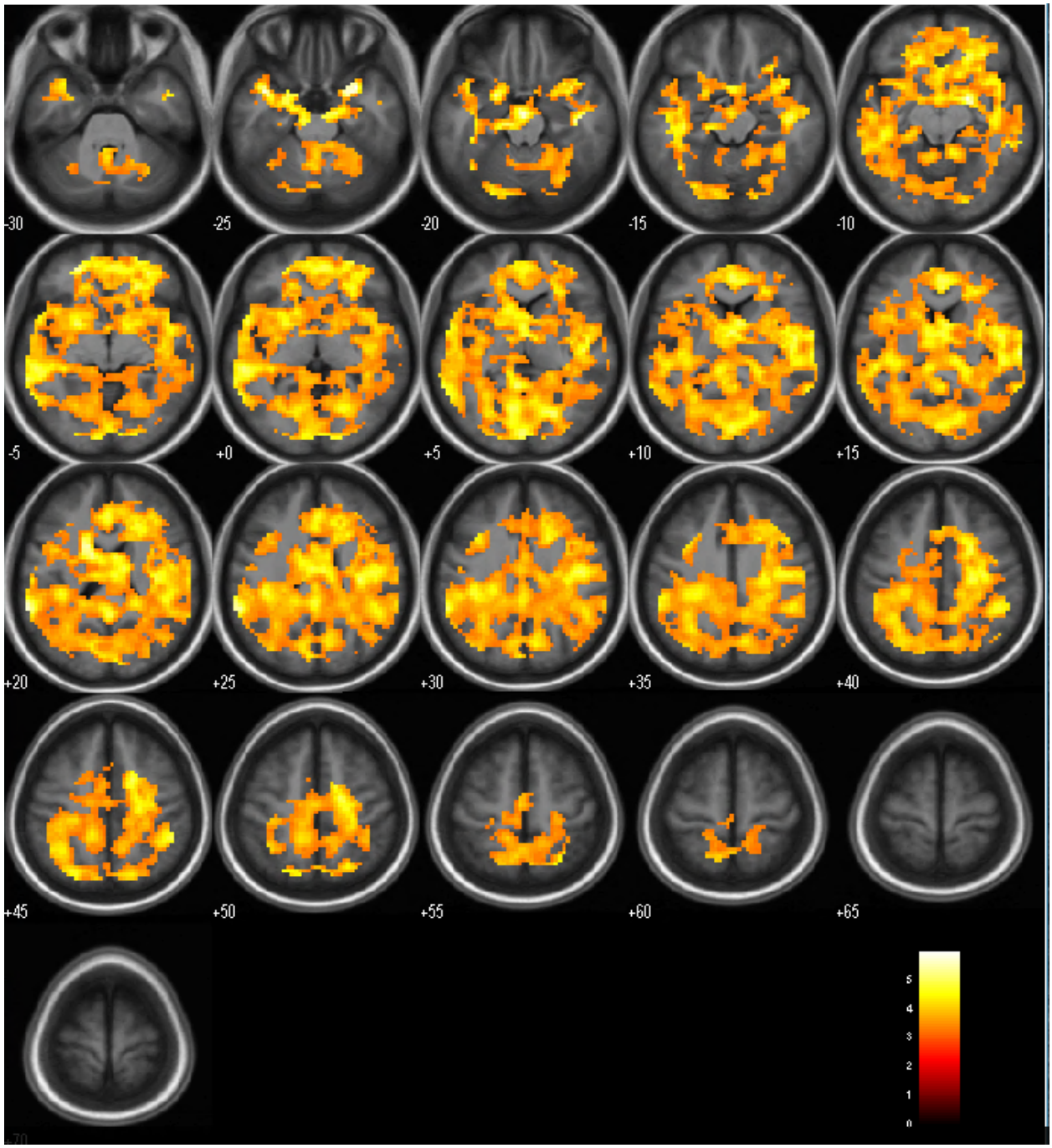


Figure 20. Main effect of neutral faces in participants with obesity at time point 1 and time point 2, $p<0.001$ uncorrected, $K>120$.

Table 9. Main effects of conditions in both groups, $p<0.05$, $k>120$ voxels.

A. Main effect of all faces in participants before and after weight loss					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
R. Globus Pallidus	30900	6.42	21	-1	-10
R. Frontal White Matter		6.33	30	44	-4
L. Anterior Cingulate		6.33	-3	8	-16
B. Main effect of Affective faces in participants before and after weight loss					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
L. Insula	17003	5.32	-39	5	-1
R. White Matter		5.2	42	5	-16
L. Anterior Cingulate		5.16	-12	47	-10
C. Main effect of neutral faces in participants before and after weight loss					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
R. Uncus	20554	5.41	30	8	-28
R. Globus Pallidus		5.34	21	-1	-10

We also examined each time point individually. There was a main effect of facial stimuli at time point 1 (Figure 21, Table 10A) which resulted in more global activation than in the main effect of facial stimuli at time point 2 (Figure 22, Table 10B).

We then examined each time point individually. Participants with obesity did not show any activation in either contrast (affective > neutral faces or neutral > affective faces) at either time point, at a threshold of $p<0.05$ uncorrected, $k>120$ voxels (Table 11). Additionally, participants with obesity did not show any effects of either affective > neutral faces, or neutral > affective faces at either time point 2 > time point 1, or time point 1 > time point 2 (Table 12).

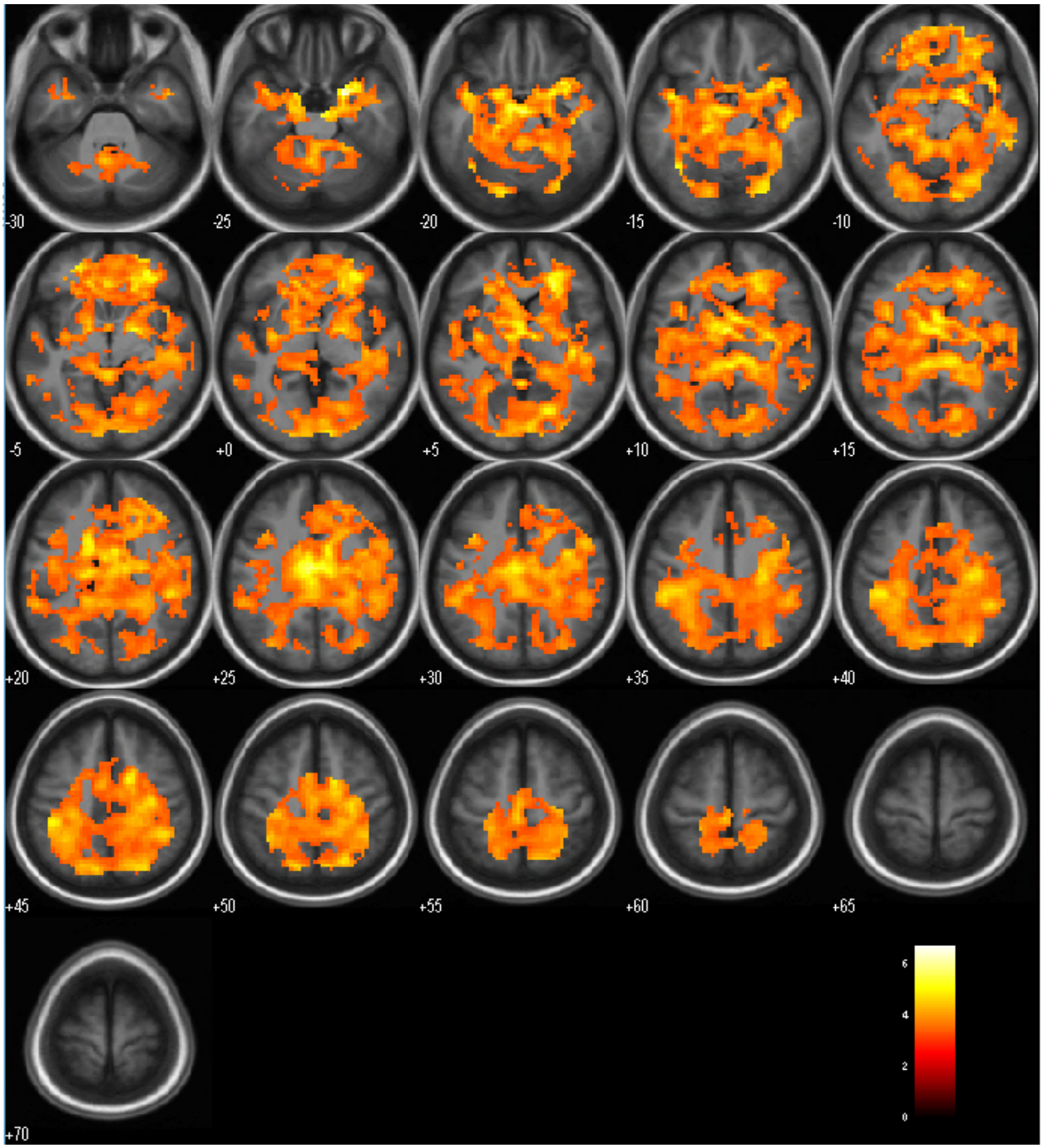


Figure 21. Main effect of facial stimuli at time point 1 in participants with obesity before weight loss, $p<0.05$, $k>120$ voxels.

