Neurobiological responses to images of food and psycho-behavioral correlates in obese binge eaters: a functional MRI study

Roni Aviram

Submitted in partial fulfillment to the requirements for the degree of

Doctor of Philosophy

under the Executive Committee

of the Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY

2015

ABSTRACT

Neurobiological responses to images of food and psycho-behavioral correlates in obese binge eaters: a functional MRI study

Roni Aviram

Obesity is on the rise, and its associated comorbidities and health care costs are tremendous. A contributing factor to chronic obesity is binge eating disorder (BED), which is prevalent in 2 to 3 percent of the morbidly obese population, but the distinction between obesity versus obesity with BED is still unclear. The present dissertation project investigated forty two adult men and women, thirteen obese + BED and twenty nine obese controls for multiple psycho-behavioral constructs (rigid dietary restraint, disinhibition, anxiety, and behavioral activation/behavioral inhibition). On a different day, following a 12-hour fast, the participants consumed a fixed liquid meal, and their brain function examined while images of high energy food (e.g. pizza and cakes), low energy food (e.g. cucumber and tomato) and control items (i.e. office supplies) presented to them on a screen. Using a whole brain analysis approach, functional brain activity in response to: 1/food versus nonfood, and 2/high energy food versus low energy food revealed eight brain areas significantly different between the groups: for 'food versus nonfood', activated were seven areas functionally involved in the integration of somatosensory experience with internal state, processing of sensations, cognitions, thoughts, and emotions, integration of sensory functions and memory, visual object recognition and motion, visual - somatosensory functions and associations, integration of emotional value with a sensory stimulus, mediation of motivation and expectancy for outcomes, and the integration of diverse sensory information and visuo-spatial cognition. . One area significantly differed between the groups in response to the comparison of 'high energy food versus low energy food'. This area is functionally involved in thought, cognition, movement, planning, and motor behaviors in response to emotions and drives Thus, in response to cues representing binge-

triggers, obese + BED showed greater visual attention, emotional, motivational and reward processing, as well as motor planning of future actions and heightened somatosensory experience, compared with the obese group. Scores on the 'disinhibition' scale were significantly higher in the obese + BED group compared with the obese. Correlation between 'disinhibition' scores and brain activation results in each group showed significant differences between the groups in two brain areas: right anterior cingulate gyrus-Brodmann area #32, and the left postcentral gyrus. Scores on the Behavioral Activation Scale (reward drive) were significantly lower in the obese + BED group, but the correlations between brain activation and scores on this scale did not differ between the groups. To sum the results altogether, the obese + BED may be marked by hyperactive visual-attentional-emotional- and cognitive processing of cues representing binge-triggers, with heightened somatosensory response. The psycho-behavioral construct of 'disinhibition' highly characterizes BED, and its neurobiological substrates may include the right anterior cingulate cortex-Brodmann area #32 and left postcentral gyrus. Reduced reward responsiveness in obese + BED may reflect weak 'liking' response to food, but this behavioral construct and its' relationship to BED are still inconclusive. Future studies may use the results of this dissertation project to further investigate frequent binge eating in the absence of compensatory behaviors in the obese population.

Table of Contents

II: LIST OF TABLES

III: LIST OF FIGURES

IV: LIST OF BOXES

ACKNOWLEDGMENT

Several individuals spent many hours and dollars in bringing this research project to completion. I would like to thank Dr. Allan Geliebter for not only making this research possible, but also having me on board and supporting my functional MRI education. Dr. Isobel Contento has led me through this journey with her continuous belief in my scientific drive and a consistent support in bringing this project to fruition, despite my unusual personal circumstances. Dr. Randi Wolf has consulted me through the analysis of the results of this research project. Dr. Nerys Astbury elegantly led me through brain imaging analysis, without which this project has not been adequately completed. Dr. Spiro Pantazatos patiently responded to inquiries and tutored me on brain imaging analysis. Ian Ang, M.A., supported my research and administrative inquiries from across the Atlantic Ocean, and numerous former and current members at Dr. Geliebter's lab conjointly assisted in planning, initiating, and completing this project. I thank my dearest husband and my family, who consistently supported me on this journey.

With the sincerest of gratitude,

I thank you all.

PREFACE

Palatable foods carry a motivational power. A Palatable food stimulus, such as the sight or smell of a freshly baked cookie, may evoke a sudden urge to eat, and a few bites of a tasty treat can light up the urge to eat more of it. In the United States' food-rich environment, palatable foods are all around us. They act as cues for our appetitive urges to work, getting us motivated to consume foods high in fat, sugar and salt the moment we encounter them. In times when food is scares, this can provide an evolutionary benefit, due to the consumption and storage of energy in the absence of homeostatic needs (Kelley & Berridge, 2002), but at times of plenty, cue-triggered urges may contribute, over the long-term, to overeating and obesity (Berridge, Ho, Richard, & DiFeliceantonio, 2010; Berthoud & Morrison, 2008; C. Davis & Carter, 2009). The prevalence of obesity continues to rise in the US and worldwide (Caballero, 2001; Ogden et al., 2006) with recent population data placing > 30% of Americans in the obese category. Obesity is associated with serious chronic conditions, such as heart disease, hypertension, diabetes, and the metabolic syndrome, (Kip et al., 2004) and it represents a significant burden on the nation's healthcare budget (Colditz, 1999).

Obesity is associated not only with physical health impairment but also with serious mental health conditions. Among the obese adults, 2-3.5% have Binge Eating Disorder (BED) (Uher & Rutter, 2012), which is the most common eating disorder in the United States (Hudson, Hiripi, Pope, & Kessler, 2007; Wilfley, Wilson, & Agras, 2003). BED is characterized by repeated episodes of uncontrollable overeating in the absence of compensatory behaviors, such as purging (American Psychiatric Association, 2000). During a binge, individuals with BED rapidly ingest an abnormally large meal size within two hours, usually in the evening (Harvey, Rosselli, Wilson, Debar, & Striegel-Moore, 2011), and they often restrict their food intake throughout the day. Since individuals with BED do not engage in compensatory behaviors, such as vomiting, as is often seen in Bulimia Nervosa, they gain weight and become morbidly obese. In fact, within the obesity sub-categories, ranging from a BMI of 30 ("obesity class I")

to 70 or more ("super-mega-morbid obesity") (Bochicchio, Guzzo, & Scalea, 2006), individuals with BED tend to have a higher BMI compared with those with no BED (Grucza, Przybeck, & Cloninger, 2007). Obese with BED (herein, obese + BED) are more resistant to weight loss (Pagoto et al., 2007), have higher dropout rates, and show greater recidivism (Yanovski, 1993) than other obese participants (herein “obese”). BED is a chronic condition (Wilfley & Cohen, 1997), it may be symptomatic for about 10 years (Pope et al., 2006; Spitzer et al., 1993), and it is similarly prevalent across racial/ethnic groups (Alegria et al., 2007; Nicdao, Hong, & Takeuchi, 2007; C. B. Taylor et al., 2006). Relative to other eating disorders, there is a greater likelihood of male cases (Spitzer et al., 1993), older age (Hudson et al., 2007; Striegel-Moore et al., 2003), and a later age of onset (American Psychiatric Association, 2000). The need to study BED, besides its strong link with obesity, stems from its association with overall life impairment, general psychopathology (Striegel-Moore, Wilfley, Pike, Dohm, & Fairburn, 2000; Telch & Agras, 1994), adverse medical consequences such as heart disease, high blood pressure, and type 2 diabetes (Bulik, Sullivan, & Kendler, 2002; Hasler et al., 2004; Yanovski, Nelson, Dubbert, & Spitzer, 1993), poor prognosis and resistance to treatment (Spitzer et al., 1993).

Despite some known differences, the distinction between obesity versus obesity + BED is not intuitive; they both involve overeating, they cause significant weight gain which is associated with serious co-morbidities, and they both seem hard to treat. However, some individuals proceed to developing BED, or sub-BED [partial fulfillment of the Diagnostic and Statistical Manual of mental disorders edition five (DSM-V) criteria for a diagnosis of BED] (Striegel-Moore et al., 2000), and some do not. Psychological and neurobehavioral distinction between obese and obese + BED has been extensively reviewed, but clear discriminative validity between the two conditions, and most importantly, the predictive power of BED, remain unanswered (Wonderlich, Gordon, Mitchell, Crosby, & Engel, 2009). Research suggests that obese + BED tend to consume more calories in laboratory studies of eating behavior (Galanti, Gluck, & Geliebter, 2007; Goldfein, Walsh, LaChaussee, Kissileff, & Devlin,

1993; Raymond, Bartholome, Lee, Peterson, & Raatz, 2007; Sysko, Devlin, Walsh, Zimmerli, & Kissileff, 2007; Telch & Agras, 1996; Yanovski et al., 1992), for which multiple factors, such as their high rates of negative affect/depression/anxiety and other types of psychopathology (Telch & Agras, 1994, 1996; Yanovski et al., 1993), a disturbance in satiety mechanism (Sysko et al., 2007), disinhibitive tendencies in response to food (Guss, Kissileff, Devlin, Zimmerli, & Walsh, 2002), or impulsive trait (Galanti et al., 2007), may be responsible. In ecological studies, where subjects are studied in their natural environment, obese + BED participants showed more psychological distress prior to a binge, compared with their obese counterparts (Greeno, Wing, & Shiffman, 2000).

The project described in this dissertation paper aimed to add to existing knowledge about the psycho-behavioral and neurobiological distinction between obesity versus obesity + BED. Forty-two obese adults, men and women, were selected and divided into two groups, based on their diagnosis of BED (per the DSM V criteria). Using validated questionnaires, both groups were assessed for psycho-behavioral characteristics implicated in BED, and following a pre-load meal, participants' brains were scanned using a functional MRI protocol, while images of different types of food, and control images, were shown on a screen. Participants' functional brain response to the different types of images was compared between the groups and correlated with significant psycho-behavioral differences between them. Results of this research project, and their interpretation follows, are highlighted in this paper in an attempt to add to current knowledge about psycho-biological markers of BED.

In BED there seems to be a psychological and possibly biological prototype of people who engage in binge-eating, characterized by their lack of capability to adequately regulate emotions, putting them at risk for experiencing anxiety and using palatable food to regulate it. Obese + BED score significantly higher on psychological constructs of Novelty Seeking, Harm Avoidance, and Mood Dysregulation (Grucza et al., 2007; Leombruni et al., 2014) and lower on character constructs such as Self-Directedness and Cooperativeness (Grucza et al., 2007).

These personality characteristics of obese + BED may explain their high rates of anxiety and depression, as well as their increased impulsive drive for new situations and stimuli (Leombruni et al., 2014). Also, compared with U.S. norms, obese + BED seem to be more reward-dependent (Leombruni et al., 2014), explaining why some researchers refer to BED as an addictive disorder (Berridge et al., 2010; Michaelides, Thanos, Volkow, & Wang, 2012). Thus, researchers have been attempting to subtype BED according to psychopathological constructs and personality characteristics, to which a slightly different treatment may be necessary (Leombruni et al., 2014). Treatment approaches to BED to date have concentrated on either weight loss (including a Very Low Calorie Diet (VLCD), exercise program, and bariatric surgery), in addition to psycho-behavioral approaches, i.e. treatment targeting eating disorder psychopathology including Cognitive-Behavior-Therapy (CBT), or Inter-Personal Therapy (IPT). Treatment specificity studies have been showing an overall efficacy of CBT and to a lesser extent also Inter-Personal-Therapy (ITP), in reducing binge-eating, but to what extent these psycho-behavioral treatments should be administered together with other weight loss approaches to resolve BED is still unclear (Wonderlich et al., 2009).

Evidence for a biological basis to BED stems from findings of heritability of 0.50 (Bulik, Sullivan, & Kendler, 2003) and an association with genetic mutation of the melanocortin-4 receptor (MC4R) (Branson et al., 2003) and the dopamine transporter gene (C. Davis et al., 2007). BED may also be differentiated from other types of eating disorders and obesity on the basis of differences in the functioning of various peptides and hormones, such as ghrelin (Geliebter, Gluck, & Hashim, 2005), cortisol (Coutinho, Moreira, Spagnol, & Appolinario, 2007; Gluck, Geliebter, Hung, & Yahav, 2004), and PYY (Geliebter, Hashim, & Gluck, 2008). For example, evidence indicates that obese + BED have lower ghrelin levels at baseline and less ghrelin decrease after a meal compared with their obese counterparts (Geliebter et al., 2005; Geliebter et al., 2008; Geliebter, Yahav, Gluck, & Hashim, 2004), wherease cortisol following an acute stress may increase up to a treshold, where is becomes blunted, in obese + BED but not in obese or normal-weight controls (Rosenberg et al., 2013). Despite these findings,

evidence is inconclusive and the underlying biological mechanism of BED still remains unclear. A better understanding of the characteristics of those two groups, obese versus obese + BED, is growing, but the question of why some individuals develop BED and others do not, remains unanswered.

CHAPTER ONE: Introduction

1.1 Background and rationale

In BED, decision making in the face of a binge-trigger may be impaired. When individuals with BED encounter a cue associated with a particular food reward, i.e. smell, sight or image of binge-type foods, which are usually high in fat, sugar and salt (Ng & Davis, 2013), they often face a moment when they have to make a decision if to go after their motivational urge to pursue that reward, despite their previous commitment to avoid it. Their motivational urge may escalate to compulsive levels of intensity, causing them to approach the food. Thus, this binge-type food momentarily dominates their decision making, causing relapse into bingeing again. This irrational goal pursuit (Berridge & Aldridge, 2008), to which multiple brain systems may contribute, seem to include a complex interaction of neuro-psycho-behavioral parameters ill affected in BED.

To recognize neuro-behavioral pathology involved in abnormal eating behavior, a clear understanding of how food is normally processed in the brain is necessary. Our motivation to consume food involves multiple channels, including gustatory, hedonic, and homeostatic, working together in harmony unless interrupted, to keep a steady energy balance and therefore, healthy body weight. Gut-brain communication is important throughout the eating process, starting with the somatosensory signals acquired through the sight and/or smell of food (i.e. food cues) at pre-meal. Once food is in our mouth and our taste perception recognizes it as safe and beneficial for consumption, the process of digestion begins. Signals from the gut to the brain, via hormones, the vagus nerve, and the sympathetic nervous system, are ongoing to inform the brain about energy homeostasis. It is also possible that the gut generates reward signals to the brain via sub-conscious messages (Craig, 2003; Sclafani, 2004), but this area of research is still in its infancy. Autonomic and endocrine signals from the periphery, sensory inputs (i.e. insular and olfactory cortex), and sensory motor and arousal

signals (brain stem), are integrated in several neuronal populations in the brain. In the hypothalamus, including the arcuate nucleus and the paraventricular nucleous, homeostatic signals are processed, and the output messages are delivered to multiple brain sites to adjust endocrine, autonomic, cognitive and motor responses (Berthoud & Morrison, 2008). The internal regulatory system described above is termed the "metabolic" system, and it is constantly working together with the "cognitive-hedonic system" described further below, involving signals coming from brain areas associated with reward, motivation, learning and memory (e.g. ventral tegmental area, nucleus accumbens, orbitofrontal cortex, & amygdala). Thus, in the control of food intake, there is a constant interaction between metabolic-homeostatic and cognitive-hedonic processes.

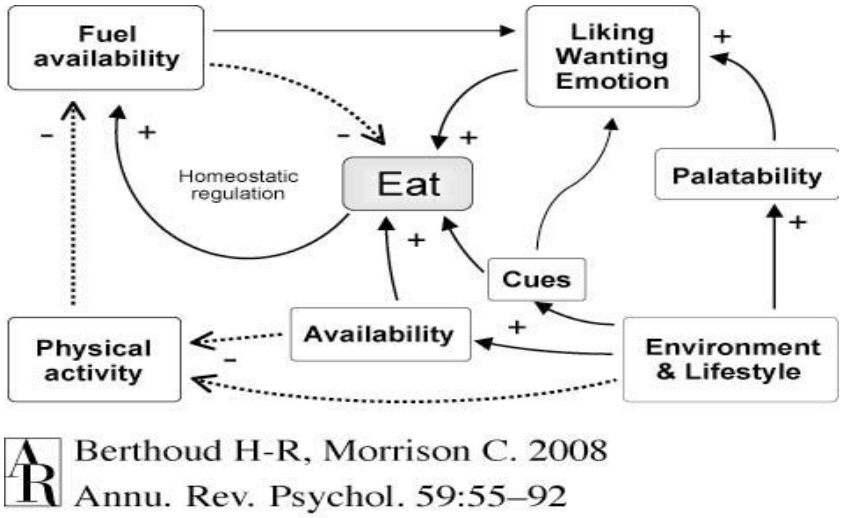


Figure 1: Interaction between "metabolic-homeostatic" signals and "cognitive-hedonic" signals (Berthoud & Morrison, 2008)

Depicted in Figure 1 above (Berthoud & Morrison, 2008) is the interaction between metabolic-homeostatic signals (herein, "Fuel availability" on the upper-most left side of the figure) and "cognitive-hedonic" signals (herein, "Environmental & Lifestyle" on the bottom right side of the figure).

Food cues operate via several channels to stimulate eating. Involved brain processes include learning and memory, visual, olfactory, auditory, and somatosensory areas, in conjunctions with homeostatic control of food intake from the brain and the periphery. A mental representation of our experience with food is acquired through all sensory modalities, and in our brain, food is represented through shape, color, taste, and flavor, as well as links to time, location, social context, and negative or positive consequences of ingestion of food and its reward value. Thus, in addition to brain areas involved in autonomic and homeostatic control of food ingestion and absorption, a number of other brain areas are involved in processing food stimuli, and they include the thalamus, orbitofrontal cortex and its functional connections (for auditory and visual stimuli), the pre-frontal cortex, anterior cingulate cortex, the striatum (including the nucleus accumbens and the ventral pallidum), the hippocampal formation, the insular cortex, and the amygdala. These areas are thought to store, update and retrieve information guiding appetitive behavior. Food cues, such as the smell of a freshly baked cookie, that have previously been linked to specific rewarding properties of these foods can serve as conditioned stimuli to recall their memorial representations. In normal conditions, all systems controlling food intake work in harmony to maximize health and control body weight.

1.1.A. Brain imaging and functional brain activation in eating behavior

Recent developments in technology permit viewing the live brain via neuro-imaging. Functional MRI (fMRI) uses blood oxygen-level dependent activity (BOLD) to reveal which brain areas are active during a given task. To learn about eating behavior, researchers have started using fMRI (Geliebter et al., 2006; De Silva, Salem, Matthews, & Dhillo, 2012; Kroemer et al., 2012; Porubska, Veit, Preissl, Fritsche, & Birbaumer, 2006) to observe activity of the brain while participants pay attention to food and nonfood stimuli.