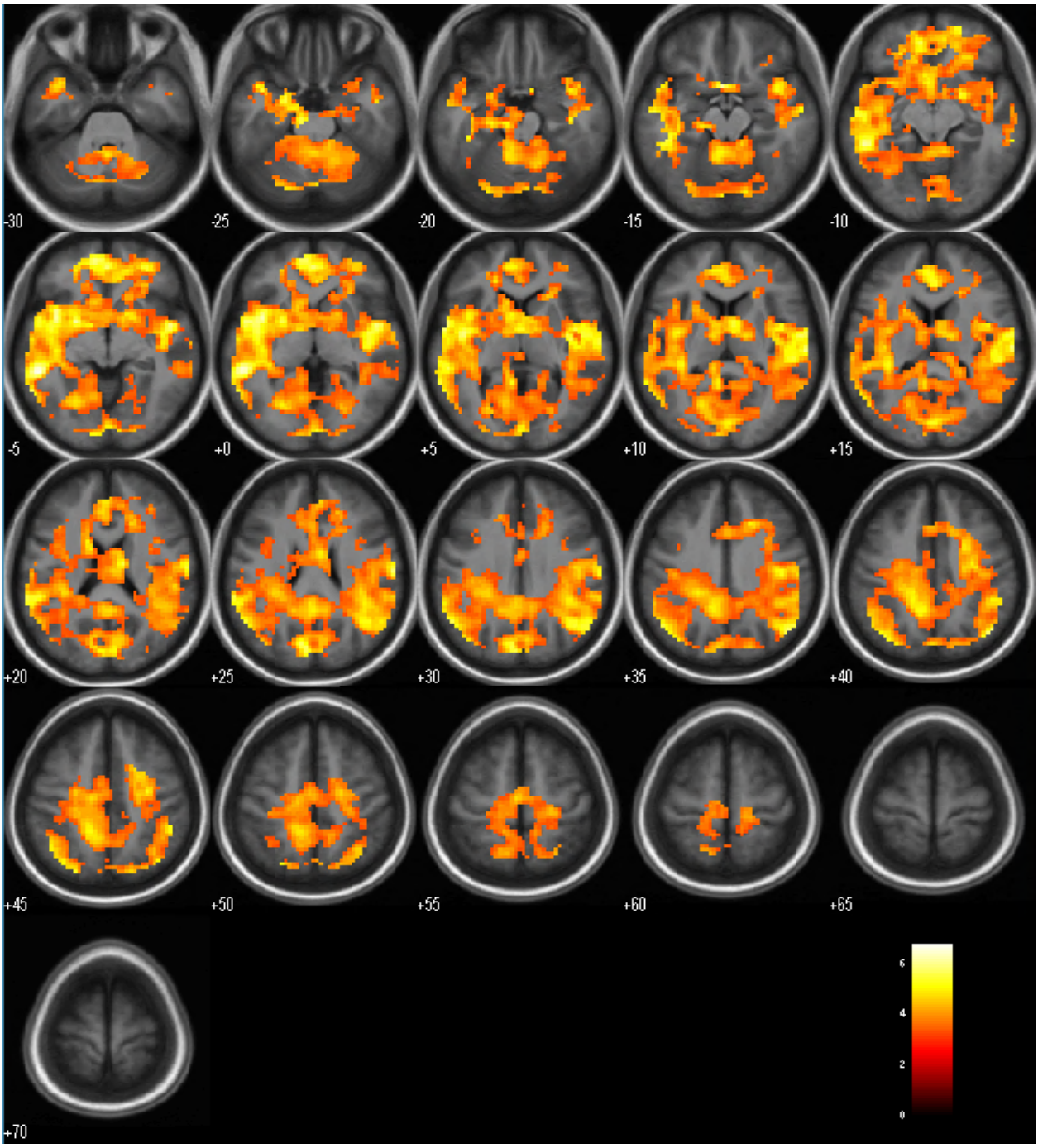


Figure 22. Main effect of facial stimuli at time point 2 in participants with obesity after weight loss, $p<0.05$, $k>120$ voxels.

Table 10. Main effects of all faces in participants at time point 1 and time point 2, $p<0.05$, uncorrected, $k>120$ voxels.

A. Main effect of all faces in participants with obesity at time point 1					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
R. Parahippocampal Gyrus	20051	5.93	21	2	-25
L. Parahippocampal Gyrus		5.4	-18	-10	-28
B. Main effect of all faces in participants with obesity at time point 2					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
L. Temporal Lobe	16678	5.98	-51	-40	-7
R. Angular Gyrus		5.65	45	-67	38

Table 11. There are no effects of either affective > neutral faces or neutral > affective faces at time point 1 (before weight loss) or time point 2 (after weight loss) in participants with obesity, $p<0.05$ uncorrected, $k>120$ voxels.

A. T1 only, obese, affective > neutral faces
No suprathreshold clusters
B. T1 only, obese, neutral > affective faces
No suprathreshold clusters
C. T2 only, obese, affective > neutral faces
No suprathreshold clusters
D. T2 only, obese, neutral > affective faces
No suprathreshold clusters

Table 12. There are no effects of either affective > neutral faces or neutral > affective faces at either time point 2 > time point 1, or time point 1 > time point 2 in participants with obesity, $p<0.05$ uncorrected, $k>120$ voxels.

A. Obese T2>T1, affective > neutral faces
No suprathreshold clusters
B. Obese T2>T1, neutral > affective faces
No suprathreshold clusters
C. Obese T1>T2, affective > neutral faces
No suprathreshold clusters
D. Obese T1>T2, neutral > affective faces
No suprathreshold clusters

To address our second hypothesis, that affective processing regions would show greater functional connectivity when viewing affective faces, we performed a PPI analysis. Our a priori regions of interest (amygdala, OFC, and pSTS) were not active in either of our a priori contrasts of interest, and therefore were not suited for PPI analysis. However, the left posterior insula did show activity in Aim 1, so we chose it as the region for interaction analyses. Thus, we examined the effect of insula x affective faces > neutral faces in participants with obesity before weight loss, and after weight loss. Before weight loss, individuals with obesity showed increased functional connectivity between the left insula and the right inferior frontal gyrus, the right parahippocampal gyrus, the right insula, and the left parahippocampal gyrus in the context of affect (Figure 23, Table 13A). After weight loss, participants with obesity showed increased functional connectivity with the left insula and the right precentral gyrus, right postcentral gyrus, and the left cerebellum in the context of affect (Figure 24, Table 13B).

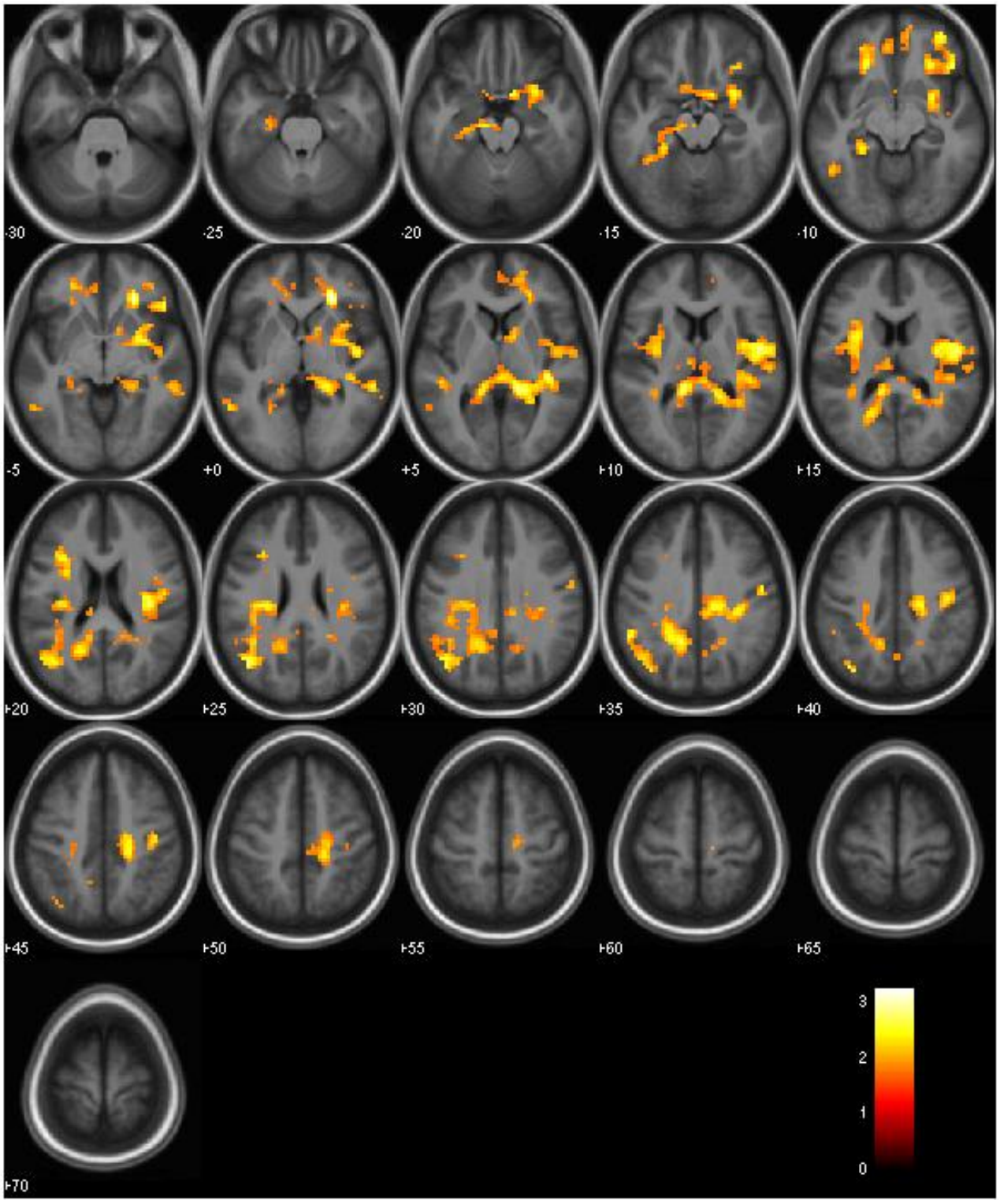


Figure 23. Insula functional connectivity in the context of affect in participants with obesity before weight loss, $p<0.05$, $k>120$ voxels.