It has been well recognized that the sight of food elicits a wide range of physiological, emotional and cognitive responses, including homeostatic system activation (e.g. insulin release) (Wallner-Liebmann et al., 2010), emotional desire to eat (Ouwehand & Papies, 2010), and cognitively mediated memory retrieval and hedonic evaluation of the food (Shin et al., 2009). This complex nature of eating behavior suggests that a number of brain areas are affected (see *Figure 2* below), including the pre-frontal cortex (Silva, Pizzagalli, Larson, Jackson, & Davidson, 2002; Simmons, Martin, & Barsalou, 2005), insular cortex (Schienle, Schafer, Hermann, & Vaitl, 2009; Simmons et al., 2005; Wang et al., 2004), anterior cingulate cortex (Menon & Uddin, 2010), nucleus accumbens and other structures in the striatum (Volkow, Fowler, & Wang, 2004), amygdala (Piech et al., 2009; Siep et al., 2009), thalamus (Piech et al., 2009), and the hypothalamus (Berthoud & Morrison, 2008). The anterior part of the insular cortex is the primary gustatory cortex (Augustine, 1996), and it is responsible for gustatory sensations, such as the experience of taste and flavor from food (Pritchard, Macaluso, & Eslinger, 1999). The anterior insular cortex and the anterior cingulate cortex are part of the 'salience network', processing cognitive, emotional, motivational, and sensory information related to food (Menon & Uddin, 2010). The anterior insular cortex borders the frontal operculum, which is known to be engaged during tasks requiring executive control, shifting attention, and working memory. Furthermore, the anterior insular cortex has significant functional connections to several other brain structures, including the orbitofrontal cortex, inferior frontal cortex, and anterior cingulate cortex (Deen, Pitskel, & Pelphrey, 2011; K. S. Taylor, Seminowicz, & Davis, 2009), all working together to evaluate sights and images of food (van der Laan, de Ridder, Viergever, & Smeets, 2011). In obese participants this system have shown reduced activity at rest (Kullmann et al., 2012) and heightened activity in response to food cues (Garcia-Garcia et al., 2013).

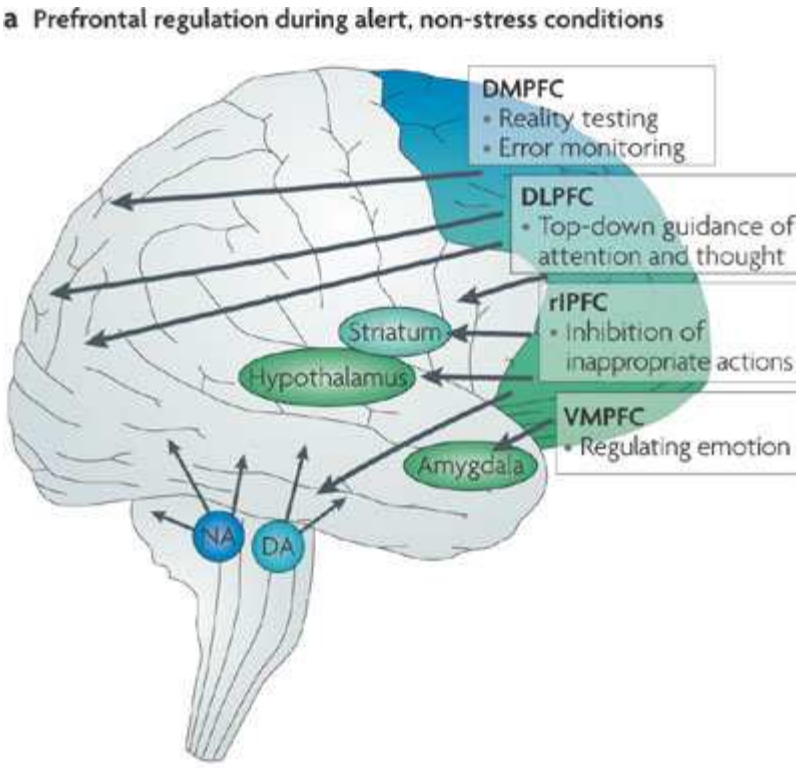


Figure 2: Pre-frontal cortex main connections in the brain for the regulation of behavior, thought and emotions (Arnsten, 2009)

A sub-division of the pre-frontal system, the medial pre-frontal cortex, is involved in feeding, complex goal-directed behavior, and control of mood and affect (Davidson, 2003). Via the 'salience network', food related cues activate mesolimbic-cortical reward pathways, as well as areas of the brain associated with learning and memory, analogously to drug addiction (Kelley, Schiltz, & Landry, 2005; DiLeone, Taylor, & Picciotto, 2012). Another frontal brain area, the orbitofrontal cortex is connected with subcortical structures responsible for generating emotional responses and habits (Arnsten, 2009). For example, the orbitofrontal cortex is extensively linked with the hypothalamus and is responsive to the reward value of taste, odor, and flavor, and to their learned associations with visual food cues (Rolls, 2001). Thus, the orbitofrontal cortex encodes a representation of the hedonic value of food stimuli (Porubska et al., 2006; Simmons et al., 2005), and it is involved in food cravings by down-stream mediation of hypothalamic homeostatic control of food intake (Ongur & Price, 2000). The hypothalamus,

especially the arcuate nucleus, integrates peripheral hormonal signals and receives inputs from the brainstem, which in turn receives signals from the vagus nerve related to ingestion (Obici & Rossetti, 2003). The orbitofrontal cortex also works closely with the amygdala via both down- and up-stream pathways, to carry out reward functions by interaction with mesolimbic-cortical pathways, including the striatum, anterior cingulate cortex, and dopaminergic pathways in the midbrain (Goldstein & Volkow, 2002). The amygdala, in turn, is hypothesized to provide a memory link to the incentive value of a food stimulus and it then projects this information to the orbitofrontal cortex to predict reward outcomes (Murray & Izquierdo, 2007). The ingestion of palatable foods activates dopaminergic neurons within the nucleus accumbens (Kelley, Schiltz, & Landry, 2005), an area which may be recruited by BED participants to help relieve the effects of stress or negative affect (Koob & Le Moal, 2008).

The dorsolateral prefrontal cortex is a key to regulating attention, thought, and action, and it is widely connected to sensory and motor brain regions. The inferior frontal cortex (inferior prefrontal cortex) is postulated to inhibit inappropriate motor responses, and the dorsomedial prefrontal cortex has been associated with error monitoring and reality evaluation (Arnsten, 2009). During normal conditions, the pre-frontal cortex and its extensive connections orchestrate the brain's activity for the regulation of behavior, thought and emotions (see figure 2 above).

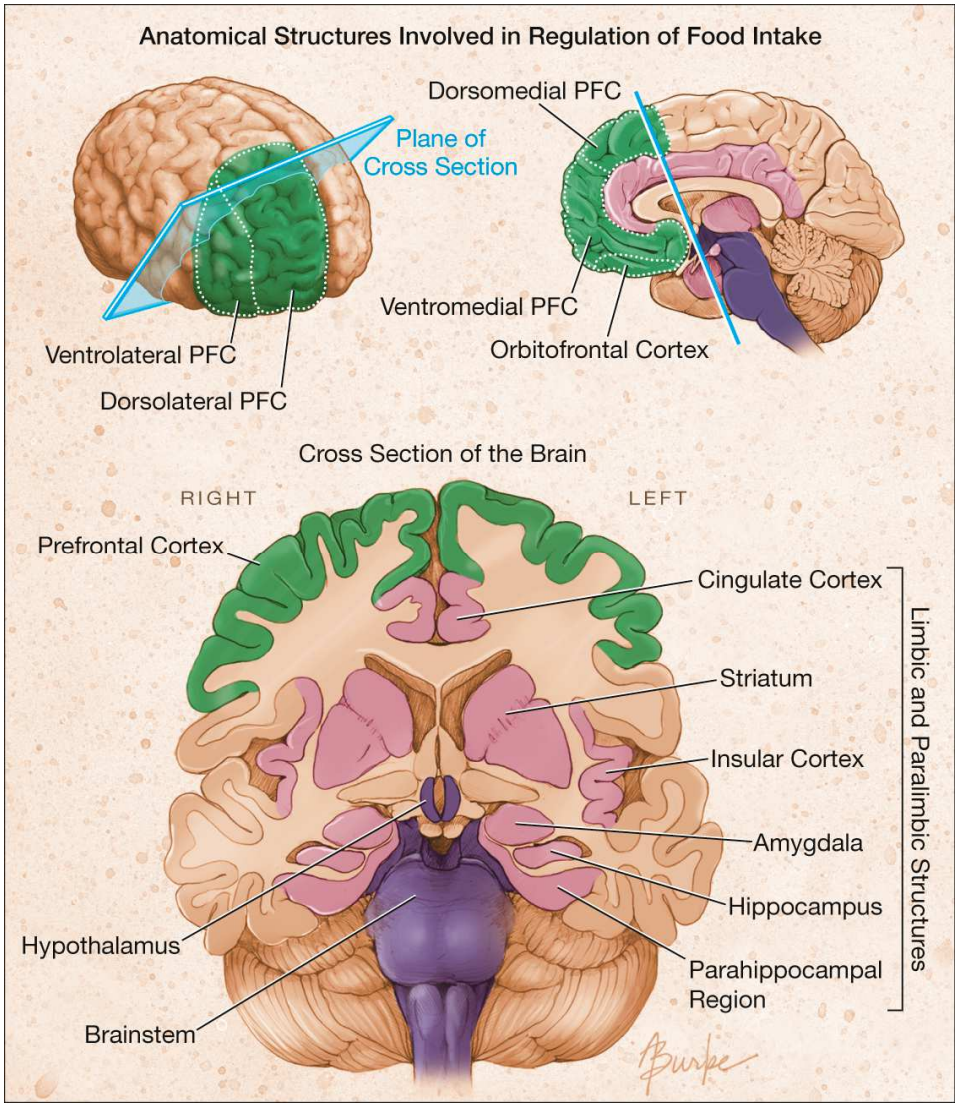


Figure 3: Anatomical position of brain areas implicated in food intake and eating behavior (Alonso-Alonso & Pascual-Leone, 2007)

Figure 3 above (Alonso-Alonso & Pascual-Leone, 2007) depicts the anatomical position of brain areas implicated in food intake and eating behavior: dorsomedial, dorsolateral & ventrolateral prefrontal cortex (dorsomedial prefrontal cortex, dorsolateral prefrontal cortex, & ventrolateral prefrontal cortex), ventromedial orbitofrontal cortex, striatum (encompassing the putamen and caudate nucleus), insular cortex (insula), limbic regions: amygdala, hippocampus, parahippocampal gyrus, hypothalamus, and brain stem (where reward pathways related to food intake are active).

Multiple brain sites are activated in response to food cues, including higher cortical brain areas, such as the pre-frontal cortex, orbitofrontal cortex, anterior cingulate cortex, anterior insular cortex (Berridge & Kringelbach, 2008; de Araujo, Rolls, Kringelbach, McGlone, & Phillips, 2003; Kringelbach, 2004, 2005; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Petrovich & Gallagher, 2007), brain pleasure "hotspots" in the striatum, such as the ventral pallidum and the nucleus accumbens, the amygdala, and lower brain areas such as the mesolimbic dopamine pathways and parabrachial nucleus in the pons (Berns, McClure, Pagnoni, & Montague, 2001; Cardinal, Parkinson, Hall, & Everitt, 2002; Kringelbach, 2004; Lundy, 2008; Wang et al., 2004). Some of these brain areas, such as the ventral pallidum and nucleus accumbens, are suspected to be recruited first upon exposure to food, and others, such as the orbitofrontal cortex, are postulated to be recruited later (Berridge & Kringelbach, 2008). Moreover, brain reward systems work in synergy with appetite regulatory systems in the brain, notably the hypothalamus. These reward systems include the brain hedonic "hotspots" mentioned above (e.g. ventral pallidum and nucleus accumbens), responsible for attaching an 'incentive salience' to a food cue (Nijs, Muris, Euser, & Franken, 2010) and make food taste better (Berridge et al., 2010). This lower brain reward system is in constant upstream communication with frontal higher brain regions, such as the prefrontal cortex, to notify about physiological appetitive needs and peripheral signals, mediating our motivation to consume food (Berthoud & Morrison, 2008). The prefrontal cortex, in return, receives sensory information from inside and outside of the body, as well as emotional and cognitive information from the limbic system inside our brain, and it is involved in planning and executive functions, including our decision to actively reach out for food.

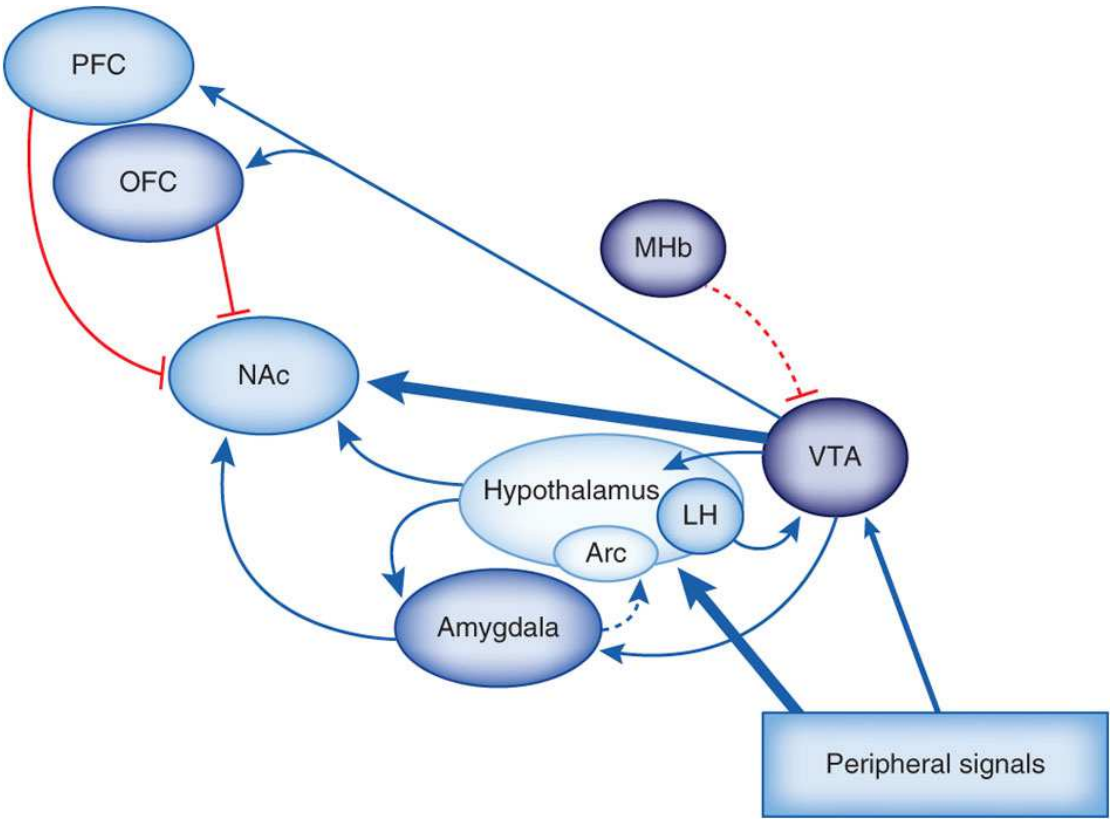


Figure 4: Communication between brain areas mediating hedonic representation of food (DiLeone, Taylor, & Picciotto, 2012); VTA = ventral tegmental area, LH = lateral hypothalamus, Arc = arcuate nucleus, MHb = medial habenulla, NAc = nucleus accumbens, OFC = orbitofrontal cortex, PFC = prefrontal cortex

Figure 4 above (DiLeone, Taylor, & Picciotto, 2012) represents a schematic illustration of communication between brain areas mediating hedonic representation of food. The hypothalamus is critical for food intake and is modulated by peripheral signals, such as hormones, and other brain areas, such as the ventral tegmental area, which, together with the nucleus accumbens is involved in attributing 'incentive salience' to food cues. Also depicted in *Figure 4* are areas in the cortex (i.e. prefrontal cortex and orbitofrontal cortex) and the amygdala, whose input provides control over food-related behaviors (see summary below).

1.1.B. Motivation to consume food: "liking" versus "wanting"

Our urges to eat can be mediated by numerous factors, including physiological, such as a woman's menstrual cycle, appetitive (i.e. hunger or satiety), or psychological, such as stress. Evolutionary processes made our brain biased to actively generate hedonic response to the consumption of fat and sugar (Berthoud & Morrison, 2008), which are cues for our brain to unlock neuronal circuits which apply pleasure of and desire for the food at the moment of encounter (Berridge & Kringelbach, 2008). Furthermore, our brain can lock or unlock these pleasure centers according to our physiological needs; for example, an intense salty paste can switch from unpleasant to pleasant during a state of salt appetite, in which the body lacks sodium (Krause & Sakai, 2007; Tindell, Smith, Pecina, Berridge, & Aldridge, 2006), and hunger can make foods more highly pleasant, while satiety can lower our motivation to consume food (Cabanac, 1971).

In the study of eating behavior, it is important to note the psychological and neurobiological distinction between "liking" and "wanting", although a deep exploration of these two concepts is beyond the scope of this project. Accumulating evidence about normal eating behavior distinguishes between these two terms: "wanting" refers to the motivational, rather than affective, aspect of reward, and it is also referred to as 'incentive salience' (Berthoud & Morrison, 2008). This system is represented by mesolimbic brain system, i.e. a neural network connecting the ventral tegmental area in the brain stem with the nucleus accumbens in the striatum (Berthoud & Morrison, 2008). It involves neurotransmitters such as dopamine and it is triggered by reward-related cues (Berridge, 2007; Berridge, Robinson, & Aldridge, 2009). In eating behavior, stimulus which was originally neutral, can be learned by Pavlovian conditioning to predict 'incentive salience' value of that stimulus (Berridge, 2007; Robinson & Berridge, 2003), making this cue and its reward more attractive and sought after. The power of a cue with an 'incentive salience' has been demonstrated by teaching a rat via Pavlovian