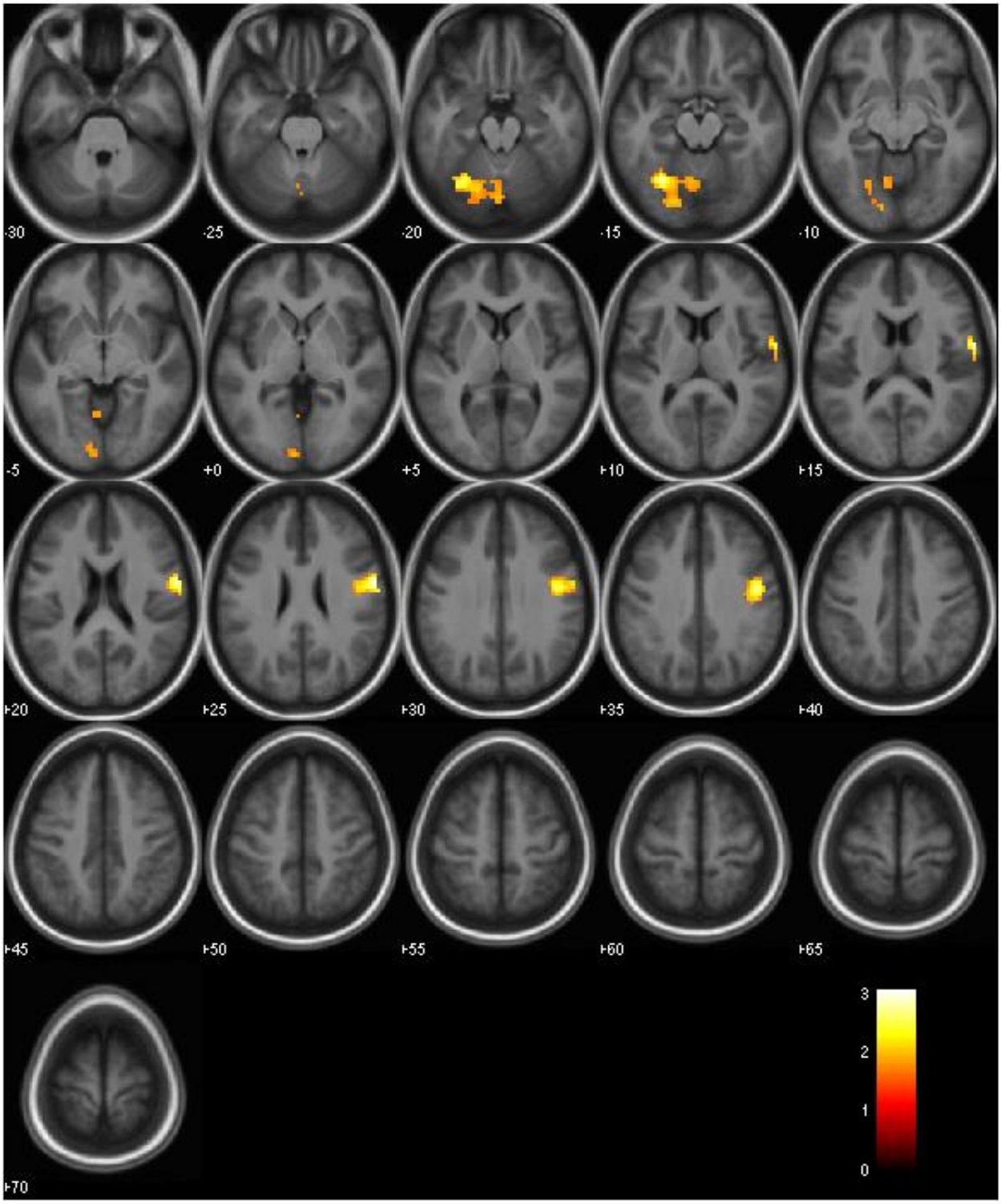


Figure 24. Insula functional connectivity in the context of affect in individuals with obesity after weight loss, $p<0.05$, $k>120$ voxels.

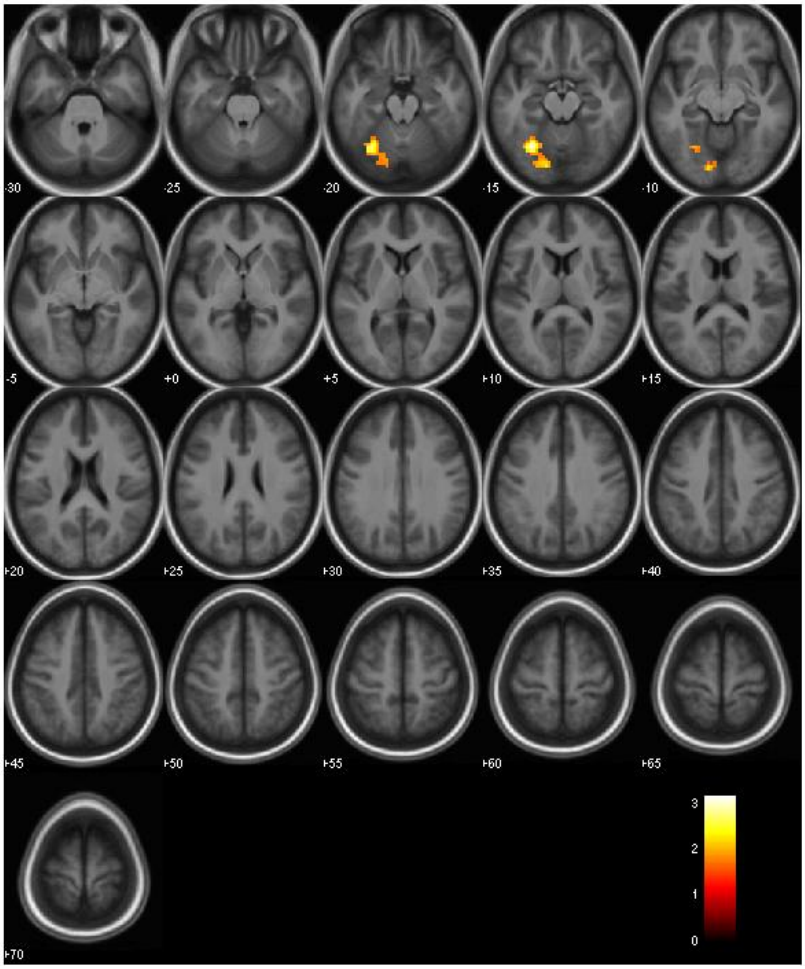
Table 13. Functional connectivity analyses in individuals with obesity before weight loss, after weight loss, and pre-post weight loss, $p<0.05$, uncorrected, $k>120$ voxels.

A. Obese T1, Insula x affective > neutral faces					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
R. Inferior Frontal Gyrus	418	2.99	24	35	-1
R. Parahippocampal Gyrus	2586	2.8	18	-40	2
R. Insula		2.75	36	-19	20
L. Parahippocampal Gyrus	187	2.58	-27	-37	-13
Middle Temporal Gyrus		2.16	-57	-52	-1
B. Obese T2, Insula x affective > neutral faces					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
R. Precentral Gyrus	191	2.87	57	-4	23
R. Postcentral Gyrus		2.7	60	-4	14
R. Precentral Gyrus		2.6	45	-10	35
L. Cerebellum: Declive	240	2.7	-30	-64	-16

In individuals with obesity before weight loss compared to after weight loss, the left insula was not functionally connected with any other region in the context of affect (Table 13C). In individuals with obesity after weight loss compared to before weight loss, the left insula was functionally connected to the left cerebellum in the context of affect (Figure 25, Table 14B).

To address our third hypothesis, whether the difference in the insular response to affective stimuli between time points is related to weight lost or BMI change, we performed a Pearson's correlation test on the number of pounds lost and the difference between peak activations in the left posterior insula (peak Z within the group level cluster at time point 2 - peak Z within the group level cluster at time point 1). There was no correlation between weight lost and change in left posterior insula activity, $r(7)=-0.02$, $p=0.9$ (Figure 26). Similarly, there was no correlation between BMI change and change in left posterior insula activity, $r(7)=-0.11$, $p=0.77$ (Figure 27).