conditioning to expect a sugary solution upon exposure to a metal object, which made the object cue appear rather food-like to the rat, causing the animal to bite it (Flagel, Watson, Akil, & Robinson, 2008; Mahler & Berridge, 2009; Tomie, 1996). Thus, the conditioned stimulus acquires incentive motivational properties via learning, and it becomes attractive and guiding motivational behavior toward it, by predicting reward if re-encountered (Berridge, 2001; Berthoud & Morrison, 2008). To sum, our motivation to consume food is normally powered by synergistic interaction between a food cue, which has been previously primed with an 'incentive salience', a "wanting" reaction, and our current energy state, including hunger or satiety (Berridge et al., 2010; Zhang, Berridge, Tindell, Smith, & Aldridge, 2009). The "wanting" reaction in response to a food cue is not working in isolation but together with "liking", referring to the conscious pleasure produced by consuming highly palatable food (Berridge et al., 2010). The degree of a "wanting" reaction in response to food predicting a reward can change across individuals due to structural and functional brain differences (Zhang et al., 2009). In vulnerable individuals, these learned associations may evoke a compulsive approach (Robinson & Flagel, 2009), by increasing motivation to seek other rewards in the same time and/or increase the vigor with which the same rewards associated with food are sought (Berridge et al., 2009). Furthermore, failure of peripheral and central signals to suppress brain reward "hotspots" activation can cause abnormal persistence of hedonic drives for food even during satiety (Farooqi et al., 2007). Unfortunately, brain "liking" and "wanting" systems never generate a strong enough signal to stop the desire for palatable food intake, even in a state of satiety, nor can food pleasure be completely eliminated (Cromwell & Berridge, 1993); however, in satiated healthy people the desire for food is toned down in intensity (Berridge et al., 2010). Brain substrates for "wanting" originate sub-cortically and are more widely distributed, and they may be more easily recruited in the brain, as compared with brain substrates for "liking" (Aragona & Carelli, 2006; Berridge, 2007; Volkow et al., 2006). A discrepancy between "wanting" a reward without equally "liking" the same reward is possible (Berridge et al., 2009), and it is often happens in disordered eating (Berridge et al., 2010). Therefore, future therapeutic strategies in binge eating disorder may focus on parsing apart

the learned prediction (reward-related cues) and their associated rewards (incentive salience) (Berridge, 2007; Berridge & Aldridge, 2008; Robinson & Flagel, 2009).

Despite major advancements in the field of functional brain activity in eating behavior, differences in methodology make it difficult to come up with a conclusive pattern of brain activation (Wonderlich et al., 2009). For example, some studies have compared between obese versus obese + BED participants, while others have compared between obese + BED and lean + BED, although the latter is less common (Drewnowski, Krahn, Demitrack, Nairn, & Gosnell, 1995; Dalton, Blundell, & Finlayson, 2013). Also, differences in the diagnostic approach of BED have been noted, while some studies have used self-reported questionnaires, but others have used a diagnostic interview. Lastly, differences in fMRI analysis methods, such as differential brain activation (Schienle et al., 2009) versus pattern recognition techniques (Weygandt, Schaefer, Schienle, & Haynes, 2012), may have influenced the inconsistencies of the findings.

1.2 Purpose of the study

The project reviewed in this paper was supplemental to a parent NIH funded project, "fMRI and Ghrelin in Obesity and Eating Disorders" (Geliebter: PI). The parent study examined neurobiological aspects of BED using functional magnetic resonance imaging (fMRI) to assess brain activity in response to visual and auditory stimuli of high energy food, low energy food, and nonfoods. Its main hypotheses were that: 1) for all participants, there will be greater brain activation in response to the two food groups than to the nonfood images; 2) obese + BED participants will show greater brain activation in brain regions of interest (ROI), i.e., amygdala-hippocampus and orbitofrontal cortex, in response to the high energy foods compared with obese control non-binge-eaters, and 3) obese control non-binge-eaters will show a greater differential response between the fasted and the fed states to the two food groups than the binge-eaters.

This dissertation project used brain imaging data collected in the parent study to examine new hypotheses, and three additional questionnaires to assess psycho-behavioral parameters were added. This project was composed of two stages: first, differences between obese + BED versus obese on several psycho-behavioral parameters were assessed, i.e., participants' behavioral activation system, anxiety level, and restraint eating-and disinhibition. Secondly, brain imaging data of the participants, following a pre-load meal and in response to visual images, were analyzed using exploratory whole brain analysis, and differences between the two groups were correlated with psycho-behavioral measures found to be significantly different between the two groups, obese + BED versus obese. The overall purpose of this dissertation study was to examine the differences between the groups in response to the sight of food to created new hypotheses about possible mechanisms responsible for the development and maintenance of BED in obese adults (Rutters, Nieuwenhuizen, Lemmens, Born, & Westerterp-Plantenga, 2009).

1.3 Statement of the research questions or hypotheses

1.3.A Behavioral measures

Do obese + BED participants score significantly different on behavioral measures concerning behavioral activation, anxiety, restraint eating and disinhibition?

Hypotheses

A. Compared to obese, obese + BED will score significantly higher on the Behavioral-Activation Scale (BAS). Rationale: obese participants with BED may have difficulties regulating emotions, and thus they may tend to approach reward more impulsively and be susceptible to reward-based eating.

B. Obese + BED will score higher on the anxiety scale compared to obese. Rationale: binging on food high in sugar and fat has been suggested to alleviate negative emotions, such as anxiety. Individuals who are chronically anxious may consume highly palatable food to reduce the intensity of their negative emotions.

C. Obese + BED will score higher on the dietary restraint & disinhibition scales. Rationale: Binge eaters may be restricting dietary intake following a binge to try to control their weight. Concurrently, they may be prone to high disinhibition, which leads to further binging, thereby reinforcing the binge-fasting cycle. In response to food cues, rigid dietary restraint associated with binge-eating has been shown to be coupled with high disinhibition (Howard & Porzelius, 1999; Westenhoefer, Stunkard, & Pudel, 1999).

1.3.B.Brain activation

A. Following a pre-load meal and comparing between the two groups, i.e. obese + BED versus obese: does functional brain activity in response to food compared with control visual cues differ between the groups? Does it differ in response to high energy food compared with low energy food visual cues?

B. Do differences between obese + BED versus obese in psycho-behavioral measures identified in aim # 1.3.A correlate with functional brain activity in response to food versus nonfood, and high energy food versus low energy food, visual cues?

Hypotheses

A. When fed, obese + BED will show greater brain activation in response to the food versus nonfood visual cues, as well as in response to high-energy food versus low-energy food visual stimuli, in brain areas implicated in the control of feeding behavior.

B. Behavioral measures significantly different between obese + BED and obese, obtained in aim #1.3.A., will strongly correlate with brain activity in response to the food versus nonfood visual cues, and in response to high energy- versus low energy food visual cues.

Rationale: obese individuals have repeatedly shown differential brain activation in response to food versus nonfood images. Differences in the behavioral measures postulated to contribute to BED and examined in aim # 1.3.A. of this research study, had been previously shown in non-clinical populations to be associated with impaired functional brain activity in response to food and nonfood stimuli in various cortical and sub-cortical brain areas. Since binge-eating often occurs in the absence of hunger (Rutters, Nieuwenhuizen, Lemmens, Born, & Westerterp-Plantenga, 2009), it was reasonable to study participants in the fed state. The answer to whether differences in behavioral measures between obese + BED and obese correlate with brain activity in response to binge-triggers is postulated to lead further studying of neurobehavioral markers of BED.

A schematic illustration of the research questions is depicted below:

1. Psycho-behavioral Measures

-Anxiety -Restraint-Disinhibition -Behavioral Activation System

$\rightarrow [(\text{obese + BED}) - (\text{obese})] \neq 0$

2. Functional Brain imaging

2a.

2a.1 In fed obese + BED:

[(Brain activation in response to food) – (Brain activation in response to nonfood)] ≠ 0

[(Brain activation in response to high energy food) – (Brain activation in response to low energy food)] ≠ 0

2a.2 In fed obese:

[(Brain activation in response to food) – (Brain activation in response to nonfood)] ≠ 0

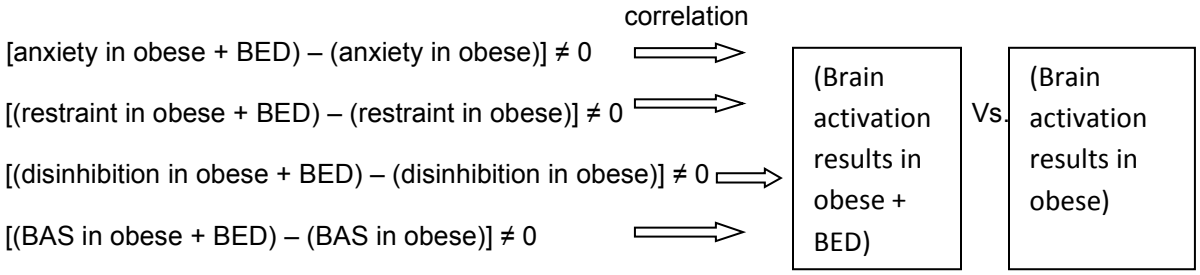
[(Brain activation in response to high energy food) – (Brain activation in response to low energy food)] ≠ 0

2a.3

(Brain activation in response to food in fed obese + BED) > (Brain activation in response to food in fed obese)

(Brain activation in response to high energy food in fed obese + BED) > (Brain activation in response to high energy food in fed obese)

2b.



1.4. Significance of the study

With a high prevalence of BED and its significant contribution to the current obesity rates, examining underlying psycho-behavioral and neurobiological factors may provide a clue to treatment approaches and prevention strategies. This dissertation study was expected to facilitate our understanding of obesity and BED to increase its diagnostic stability. The recently published Diagnostic and Statistical Manual for mental disorders edition five (DSM V; Marek, Ben-Porath, Ashton, & Heinberg, 2014) has BED as a separate disorder from other eating disorders, although its clinical validity is still debated. Despite a growing understanding of BED, currently only one study assessed the neuronal correlates of the Behavior Activation System in BED in response to images of high energy food cues (Schienle et al., 2009). Ventromedial prefrontal cortex, a brain area involved in inhibitory control and evaluation of goals and consequences (Hare, Camerer, & Rangel, 2009), was activated in response to visual stimuli of high energy food in BED participants, and this was positively correlated with their scores on the Behavioral Activation Scale, suggesting about their heightened approach response toward the high energy food stimuli. A recent study showed that diminished cognitive functional activity in BED participants in response to a cognitive task to examine their neuropsychological functioning, negatively correlated with their high dietary restraint scores (Balodis et al., 2013); the authors postulated that impaired cognitive functioning of people with BED, which was correlated with impaired activity in frontal brain regions, may distort their perceived palatability of food and/or override satiety or inhibition signals. Furthermore, large body of research indicates that emotional dysregulation predominate BED and fluctuations in stress and negative emotional state may pre-dispose individuals with BED to engage in binge-eating. However, no study to date investigated neural correlates of tension and anxiety in BED to estimate neurobiological traits of these behavioral findings. Together with previous evidence indicating high reward sensitivity and possibly addictive traits in BED, this exploratory research intended to confirm previous findings and further identify neural correlates of behavioral manifestations in obesity and BED.