A



B

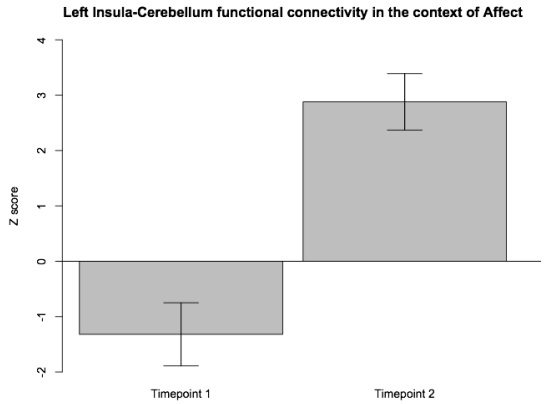


Figure 25. A. Insula functional connectivity in the context of affect in individuals with obesity after weight loss > before weight loss, $p<0.05$, $k>120$ voxels. B. Z score for peak voxel in each condition

Table 14. Insula functional connectivity in the context of affect in individuals with obesity after weight loss > before weight loss, $p<0.05$, $k>120$ voxels

A. Obese T1 > T2, Insula x affective > neutral faces					
No suprathreshold clusters					
B. Obese T2 > T1, Insula x affective > neutral faces					
Region	**Cluster size (voxels)**	**Peak Z**	**x**	**y**	**z**
L. Cerebellum: Declive	135	2.94	-30	-64	-16

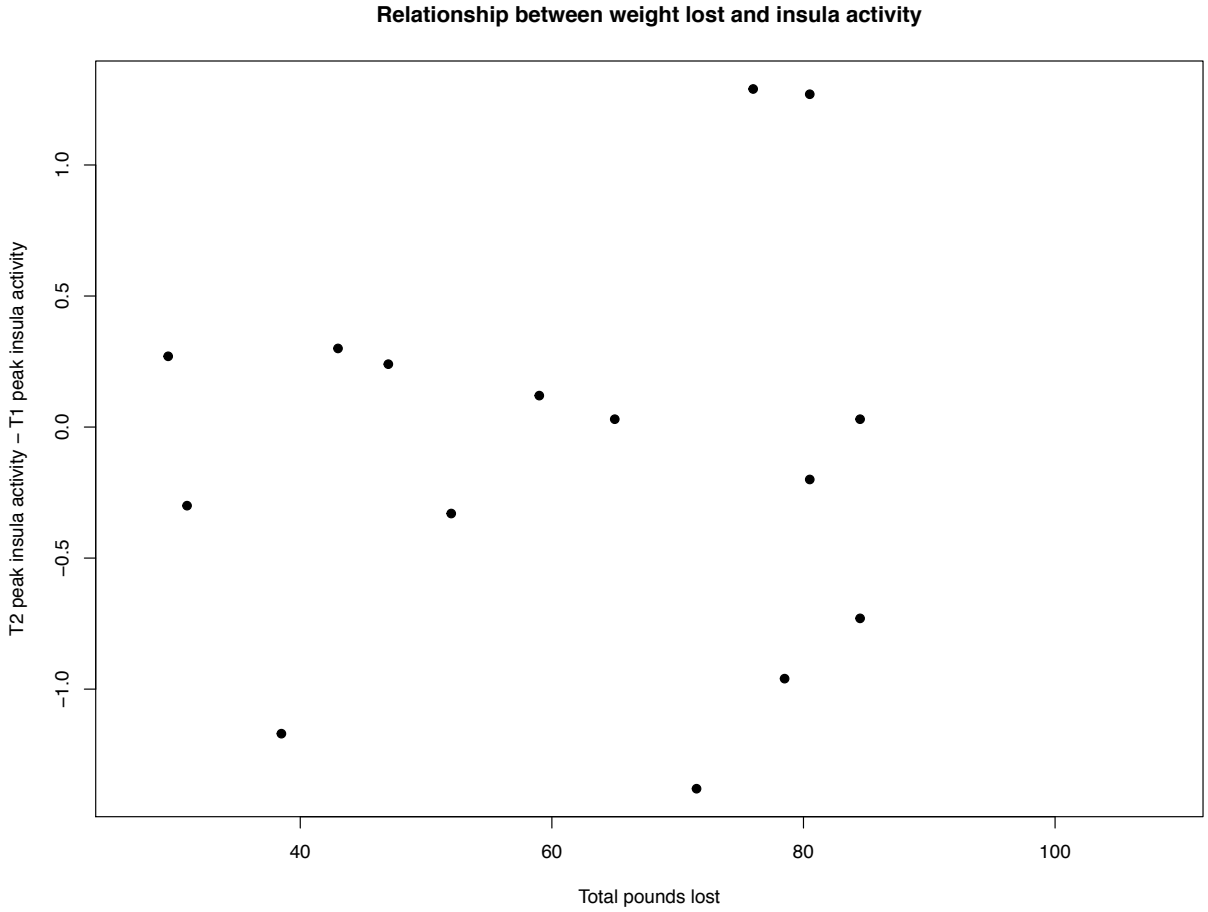


Figure 26. There is no relationship between total weight lost in participants with obesity and the difference between their left posterior insula activity (peak Z score T2 minus peak Z at T1).

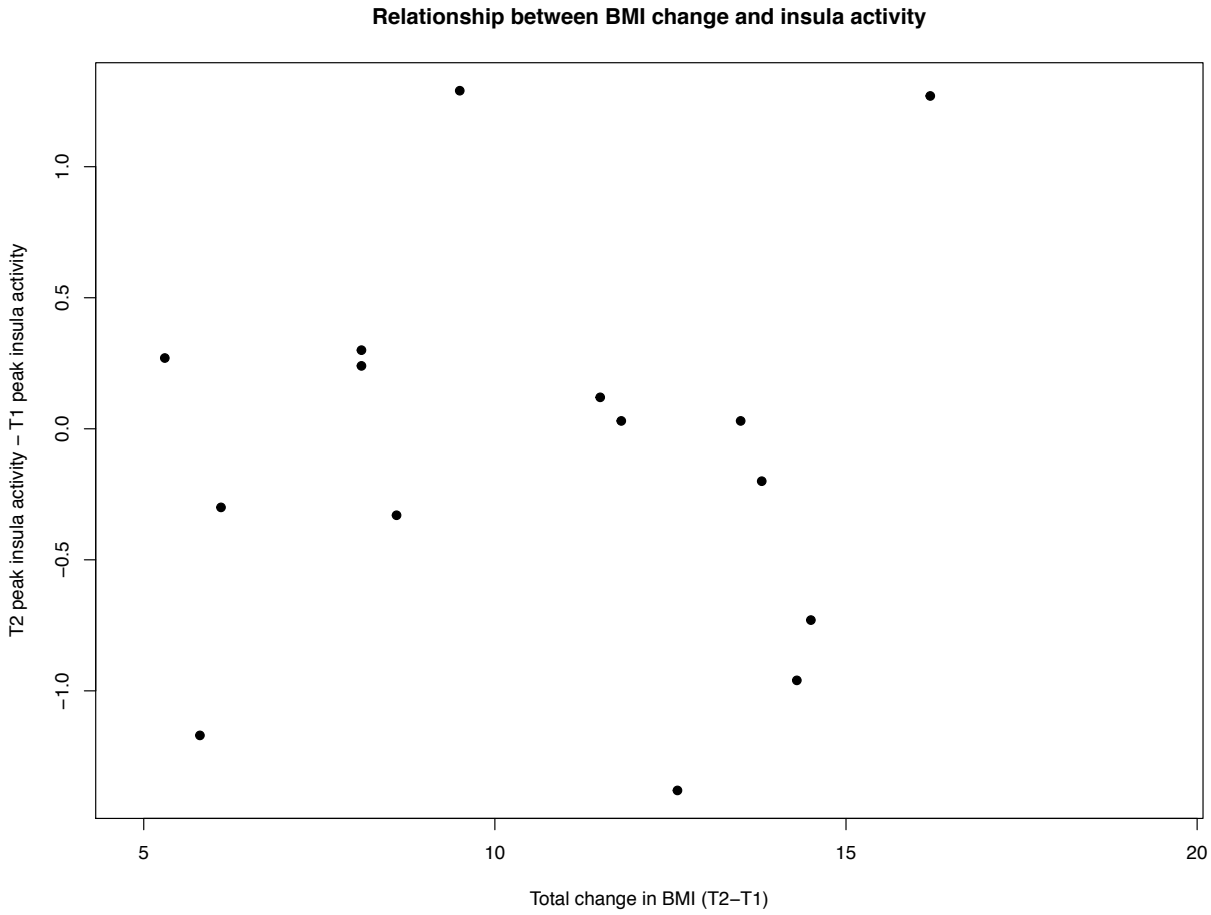


Figure 27. There is no relationship between BMI change in participants with obesity and the difference between their left posterior insula activity (peak Z score T2 minus peak Z at T1).

Post hoc manipulation check

To ensure that any differences in blood flow in our regions of interest were due to our effects of interest and not changes in vasculature associated with differences in weight, we performed a post-hoc analysis to ensure there were no differences in blood flow in regions that were not associated with salience, visual processing, or somatosensory processing. Thus, we performed a t test to determine potential differences between: (1) lean controls and participants with obesity, and (2) participants with obesity at time point 1 compared to time point 2 in the

right Broca's area (Figure 28). This revealed no difference in activity between lean participants and participants with obesity in the right Broca's area at time point 1, $t(31) = -0.62$, $df = 31.13$, $p = 0.54$, and no difference in activity between participants with obesity in the right Broca's area at time point 1 and time point 2, $t(40) = 0.13$, $p = 0.90$.