The aim of this study was to examine potential markers of developing BED. Its hypotheses outlined possible interaction between psycho-behavioral traits, i.e. anxiety, behavioral activation, and dietary restraint-disinhibition, and a predisposition to developing BED. The findings of the proposed study were postulated to help advance the field of eating behavior, by opening new avenues for research to better understand psychological and behavioral predispositions of BED and their interaction with brain activity in response to binge-triggers. This, in turn, may help characterize BED and to identify individuals who may be prone to developing BED, as well as target a better treatment to those affected by it. Overall, the results of this dissertation study join accumulating information about possible predisposing conditions to BED, and the progression and treatment of BED, to come up with a strategy for reducing morbidity, mortality and health care costs.

1.5. Scope and delimitations

BED is a serious disorder with multiple co-morbidities, causing impaired quality of life for individuals affected by it and their families, and taking a toll on the health care system due to associated high healthcare costs. BED is often referred to as a sub-type of obesity (Davis et al., 2009), but the differences between obese with- and without BED is still unclear. In the proposed study two groups of participants were investigated: obese versus obese + BED. The purpose of it was to identify neurobehavioral markers possibly associated with differences between the two groups. Thus, the results of the discussed study are intended to generalize to adult obese and obese + BED in the larger American population and to those who may be prone to developing BED.

CHAPTER TWO: Literature review

2.1. Behavioral correlates of binge eating disorder

2.1.A. Dysfunctional mood regulation and anxiety

Multiple constructs of psychopathology associated with BED work in synergy and contribute to the development and maintenance of the disorder. Gianini, White, & Masheb (2013) examined the relationships among eating pathology and multiple constructs of psychopathology previously have been associated with BED: 1. emotion regulation, 2. emotional overeating, and 3. general eating pathology (Gianini, White, & Masheb, 2013). They administered pertinent questionnaires and found that difficulties with negative affect regulation were the strongest predictor of eating pathology. In BED, like its' related disorder, Bulimia Nervosa (BN), binge eating may be used to cope with stress and dysregulated mood. Specific emotions such as anger, fear, sadness, and joy, have been found to influence eating responses, including motivation to eat, affective response to food, food choice, and amount ingested (Macht, 2008). Negative emotions can increase the tendency to binge eat in BED (Alpers & Tuschen-Caffier, 2001; Gluck, Geliebter, Hung, & Yahav, 2004) by activating the Hypothalamic-Pituitary-Adrenal (HPA) axis, which increases cortisol release and opioids in the brain (Epel, Lapidus, McEwen, & Brownell, 2001). This may lead to preference for high-fat, high-calorie food (Teegarden & Bale, 2008; Maniam & Morris, 2010) and increase the total calorie intake.

Possible reasons for the association between affect regulation and binge eating are currently unknown, but they may lead to new therapeutic approaches. One possible explanation for the function of binge-eating is illustrated in the Affect Regulation model (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Gianini et al., 2013; Wedig & Nock, 2010), which proposes that maladaptive behaviors, e.g. binging on food, function to decrease negative emotions (Gross, 2007). Binge foods, according to this theory, act to alleviate negative affect

by providing comfort and distraction (Hawkins, 1984). With time, binge eating becomes a conditioned response, thus individuals with BED learn to condition binge-type foods with negative emotions (Heaner & Walsh, 2013), thereby reinforcing the binge cycles. This model is based on two main hypotheses: 1. Increase in negative affect represents a proximal antecedent to binge eating, and 2. binge eating is associated with an immediate decrease in negative mood (Haedt-Matt & Keel, 2011). Research has provided support for the former hypothesis; between 69% and 100% of individuals who binge-eat report negative mood as a trigger to binge eating (Abraham & Beumont, 1982; Arnow, Kenardy, & Agras, 1992; Lynch, Everingham, Dubitzky, Hartman, & Kasser, 2000). Lab studies using experimentally-controlled negative mood induction have shown significantly greater food consumed following the experimental manipulation in participants with BED (Chua, Touyz, & Hill, 2004) and more frequent binges in these individuals compared with controls (Agras, 1998). These studies have some limitations, however, since studying binge-eating behavior in a lab is difficult, as binge episodes usually occur in secrecy (Loeb, Lock, Grange, & Greif, 2012; Pettersen, Rosenvinge, & Ytterhus, 2008). Moreover, the artificial lab environment may not have ecological validity, thus findings may not be generalized to participants' natural environment, and retrospective designs are limited in respect to participants' memory and cognitive bias (Haedt-Matt & Keel, 2011). In response to these concerns, researchers have been using the Ecological Momentary Assessment (EMA) (Haedt-Matt & Keel, 2011; Munsch, Meyer, Quartier, & Wilhelm, 2012) to examine the daily experiences, behaviors, and psychological states of individuals in their natural environment (Stone, 1994). The use of EMA to test affect has some limitations, though, since it requires the participants to be aware of their binge episode before-, after-, and as it happens, possibly interfering with the natural course of the binge.

Mixed empirical support has emerged for the second hypothesis of the Affect Regulation model (Haedt-Matt & Keel, 2011); it is still unclear whether individuals with BED feel a decrease or increase in negative mood following a binge, and if the decrease in negative mood reported to date reflects the consequences of binge-eating or the passage of time

following a binge (Agras, 1998). Also, researchers have been attempting to answer a clinically relevant question: what reinforces binge-eating episodes? It is possible that the positive affect individuals with BED feel during a binge is related to the hedonic aspect of consuming binge-type foods (Small, Jones-Gotman, & Dagher, 2003), which tend to be high in energy, fats, sugar and/or salt (Heaner & Walsh, 2013), and this hedonic response to food is addictive, thereby reinforcing the binge-eating cycles (Kelley, Schiltz, & Landry, 2005). However, insufficient research to test this hypothesis has been conducted to date. Results of a meta-analytic study to examine the hypotheses of the Affect Regulation model refuted the second hypothesis referring to a decrease in negative mood following a binge in BED (Haedt-Matt & Keel, 2011). However, there is also the possibility that the 'post-binge phase' may have been differently defined among the studies examined in this meta-analysis. Thus, to get a clearer picture of the post-binge phase affect regulation in participants with BED, mood ratings should be measured immediately after a binge, as well as for a period of a few hours after (Haedt-Matt & Keel, 2011).

In a recent study (Munsch et al., 2012) mood shifts in BED have been examined, using an EMA design. Adult women with BED recorded their affect on a diary immediately before and after a binge, as well as on steady intervals throughout waking hours, in their own natural environment. They also completed specific questionnaires to report their daily course of negative mood, positive mood and level of tension. As expected, most binge episodes occurred in the afternoon and evening, while participants were at their home (Harvey, Rosselli, Wilson, Debar, & Striegel-Moore, 2011). While negative mood was higher and positive mood lower on binge-, compared with non-binge days, participants' level of tension increased until the afternoon and then gradually decreased. Immediately (30 to zero minutes) prior to a binge, negative mood sharply increased and positive mood significantly decreased, while over the post-binge phase a rather slow but lasting improvement over several hours following the binge emerged. This study has demonstrated a steady, possibly accumulating, increase in negative mood and concurrent decrease in positive mood over several hours prior to a binge. Right

before a binge, an immediate breakdown of emotion and impulse regulation occurred, with a sudden increase in negative affect and tension in the same time. This, the authors commented, is in line with the "Escape Theory" (Heatherton & Baumeister, 1991), in which an attempt to escape from unpleasant emotional state brings on a short but sudden decreased in self-awareness (Heatherton & Baumeister, 1991), narrowing one's attention to the immediate stimulus. This, in turn, is thought to inhibit usual cognitive control over eating and, together with an accumulating negative mood, fosters a focus on the immediate hedonic goal and triggers a binge. The evidence reported above points to multiple psychopathological dimensions which, when grouped together, may propel a binge-eating behavior. This refers to dysregulated mood and negative affect, fragile impulse control, and impaired executive functions in the face of a trigger, i.e. the sight/smell of binge-food. Despite these findings, the relationship between affect regulation and binge eating is still vague, and a better understanding of the interaction between the various behavioral parameters previously identified as related to BED, is necessary.