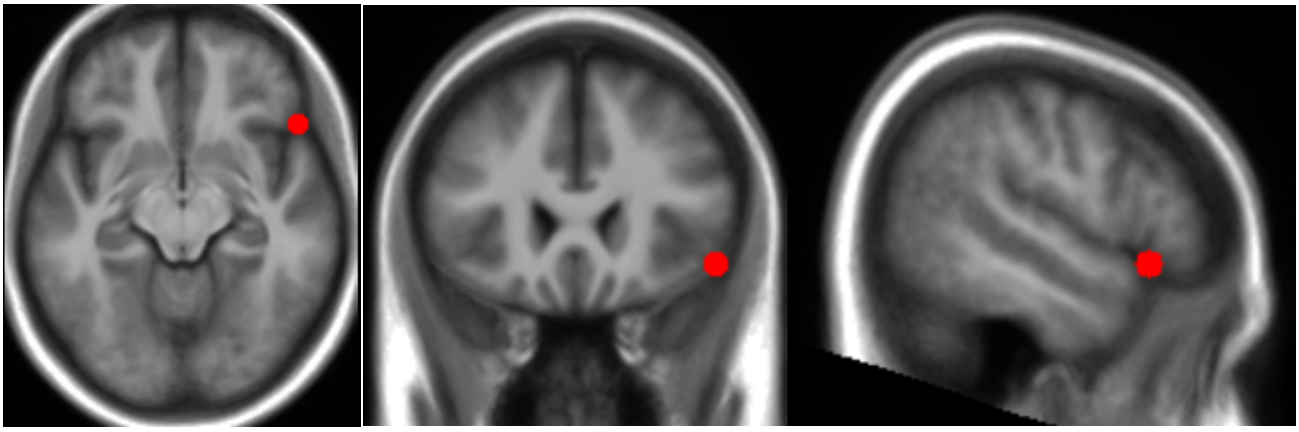


Figure 28. The seed for the post-hoc manipulation check in right Broca's area, 5 mm radius, [52 22 -10].

CHAPTER 4

DISCUSSION AND CONCLUSIONS

4.1 General discussion

In this study, we examined whether participants with obesity differed from lean controls in their neural response to affective stimuli, and whether this alteration changes after weight loss. Contrary to our hypotheses, our a priori regions of interest were not activated at the group level for either aim. However, results addressing Aim 1 show greater bilateral posterior insula activity in lean participants compared to participants with obesity, particularly when viewing neutral faces. Individuals with obesity showed greater global activity in all conditions compared to lean controls, suggesting greater within-network activation when viewing stimuli. Finally, there was no difference in neural response to affective stimuli after weight loss compared to before weight loss, however, participants with obesity showed greater insula-cerebellum functional connectivity when viewing affective stimuli after weight loss compared to before weight loss.

Surprisingly, we did not see increased neural activity in either group when viewing affective faces compared to controls. Instead, lean controls demonstrated greater activity in the bilateral insula as well as the left inferior parietal lobule when viewing neutral faces compared to affective faces, while participants with obesity demonstrated no activation for either condition over the other. The insula is known as a region of interoception, or awareness of one's internal state. Interoception encompasses sensations such as hunger and satiety, as well as internal responses to both positive and negative affective stimuli (Menon & Uddin, 2010). The posterior insula is also implicated in exteroception, or awareness of external stimuli. Sensory and exteroceptive information are integrated in the posterior insula, which is functionally connected

with the supplementary motor area, as well as the somatosensory cortex (Chang, Yarkoni, Khaw, & Sanfey, 2013; Craig, 2003). While the external sensory information processed by the posterior insula is primarily physical, such as pain and temperature, other work has shown the posterior insula to be involved in cognitive functions.

Previous work has implicated the bilateral insula in the integration of attention and processing salient stimuli (L. Pessoa, McKenna, Gutierrez, & Ungerleider, 2002). Additionally, the posterior insula, in conjunction with the inferior parietal lobule, is involved in uncertainty, such as during a gambling task (Critchley, Mathias, & Dolan, 2001; Singer et al., 2004; Xue, Lu, Levin, & Bechara, 2010). Thus, their activation in our results may be due to the role of uncertainty when viewing neutral faces, perhaps in an effort to decipher expression. Previous work has showed that affective faces hold attention more easily than neutral faces (Fenske & Raymond, 2006). In our task, participants were asked to attend to the images of butterflies. Thus, greater activation in the bilateral insula could indicate greater attention efforts toward neutral faces because of uncertainty in facial expression, compared to the more overt expressions of affective faces.

Our results also showed that participants with obesity demonstrated greater activity than lean controls in the dorsolateral prefrontal cortex (dlPFC) when viewing neutral faces compared to affective faces. The dlPFC is involved in allocation of attention, and greater activity in this region has been associated with greater attention bias (Clarke, Browning, Hammond, Notebaert, & MacLeod, 2014). Thus, greater dlPFC activation in participants with obesity could indicate greater attention to faces overall, but particularly neutral faces, which could be associated with an effort to decipher facial expression.

Functional connectivity analyses showed that in participants with obesity compared to lean controls, the left insula demonstrated greater functionally connected with itself, as well as the right lingual gyrus. For both regions, the difference is driven by deactivation in lean participants, with only a moderate activation in participants with obesity. This activation also spans the posterior cingulate cortex and right amygdala, which are implicated in exteroceptive affective processing (DeWitt, Ketcherside, McQueeny, Dunlop, & Filbey, 2015).

Previous studies of social and affective processing have identified similar increases in insula functional connectivity with salience networks, particularly in autism spectrum disorder (ASD). Individuals with ASD show greater within-network connectivity in salience networks including the insula compared to stronger cross-network connectivity in control participants (Odriozola et al., 2016; Uddin et al., 2013). In our study, this may indicate that the increased within-network connectivity in participants with obesity is associated with impaired affective processing. The coactivation of visual and external processing regions, such as the posterior cingulate cortex, may also implicate the perception of external salient stimuli in this affective network (DeWitt et al., 2015).

Aim 2 results showed that there is no difference in processing affective and neutral faces in individuals with obesity before and after weight loss. This is further supported by the lack of correlation between weight and peak insula activity at baseline, or changes in peak insula activity after weight loss. Results from Aim 2, contrasted with Aim 1, suggest that any differences in affective processing with BMI may not be re-established after weight is lost. The lack of insula after weight loss indicates that increased awareness of external stimuli like food, required for weight loss, may not transfer to evaluation of socially relevant stimuli. This may indicate that the

integration of perceptive and affective processing after weight loss is complex and may involve different networks.

PPI results showed greater functional connectivity between the left insula and left cerebellum during the affective conditions in participants with obesity after weight loss compared to before weight loss, which is driven by the deactivation of the cerebellum at time point 1. The cerebellum is known primarily for its role in coordination and motor control, which extends into sensorimotor interaction with the environment (Koziol, Budding, & Chidekel, 2012). The cerebellum has also been implicated in cognitive functions, particularly involving visual processing (Stoodley, 2012). Previous work has also shown increased cerebellum connectivity with the inferior parietal lobule in the context of uncertainty regarding visual stimuli (Blackwood et al., 2004). Thus, in conjunction with our findings from Aim 1 showing activation in the insula and inferior parietal lobule, the increase in insula-cerebellum connectivity in the condition of affect after weight loss may indicate greater integration of visual processing and uncertainty regarding affective faces.

Finally, contrary to our hypothesis, there was no correlation between change in weight or BMI and the difference in left insula activity before and after weight lost. Given that participants with obesity did not demonstrate an increase in insula activity after weight loss, this is not surprising. However, it may indicate that, after weight loss, participants with obesity do not demonstrate the same increase in uncertainty when viewing neutral faces as lean controls.

4.2 Limitations

The most notable limitation of our study is the lack of robust neural response to facial and emotional facial stimuli, such that no neural activity passed our cluster threshold of 97 voxels, as

determined by 3dClustSim. This may be due to a sub-optimal task design: each participant passively viewed a total of 90 affective faces and 30 neutral faces, rendering the contrast imbalanced. A more interactive design (e.g. assessing intensity of emotion expressed) may elicit a more robust response.

All participants in this study were female, and the neural responses to affective stimuli in this group may differ in males. Because females have shown greater sensitivity than males to social cues such as facial emotion, particularly in the insula (Baron-Cohen & Wheelwright, 2004), a different task design may be more suitable to test affective processing in men with obesity. Additionally, the final sample size of eight controls and 23 participants with obesity in this study is relatively small and should be replicated in a larger group.

This study also contained no psychological measures of affective processing other than the QIDS. Further psychometric testing may help elucidate the neural differences in lean participants compared to participants with obesity, as well as mechanisms of change in neural processing of affect after weight loss (Brewer et al., 2015). It is possible that disrupted affective processing in those with obesity is mitigated by satiety. To determine this, future studies should include a fasted state with a fed state to determine the effects of satiety of affective processing that may be related to feeding behavior in this population. However, the Faces Task was initially included in this study during a fed state, and difficulties in data collection arose as participants were more likely to fall asleep after the meal.

Because this task involves the viewing of affective faces, it elicits neural activity related to emotion, but also social processing. While these two systems are likely highly intertwined, future work should determine how our results might differ with other task designs that could

differentiate social processing and affective processing (Norris, Chen, Zhu, Small, & Cacioppo, 2004).

Finally, there is evidence showing the re-gaining of weight 5–10 years after bariatric surgery (Christou, Look, & MacLean, 2006). Future work should examine affective processing in these individuals to determine if this re-gaining of weight is coupled with blunted affective processing and interoception.

4.3 Conclusions and future directions

In this study, we examined whether altered affective processing is associated with obesity, and whether this alteration is specific to changes in body weight. Our results show that participants with obesity demonstrate less bilateral insula activity but more dorsolateral prefrontal cortex activity when viewing neutral faces compared to to lean controls. This could indicate that participants with obesity show less uncertainty, but more effort to maintain attention when attempting to distinguish facial expression. We identified few changes in response to affective or neutral faces after weight loss, but we did find an increase in insula-cerebellum functional connectivity. These findings have important implications for the treatment of individuals with obesity, as they highlight differences in brain regions involved in exteroception and valuation of salient stimuli. Weight loss treatments require a behavioral management component, and knowledge about affective processing and therefore potentially approach/avoidance behavior could help guide treatment efforts. Future studies should examine measures of affective processing in a larger and more heterogeneous sample, with more extensive psychometric testing, to determine if these results can be replicated. Additionally,

long-term follow up of participants after weight loss could determine if these effects are sustained.