Anxiety Participants with BED tend to have higher levels of anxiety (Isnard et al., 2003; Schulz & Laessle, 2010), which can be subdivided into: State Anxiety (A-State) and Trait Anxiety (A-Trait). A-State relates to a transitory emotional state of arousal to perceived dangerous stimuli and can vary in intensity and fluctuate over time (Hedberg, 1972). A-State reflects the process taking place at a given time and level of intensity and the extent to which one perceives a specific, often objectively stressful, situation as psychologically dangerous or threatening. A-Trait is an enduring behavioral disposition to respond with anxiety to a wide range of psychologically threatening stimuli (Spielberger, 1970), and it is influenced by past experiences**.** Thus, A-Trait is considered to be a feature of one's personality, and it predicts the frequency and intensity with which one experienced A-State in the past and the probability of experiencing A-State in the future. Individuals with a high A-Trait are more likely to respond with greater increase and intensity of A-State in stressful situations. The State Trait Anxiety Inventory (STAI) is a reliable and brief self-report scale used to measure A-Trait and A-State

(Hedberg, 1972). Spielberger, Gorsuch &, Edward (1970) have shown that A-trait items demonstrate stability over alternating conditions of experimental stress and relaxation, while at the same time yielding significant correlations with other accepted measures of A-Trait . In contrast, A-State items consistently yielded different values with various experimental states of stress. However, A-State, although transitory, can recur when evoked by appropriate stimuli, and it may endure over time when the evoking conditions persist (Spielberger, Gorsuch, Edward, 1970). In the proposed study, A-State will be used since it is related to one's sensitivity to the stimulus experimentally provided. A-State reflects intense feelings of tension (Noto, Sato, Kudo, Kurata, & Hirota, 2005), which may propel binge-eating (Munsch et al., 2012), nervousness and worry, and it is characterized by activation of the autonomic nervous system (Spielberger, Gorsuch, Edward, 1970). Therefore, measuring anxiety right before a binge-trigger may help reveal the relationship between this emotional state and binge-eating.

Anxiety is an aversive emotional state, with which individuals with BED may be using palatable food to cope. The concept of "hedonic self-medication" has been proposed to describe the process by which stress increases Hypothalamic-Pituitary-Adrenal (HPA) axis activity, causing the release of corticotropin-releasing factor (CRF), which can be reduced back to normal levels by consumption of highly palatable food (Adam & Epel, 2007; Dallman et al., 2003). Thus, the presence of CRF in the brain can potentiate the attractiveness of a highly palatable food cues (Berridge et al., 2010) by sensitizing the brain reward system to the food cue (Covington & Miczek, 2005) and to its predictive value (Pecina, Schulkin, & Berridge, 2006; Wagner et al., 2012), thereby increasing reactivity to the appetitive stimuli, and this can bring to excessive food consumption. Individuals who experience high cortisol reactivity have been shown to eat more under stress and to choose high energy food (Lo Sauro, Ravaldi, Cabras, Faravelli, & Ricca, 2008; Adam & Epel, 2007). Thus, it is possible that "stress-induced food reward dependence" in BED helps regulate their emotions (Wagner, Boswell, Kelley, & Heatherton, 2012). Ingestion of palatable food in an attempt to relieve the effects of stress has been shown in BED participants, and this was associated with recruitment of dopaminergic

neurons in the brain's “hedonic hotspot", the nucleus accumbens (Kelley, Schiltz, & Landry, 2005). Thus, dopamine interactions with the brain's pleasure "hotspots" (the nucleus accumbens and the ventral pallidum) contribute to the 'incentive salience' of palatable food (Berridge, 2007), which can alleviate stress and negative affect by reducing CRF levels and toning down HPA activity, while promoting pleasurable experience. Moreover, chronic activation of the HPA may cause its' down-regulation (Rosenberg et al., 2013), supporting the hypothesis of excessive consumption of highly palatable food to alleviate chronic stress in BED.

Accumulating evidence indicates that negative affect accompanying distress is a primary determinant of self-regulatory failures across a range of maladaptive behaviors (Baumeister, 1997; Heatherton, 2011), and this may be true for BED. Using an "eating in the absence of hunger" paradigm, Rutters, Nieuwenhuizen, Lemmens, Born, and Westerterp-Plantenga (2009) showed that overweight participants eat more following a stress-inducing task compared with controls, despite being satiated. These positive relationships were stronger in participants with high disinhibition and greater A-State scores, which is correlated with increased A-Trait scores (Rutters, Nieuwenhuizen, Lemmens, Born, & Westerterp-Plantenga, 2009). Trait anxiety appears to create a chronic stress, where the HPA axis is chronically stimulated (Adam & Epel, 2007), possibly contributing to its down regulation in BED (Rosenberg et al, 2013). The conditioned stimulus, i.e. the sight/smell of HPF, may have an anxiolytic effect in BED (Cottone et al, 2008), and the severity of this response may be a function of anxiety. In agreement with the "Escape Theory" (Heatherton & Baumeister, 1991), this emotional response to the highly palatable food cue may disrupt cognitive control over eating inhibition (Arnsten, 2009), and disinhibition may follow. Indeed, difficulties engaging in goal-directed behavior in the face of negative affect have been found to be the emotion regulation difficulty most strongly associated with eating pathology in a clinical group of obese women with BED seeking treatment (Gianini et al., 2013). Thus, it is plausible to hypothesize that binge eating severity is a function of anxiety, contributing to a vulnerability to experiencing

excessive tension and stress in the presence of triggers, coupled with the lack of adequate coping mechanisms.

2.1.B. Dietary restraint and disinhibition

The development of BED has been linked with dietary restriction coupled with high disinhibition (Howard & Porzelius, 1999; Westenhoefer, Stunkard, & Pudel, 1999). Dishibition is a behavioral trait (Bryant, King, & Blundell, 2008), that can influence eating behavior and possibly also other areas of life (Bryant et al., 2008). Disinhibition has come to prominence in the clinical and scientific communities about 30 years ago with the development of the widely used Three Factor Eating Questionnaire (TFEQ) (Stunkard & Messick, 1985), designed to measure three related concepts: dietary restraint, disinhibition, and hunger (Bryant et al., 2008). Dietary restraint refers to a tendency to restrict food intake to control body weight (Herman & Mack, 1975). Thus, dietary restraint is a form of inhibitory control over food intake. Two sub-types of the restraint scale of the TFEQ have been suggested: 'Rigid Restraint' and 'Flexible Restraint' (Westenhoefer et al., 1999), based on their correlation with the disinhibition score of the TFEQ. Rigid restraint is characterized by a dichotomous, all-or-nothing approach to eating, dieting, and weight, while flexible restraint is characterized by a more lenient approach to eating, dieting, and weight, in which “fattening” foods are eaten in limited quantities without feelings of guilt. It was the 'rigid' subscale that correlated with a higher disinhibition score, and the flexible subscale showed the opposite. Therefore, the following discussion about dietary restraint in obesity and BED refers to the 'rigid' sub-type.

A high dietary restraint can lead to weight loss in obese individuals, but only when it is coupled with low disinhibition (Contento, Zybert, & Williams, 2005; Stunkard & Messick, 1985). "Disinhibition effect" (Bryant et al., 2008) refers to the counter-regulatory eating that results from a disruption of dietary restraint, i.e. disruption of the inhibition of dietary intake (Herman & Polivy, 1975). This disruption of inhibitory control over eating is positively related to trait

disinhibition, reflecting on the susceptibility to eat in response to emotional factors and sensory cues (Bryant et al., 2008; DelParigi, Chen, Salbe, Reiman, & Tataranni, 2005). Also, high disinhibition has been associated with the use of certain food and food components, such as dietary fat and sugar, alcohol and caffeine, to aid in emotional regulation (Borg, Fogelholm, & Kukkonen-Harjula, 2004; Bryant et al., 2008; Hetherington & MacDiarmid, 1993; Higgs & Eskenazi, 2007; Lahteenmaki & Tuorila, 1995). Thus, disinhibition can take the form of overeating from the inhibition of dietary restraint (Brunstrom, Yates, & Witcomb, 2004; Bryant et al., 2008), or it can take the form of high food sensitivity, (Schag et al., 2013) coupled with a failure to inhibit eating once started (French, Epstein, Jeffery, Blundell, & Wardle, 2012).

High restraint coupled with high disinhibition seems to create a conflict which may dysregulate the control of eating, increasing the risk of developing an eating disorder (Bryant et al., 2008). Furthermore, the measure of disinhibition is negatively related to psychological well-being, regardless of weight or dieting status (Provencher et al., 2007). The positive association between disinhibited eating and high BMI has been recently reviewed and established (French et al., 2012), and obese adults show high disinhibition scores not only when fed but also following a 36-h fast (DelParigi et al., 2005), when they may feel hungry, which makes it OK to eat. Individuals with BED have been postulated to show a dysfunctional inhibition-disinhibition mechanism (Tammela et al., 2010). Decreasing disinhibition while increasing both flexible and rigid restraint in obese + BED has been shown to promote binge-eating abstinence in the short term but not necessarily two years post treatment (Downe, Goldfein, & Devlin, 2009). Thus, it is evident that the etiology of BED includes the constructs of dietary restraint and disinhibition, but it is not clear how manipulation of these variables could promote treatment for BED.

2.1.C. Dysfunctional reward system and 'food addiction'

Food reward has been defined as "a composite process that contains "liking" (hedonic impact), "wanting" (incentive motivation), and learning (associations and predictions) as major components" (Berridge, Ho, Richard, & DiFeliceantonio, 2010). Normally these systems work together, but they each have a separate brain system, which permits dissociation among them in some abnormal conditions. The aforementioned hedonic brain systems can each be stimulated by neurochemicals, such as endocannabinoids or dopamine, to alter the hedonic impact of food, thereby changing food consumption. Dysfunction of these hedonic brain areas, and/or neurochemicals, has been associated with eating disorders (Berridge et al., 2010).