APPENDIX

FUNCTIONAL CONNECTIVITY ANALYSES IN THE CONTEXT OF NEUTRAL FACES COMPARED TO AFFECTIVE FACES

Because the left insula showed greater activity for lean controls in the Neutral> Affective condition, we performed a supplementary PPI analysis to determine insula functional connectivity for neutral > affective faces. In lean controls, the left insula showed greater functional connectivity with the right globus pallidus and right transverse temporal gyrus (Figure A1, Table A1.A). In participants with obesity, the insula showed no functional connectivity for neutral > affective faces (Table A1.B).

We then compared these groups to each other. Lean controls showed greater left insula functional connectivity in the context of neutral faces >affective faces compared to participants with obesity in the right subcallosal gyrus, right lateral globus pallidus right hypothalamus, and right transverse temporal gyrus (Figure A2, Table A2.A). In participants with obesity compared to lean controls, there was no greater insula functional connectivity in the context of neutral faces > affective faces (Table A2.B).

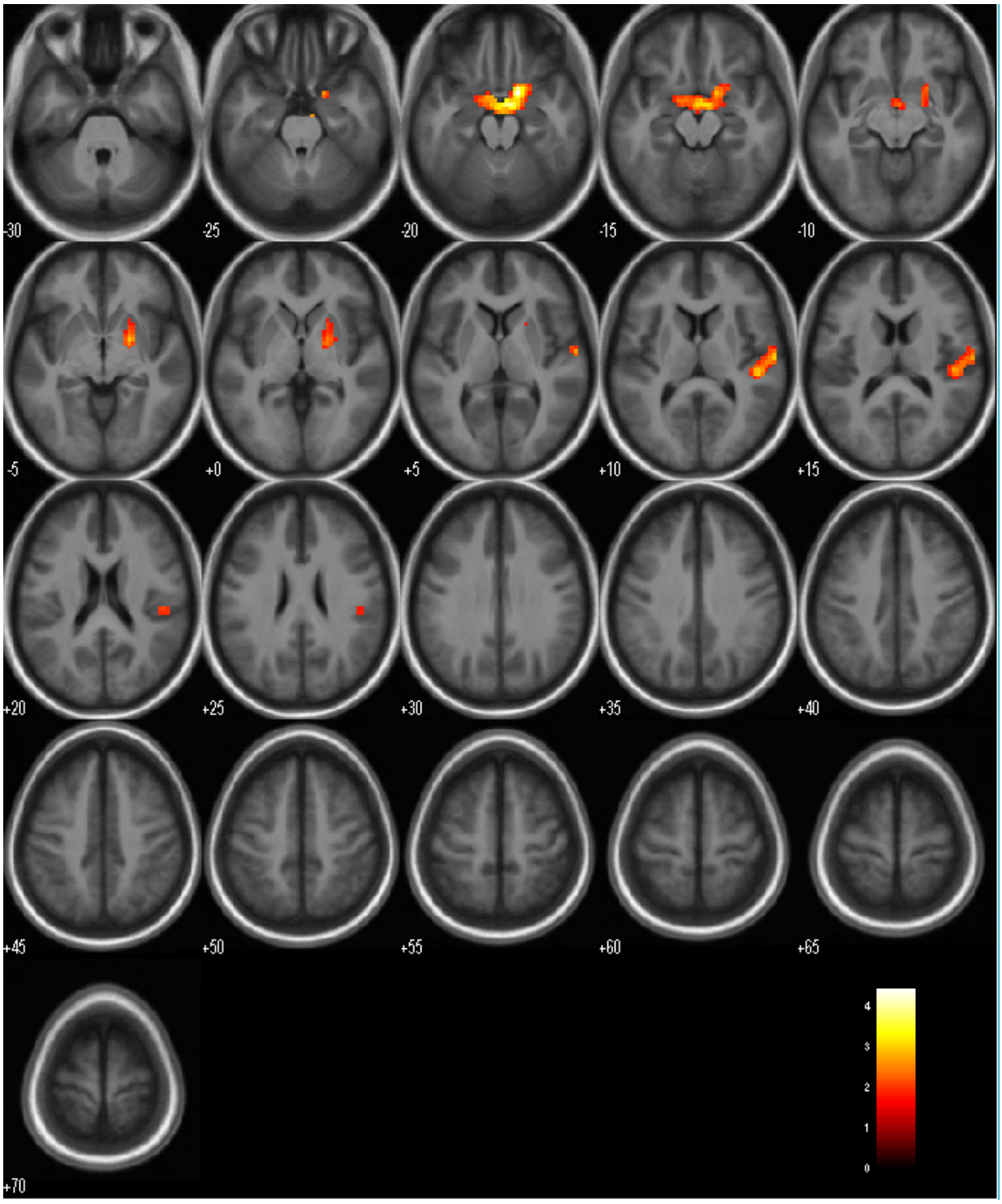
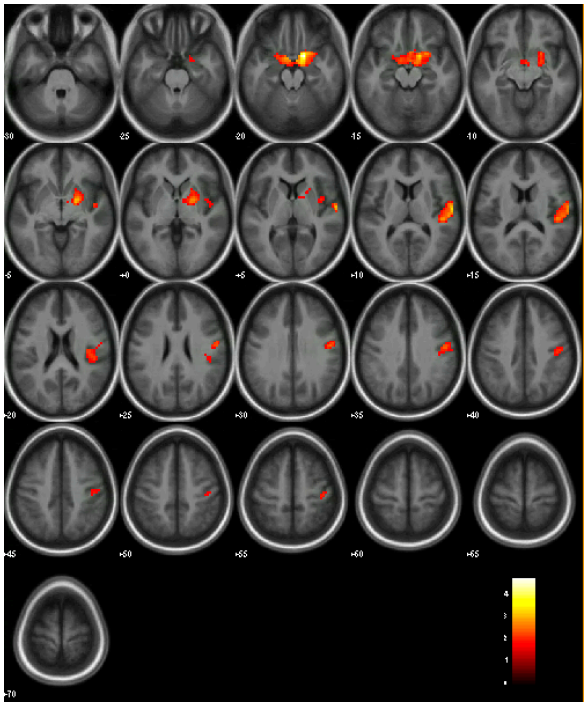


Figure A1. Lean Only, Insula x neutral > affective faces, p<0.05, k>100 voxels.

Table A1. PPI analyses in each group individually, p<0.05, k>120 voxels.

A. Lean only, Insula x neutral > affective					
Region	**Cluster Size (Voxels)**	**Z score**	**x**	**y**	**z**
R. Subcallosal Gyrus	273	3.76	15	5	-19
R. Lateral Globus Pallidus		2.68	21	-1	-4
R. Transverse Temporal Gyrus	118	2.72	60	-16	11
R. Transverse Temporal Gyrus		2.68	48	-28	11
B. Obese only, Insula x neutral > affective					
No suprathreshold clusters.					

A.



B.

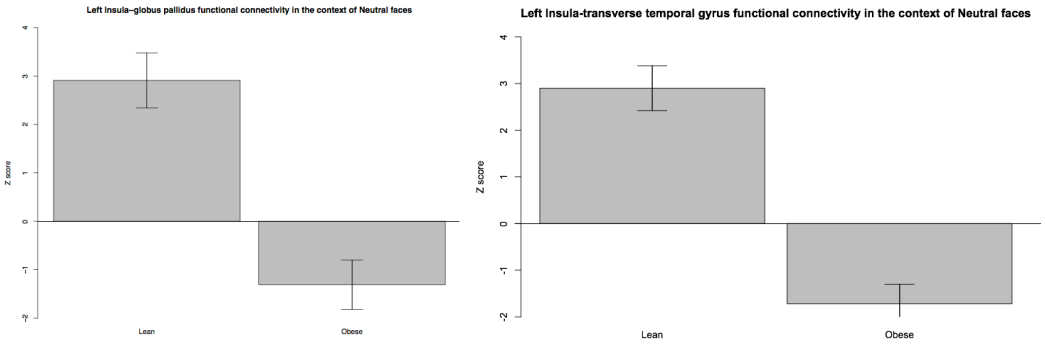


Figure A2. A. Lean > obese, insula x neutral > affective faces, p<0.05, k>100 voxels. B. Z score for peak voxels in each condition.

Table A2. Functional connectivity analyses in lean individuals and participants with obesity, $p<0.05$, $k>100$.

A. Lean> obese, Insula x neutral > affective faces					
Region	**Cluster size**	**Z score**	**x**	**y**	**z**
R. Subcallosal Gyrus	421	3.99	15	5	-19
R. Lateral Globus Pallidus		2.82	21	-1	-4
R. Hypothalamus		2.74	6	-1	-19
R. Transverse Temporal Gyrus	364	3.01	60	-13	11
R. Transverse Temporal Gyrus		2.58	45	-28	11
R. Transverse Temporal Gyrus		2.56	54	-22	11
B. Obese > lean, Insula x neutral > affective faces					
No suprathreshold clusters.					

Because participants with obesity showed greater dorsolateral prefrontal cortex (dlPFC) activity compared to lean controls when viewing Neutral>Affective faces, we examined dlPFC functional connectivity in participants with obesity before and after weight loss. At time point 1, participants with obesity showed greater dlPFC functional connectivity with the the right middle frontal gyrus, right superior frontal gyrus, and right medial frontal gyrus, in the context of Neutral>Affective faces (Figure A3, Table A3.A). At time point 2, participants with obesity showed no dlPFC functional connectivity in the context of neutral>affective faces (Table A3.B).

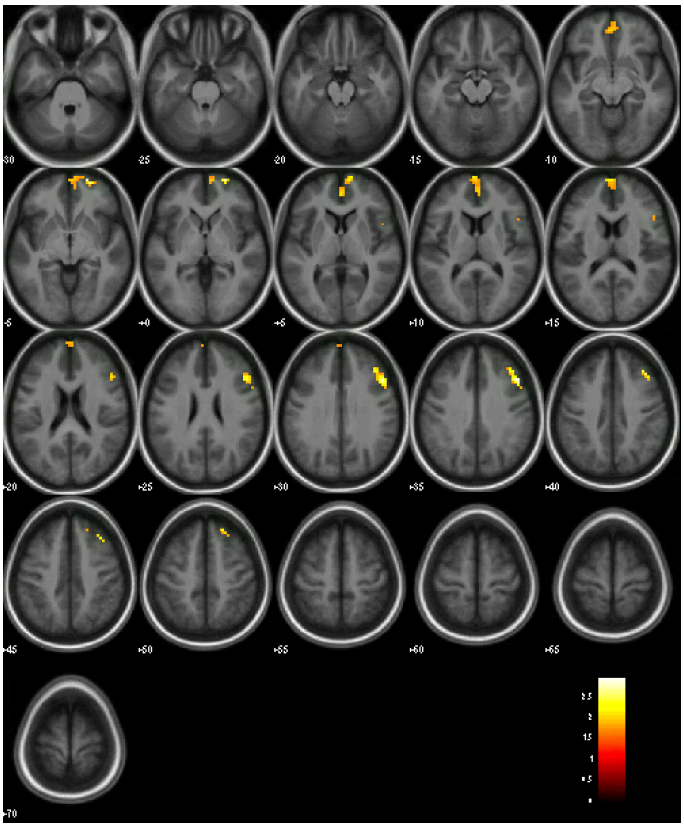


Figure A3. Obese T1 Only, dlPFC x neutral > affective faces.

Table A3. dlPFC functional connectivity in participants with obesity before and after weight loss, $p<0.05$, $k>100$ voxels.

A. T1 only, dlPFC x neutral > affective faces					
Region	**Cluster size (voxels)**	**Z score**	**x**	**y**	**z**
R. Middle Frontal Gyrus	121	2.72	48	20	32
R. Middle Frontal Gyrus		2.35	36	29	41
R. Middle Frontal Gyrus		2.30	39	32	32
R. Superior Frontal Gyrus	152	2.62	21	62	-4
R. Medial Frontal Gyrus		2.11	12	65	5
B. T2 only, dlPFC x neutral > affective faces					
No suprathreshold clusters					

We then compared dlPFC functional connectivity in participants with obesity before and after weight loss. When comparing before weight loss > after weight loss, the dlPFC was functionally connected to the bilateral cerebellum, the left cuneus, and the left precuneus (Figure A4, Table A4.A). When comparing after weight loss > before weight loss, the dlPFC showed no functional connectivity at our cluster threshold ($p<0.05$, $k>100$ voxels) (Table A4B).

A. B.

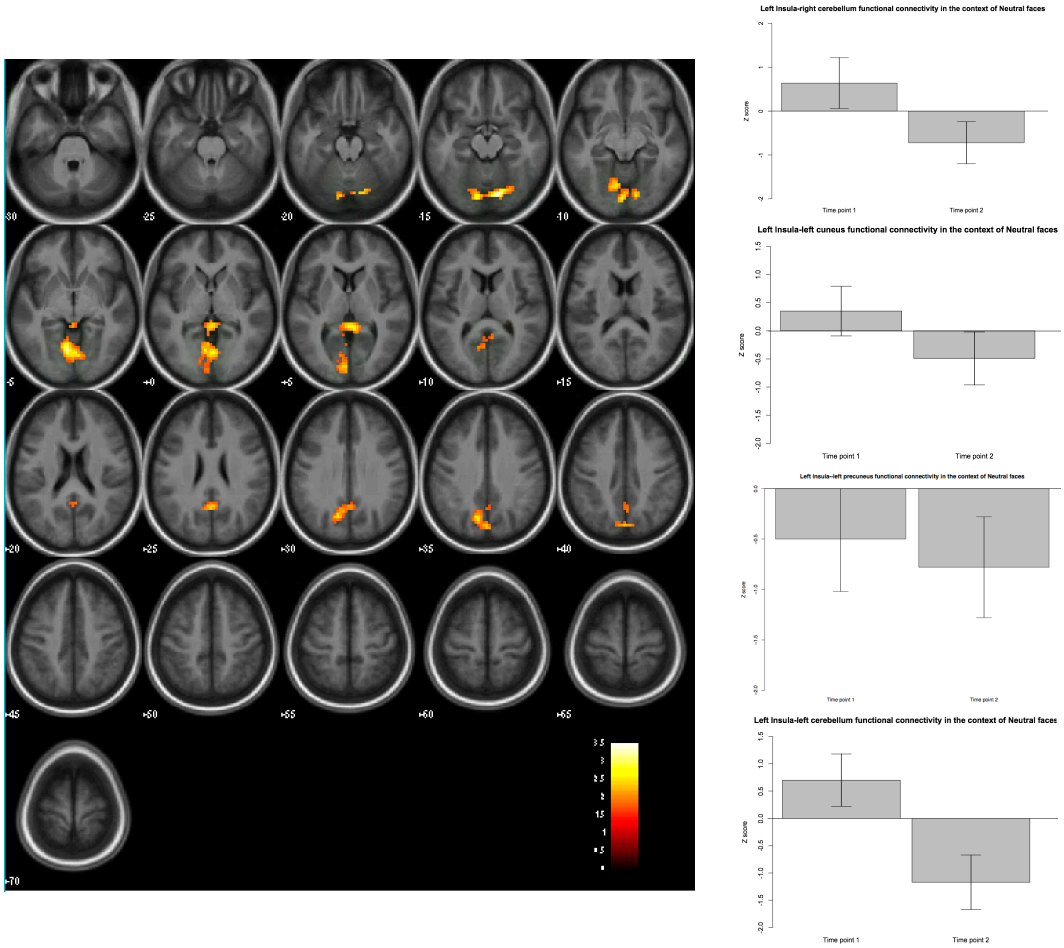


Figure A4. A. dlPFC functional connectivity in participants with obesity before weight loss (T1) > after weight loss (T2) when viewing neutral > affective faces, $p<0.01$, $k>100$ voxels. B. Z score for peak voxels in each condition.

Table A4. Dorsolateral prefrontal cortex functional connectivity in participant with obesity before and after weight loss, $p<0.05$, $k>100$ voxels.

A. T1>T2, dlPFC x neutral > affective faces					
Region	**Cluster size (voxels)**	**Z score**	**x**	**y**	**z**
R. Cerebellum: Declive	495	3.15	12	-79	-16
L. Cerebellum: Culmen		2.97	-6	-67	-4
L. Cerebellum: Declive		2.53	-9	-79	-16
L. Cuneus	156	2.73	0	-76	38
L. Precuneus		2.64	-12	-67	32
B. T2>T1, dlPFC x neutral > affective faces					
No suprathreshold clusters					

Summary

Our primarily results indicate that lean controls demonstrate greater insula activity for neutral faces compared to affective faces, and do not demonstrate any insula functional connectivity in the context of affective faces. Participants with obesity do not demonstrate insula activity when viewing neutral faces, but do show insula functional connectivity in the context of affective faces. These supplementary results indicate that in lean controls, the insula is functionally connected with the globus pallidus and right transverse temporal gyrus, while in participants with obesity, the insula shows no functional connectivity at our cluster threshold. Similarly, when examined together, lean controls showed increased insula functional connectivity with globus pallidus, and transverse temporal gyrus. The difference between groups is driven primarily by greater activity in leans, but some deactivation in obese.

The globus pallidus is involved in the regulation of voluntary movement, and has been implicated in aberrant processing of facial emotion in social anxiety disorder (Binelli et al., 2014). The transverse temporal gyrus is primarily involved in processing auditory stimuli, however, lesion studies including transverse temporal gyrus damage haves shown that this region

is important for the integration of visual awareness and emotion processing (Tamietto et al., 2015). This is in line with our interpretation of increased uncertainty and integration of visual and affective processing in lean controls compared to participants with obesity when viewing neutral and more ambiguous faces.

Since obese showed increased dlPFC functional connectivity compared to leans, we examined if this functional connectivity changed after weight loss. While our primary analyses indicated no difference in global activation before and after weight loss, functional connectivity analyses showed increased insula functional connectivity with the cerebellum after weight loss, but not before, when viewing affective faces.

Supplementary analyses indicate that participants with obesity before, but not after weight loss, demonstrated greater functional connectivity between the dlPFC and frontal regions including the middle frontal gyrus, superior frontal gyrus, and medial frontal gyrus. These regions are part of the executive control network, involved in maintaining attention during cognitively demanding tasks (Seeley et al., 2007). This supports our original interpretation that individuals with obesity are employing greater attention and executive control when viewing less overt, unemotional faces. When comparing the two time points, interestingly, the dlPFC was functionally connected to the cerebellum, the cuneus, and the precuneus when viewing neutral faces before weight loss but not after. The precuneus and cuneus are particularly involved in processing visual stimuli, and determining the relevance of that stimuli to the self (DeWitt et al., 2015). In contrast with our primary results, this could indicate that the greater overall effort to interpret and process ambiguous visual stimuli before weight loss may be mitigated after weight loss.

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BIOGRAPHICAL SKETCH

Kristen Ariel Ketcherside grew up in San Antonio, Texas. After high school, she attended Austin College in Sherman, Texas, where she double majored in Biology and Religion. At Austin College, she spent a month studying medicine in India, was the co-chair of the student board for coordinating community service, and was awarded the Oscar C. Page Servant of the year award in 2010. After graduation, she spent one year working on animal models of addiction and mood disorders in the Psychiatry department at UT Southwestern, and another year working on a drug discovery project for Human African Trypanosomiasis in the Pharmacology department. In the fall of 2012, she entered the PhD program at The University of Texas at Dallas.

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Education

2017	**Doctor of Philosophy (Cognition and Neuroscience)** UT Dallas, Richardson, TX Supervisor: Francesca Filbey, PhD Dissertation title: Neural mechanisms of affective processing in obesity and associations with weight loss
2014	**Master of Science (Applied Cognition and Neuroscience)** UT Dallas, Richardson, TX Supervisor: Francesca Filbey, PhD
2010	**Bachelor of Arts (Biology)** Austin College, Sherman, TX

Professional Experience

2012–present	**Research Assistant** Behavior and Brain Sciences The University of Texas at Dallas, Dallas, TX
2012–present	**Teaching Assistant** Behavior and Brain Sciences The University of Texas at Dallas, Dallas, TX
2011–2012	**Research Assistant** Pharmacology Department The University of Texas Southwestern Medical Center, Dallas, TX
2010–2011	**Research Assistant** Psychiatry Department The University of Texas Southwestern Medical Center, Dallas, TX
2009–2010	**Research Assistant** Biology Department Austin College, Sherman, TX
2009	**Intern** Translational Genomics Research Institute Phoenix, AZ

Honors and Awards

2016	National Science Foundation Center for Science of Information, Multidisciplinary Collaboration Award (Purdue University)
2016	National Science Foundation Center for Science of Information, Travel Award for Multidisciplinary Data Workshop (Purdue University)
2015	Friends of BrainHealth Award Finalist (UT Dallas)
2013	fMRI Training Course Scholarship (University of Michigan)

2012–present	Graduate Studies Scholarship (UT Dallas)
2010	Oscar C. Page Servant of the Year Award (Austin College)
2006–2010	Academic Scholarship (Austin College)

Peer-reviewed Publications

1. **Ketcherside, A.**, McIntyre, C.K., Filbey, F.M. (2017). Cannabinoid Receptor 1 Gene by Cannabis Use Interaction on CB1 Receptor Density. Cannabis and Cannabinoid Research, 2:1. 202-209. https://doi.org/10.1089/can.2017.0007
2. Volkov, O.A., Cosner, C.C., Brockway, A.J., Zhong, S., **Ketcherside, A.,** Kramer, M., Booker, M., Richardson, T.R., Schock, S., Wring, S.A., Peel, M., Klinger, J.D., Bruce Posner[1], De Brabander, J., Phillips, M.A. (2017). Identification of *Trypanosoma brucei* AdoMetDC inhibitors using a high-throughput mass spectrometry based assay. ACS Infectious Diseases. 3:7, 512-526. DOI: 10.1021/acsinfecdis.7b00022
3. Feldstein-Ewing, S., Chung, T., Caouette, J.D**., Ketcherside, A.**, Hudson, K.A., Filbey, F.M. (2016). Orbitofrontal cortex connectivity as a mechanism of adolescent behavior change. NeuroImage. DOI: 10.1016/j.neuroimage.2016.12.076
4. **Ketcherside, A.**, Baine, J.L., Filbey, F.M. (2016). Sex effects of marijuana on brain structure and function. Current Addiction Reports, 3:2. DOI: 10.1007/s40429-016-0114-y
5. **Ketcherside, A.,** Filbey, F.M., Jeong-Slaughter, H., (2016). Personality profiles discriminate marijuana users from concomitant marijuana-tobacco users. Psychiatry Research, 238, 356–362. DOI: http://dx.doi.org/10.1016/j.psychres.2016.02.024
6. Filbey, F.M., Dunlop, J., **Ketcherside, A.,** Baine, J., Rhinehardt, T., Kuhn, B., Alvi, T., DeWitt, S., (2016). fMRI study of neural sensitization to hedonic stimuli in long-term, daily cannabis users. Human Brain Mapping, 37:3431–3443. DOI: 10.1002/hbm.23250
7. Filbey, F.M., McQueeny, T., Kadamangudi, S., Bice, C., **Ketcherside, A.,** (2015). Combined effects of marijuana and nicotine on memory performance and hippocampal volume. Behavioral Brain Research 293 (2015) 46–53. DOI: http://dx.doi.org/10.1016/j.bbr.2015.07.029
8. Dewitt, S.*, **Ketcherside, A.***, Dunlop, J., McQueeny, T., Filbey, F.M., (2015). The hyper-sentient addict: an exteroception model of addiction. American Journal of Drug and Alcohol Abuse, 41(5) 374-381. DOI: 10.3109/00952990.2015.1049701
   *co-first authors
9. **Ketcherside, A.**, Filbey, F.M., (2015). Mediating processes between stress and problematic marijuana use. Addictive Behaviors, Jun;45:113–8. DOI: 10.1016/j.addbeh.2015.01.015
10. **Ketcherside, A.**, Matthews, I., Filbey, F.M., (2013). The serotonin link between alcohol use and affective disorders. Journal of Addiction Prevention 1(2):3.
11. Kozikowski, A.P., Gunosewoyo, H., Guo, S., Gaisina, I.N., Walter, R.L., **Ketcherside, A.**, McClung, C.A., Mesecar, A.D. & Caldarone, B. (2011). Identification of a glycogen synthase kinase-3beta inhibitor that attenuates hyperactivity in CLOCK mutant mice. ChemMedChem, 6, 1593–1602. DOI: 10.1002/cmdc.201100188

Other Scholarly Writings

Ketcherside, A. and Filbey, F.M. (2015). Addictions neuroscience. In *Neuroimaging and Psychosocial Addiction Treatment: An Integrative Guide for Researchers and Clinicians*. Sarah Feldstein Ewing, Katie Witkiewitz, Francesca Filbey (eds.), Palgrave MacMillan, Basingstone, Hampshire, UK.

Invited Oral Presentations

1. "Connection and Unity Between Mind, Body, and Nature." Crow Collection of Asian Art Earth Day Panel, Fair Park, Dallas TX. Apr. 24, 2016.
2. "Stressed is Desserts spelled backward." UT Dallas Lunch and Learn Lecture Series, Jan. 20, 2016.
3. "Stress, Drugs, and Pizza Rolls: Aberrant reward processing and a proposed intervention." UT Dallas School of Behavior and Brain Sciences, Nov. 12, 2015.
4. **"**The Neuroscience of Nirvana: Mindfulness Training for Optimal Decision making." Center for BrainHealth, Feed the Mind lecture series, Dallas, TX. Nov. 13, 2014.
5. "Multivariate Analysis of Alcohol Use Disorder Symptoms and Personality Disorders in Cannabis Users." Texas Research Society on Alcoholism annual meeting, The University of Texas Health Science Center, San Antonio, TX, February 21, 2014.
6. "Drugs and the Teenage Brain." Highland Park High School, Dallas, TX. Sept. 18, 2013.
7. "Investigating the Mechanism of Lithium in Bipolar Disorder treatment GSK-3β." Austin College, Sherman, TX. May 2010.

Published Conference Abstracts

1. **Ketcherside, A.,** Filbey, F.M. Model-based differentiation of networks of reward and impulsivity in cannabis use disorders" CNS Annual meeting, San Francisco, CA, Mar. 25–28, 2017.
2. **Ketcherside, A.**, Filbey, F.M. A novel method for the isolation and quantification of human peripheral cannabinoid receptors. Winter Conference on Brain Research, Breckenridge, CO, Jan. 23–28, 2016.
3. **Ketcherside, A.**, Filbey, F.M. The point of a joint: a multivariate classification of marijuana use motives. College on Problems of Drug Dependence annual meeting, Phoenix, AZ, Jun. 13–18, 2015.
4. **Ketcherside, A.,** Filbey, F.M. Multivariate analyses of alcohol use disorder symptoms and personality traits in cannabis users. Texas Research Society on Alcoholism annual meeting, San Antonio, TX, Feb. 21, 2014.
5. **Ketcherside, A.,** Filbey, F.M. Mediating processes between stress and problematic marijuana use. Society for Neuroscience Annual Meeting, San Diego, CA, Nov. 9–13, 2013.

Mentorship/Supervision

- Undergraduate Directed Research Advisor: Ian Matthews (2013), Ward Rushton (2016)
- Graduate Directed Research Advisor: Andrew Nabasny (2014-2015), Angela Agee (2016–present)

Relevant Teaching Experience:

1. Psychology 2317: Statistics for Psychology, Teaching Assistant, The University of Texas at Dallas, Fall 2013 - 2016
2. Neuroscience 4v90: Electroencephalography Data Analysis, Teaching Assistant, The University of Texas at Dallas, Spring 2015, 2016
3. Neuroscience 4359: Cognitive Neuroscience, Teaching Assistant and Lecturer, The University of Texas at Dallas, Fall 2012
   Lectures:
   - The Central Nervous System, Sept. 5
   - Perceptual Functions, Oct. 15

- Language, Nov. 5
- Short-term Memory, Nov. 12

4. Chemistry 221: Organic Chemistry I, Teaching Assistant, Austin College, 2009
5. Chemistry 222: Organic Chemistry II, Teaching Assistant, Austin College, 2010

Affiliations

Cognitive Neuroscience Society – Member, 2013–present
Society for Neuroscience – Member, 2013–present