Reward Sensitivity Individuals with BED might have elevated sensitivity for primary rewards, such as food (Schag et al., 2013). There is evidence to suggest a link between reward sensitivity and overeating, with studies showing positive correlations between self-reports on reward sensitivity, the degree of binging, and body mass index (Burgess, Turan, Lokken, Morse, & Boggiano, 2014). Reward sensitivity is considered to be one component of impulsive behavior related to food cues in BED (Dawe & Loxton, 2004; Manwaring, Green, Myerson, Strube, & Wilfley, 2011), mediated by heightened approach to rewarding stimuli. Thus, reward sensitivity is closely related to the Behavioral Approach personality trait (i.e. BAS) (Kennis, Rademaker, & Geuze, 2013). The following section discusses reward dysfunction in obesity and BED.

Food addiction Brain reward system dysfunction can take numerous forms, involving a few brain substrates. For example, responsible for an enhanced "liking" reaction to taste pleasure in some individuals is the endocannabinoid and opioid systems in the brain's hedonic "hotspots", i.e. the nucleus accumbens and ventral pallidum (Berridge et al., 2010). Excessive action of these brain substrates generating hedonic reaction to food cues has been associated with binge-eating, by magnifying the hedonic impact of foods, and making an individual both

"like" and "want" food more than other people (Berridge, 2009; C. Davis & Carter, 2009; C. A. Davis et al., 2009). Another example of reward system dysfunction is when "wanting" ('incentive salience') detaches from "liking" (pleasure from food) in such a way that one occurs without the other via associated separable brain systems (Finlayson, King, & Blundell, 2007; Mela, 2006). In such a case, the sight, smell, or vivid imagination of food could trigger a compulsive urge to eat, even though the person would not find the experience of eating extraordinarily pleasurable (Berridge et al., 2010). Fluctuations in striatal dopamine levels, for example, have been shown to enhance "wanting" for food without "liking" it, i.e. high motivation to get food without enjoying the pleasure of eating it (Berridge et al., 2010; Leyton et al., 2002; Volkow et al., 2002). The reduced pleasure from food consumption has been suggested to be a possible cause of over eating to attain a normal degree of pleasure (Geiger et al., 2009). Some researchers call it "irrational wanting'" (Berridge, Robinson, & Aldridge, 2009), where excessive 'incentive salience' to a food stimulus is sub-cortically in control (i.e. "wanted"), despite the food represented by this stimulus not being as much liked (Berridge & Aldridge, 2008; Robinson & Berridge, 2003, 2008). Thus, the inflicted person compulsively craves and seeks food but does not derive high pleasure from it. Berridge, Robinson and Aldridge (2009) have proposed an "incentive-sensitization model of addiction", depicted in *Figure 5* below, visually demonstrating how "wanting" for high energy food may grow over time independently of "liking" for the pleasure from this food, as the individual becomes addict while mesocorticolimbic mechanisms of 'incentive salience' in the brain become over-sensitized to the triggering stimulus and thus hyperactive (Berridge et al., 2009). These changes in brain mesolimbic system may be a consequence of exposure to dieting and binging cycles (Cabeza de Vaca & Carr, 1998; Carr, 2002; Colantuoni et al., 2001). Such a person is vulnerable to intense peaks of cue-triggered "wanting" for foods at excessive levels, similarly to drug addiction and abuse that other people would not experience in normal life (Berridge et al., 2010). Some possible causes are genetic makeup that promote elevated dopamine functioning (Campbell & Eisenberg, 2007), and reduced dopamine D2 receptors or signaling in

striatal hedonic brain "hotspots", which has been suggested to occur as a consequence of overeating and obesity, rather than its cause (Steele et al., 2010).

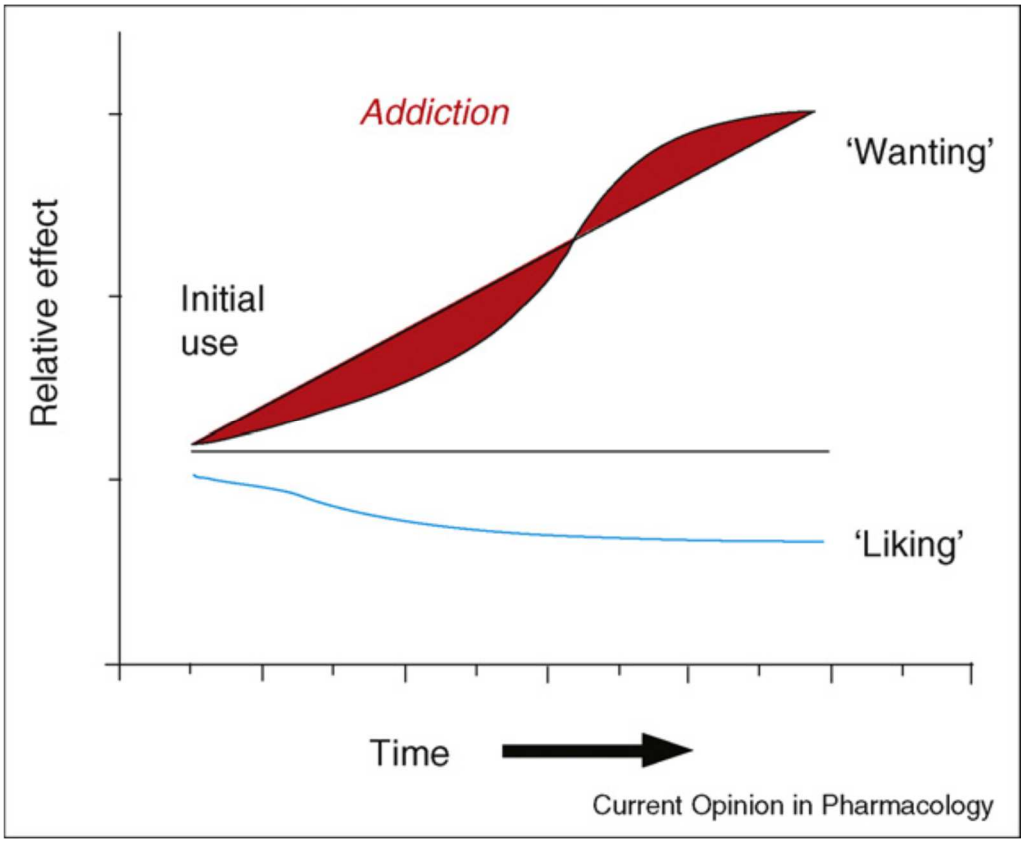


Figure 5: Incentive-sensitization model of addiction (Berridge, Robinson & Aldridge, 2009)

2.1.D. Behavioral Activation System/Behavioral Inhibition System (BAS/BIS)

Individuals with obesity + BED may have a greater tendency toward reward responsiveness (Schienle, Schafer, Hermann, & Vaitl, 2009). Reward responsiveness has been suggested to be reinforced by and reflected in the Behavioral Activation System (BAS) in response to an emotional trigger. The Behavioral Activation System is one part of a personality model proposed by Gray (1994) and Gray & McNaughton (2000), whereby three brain systems control motivated behavior in response to emotional stimuli signaling events (Gray, 1994; Gray & McNaughton, 2000). The other two systems suggested by Gray & McNaughton are the Fight-Flight-Freezing System (FFFS) and the Behavioral Inhibition System (BIS), but a

discussion of these two systems is out of the scope of this chapter, as they seem to have no relationship with BED. The BAS is engaged when signals of reward or relief from a punishment are available, and it mediates an approach or goal-directed behavior (Gray & McNaughton, 2000).Other personality traits closely related to the BAS include 'reward dependence' (Cloninger, 1994), 'novelty seeking' (Kennis et al., 2013), impulsivity, experience seeking, and risk seeking (Kennis et al., 2013).

Individuals with BED are suspected to have general deficit in executive control, and this may be related to their heightened reward responsiveness. Deficits in executive functioning may take the form of bias in information processing, thereby altering attentional processes (Svaldi, Brand, & Tuschen-Caffier, 2010,) or impairment in control functions leading to impulsive tendencies (Galanti, Gluck, & Geliebter, 2007; Nasser, Gluck, & Geliebter, 2004). Impaired executive functionings may also take the form of impaired response inhibition (Mobbs, Iglesias, Golay, & Van der Linden, 2011), or a tendency to engage in risky decisions neglecting long-term goals (Svaldi, Brand, & Tuschen-Caffier, 2010). In BED, neutral (i.e. nonfood-related) tasks have been interrupted by enhanced food-related memory bias which persisted from previously shown food-related stimulus (Svaldi et al., 2014). Thus, food-related stimulus grabs BED participants' attention in such a way that interferes with other cognitive tasks, and this was directly correlated with BED symptoms severity (Svaldi et al., 2014). Furthermore, results of a correlation analysis between a self-reported behavioral rating scale, i.e. the Frontal Systems Behavioral Scale, to assess neurobehavioral traits controlled by frontal brain regions, and the Eating Inventory scale to assess disordered eating behavior, in a community sample, have indicated positive correlation between impaired executive control functioning and two dysfunctional eating behaviors, independently, i.e. the loss of self-inhibition (i.e. disinhibition) over eating and excessive desire for food (Spinella & Lyke, 2004). This evidence for cognitive deficits in BED is in line with the hypothesis that individuals with BED have altered behavior activation system, i.e. they approach reward stimuli more impulsively (Schag et al., 2013). Resisting rewarding temptations, such as high energy food,

may require skills including behavioral inhibition, attention shifts and delay of gratification. Such skills have been associated with the function of the fronto-striatal loop, a brain area that is considered to mediate executive functions (Bonelli & Cummings, 2007). Furthermore, in our food rich environment, decision making is important in consciously practicing good nutrition and healthy lifestyle, and obese individuals have shown impaired decision making capability in an experimental task testing this construct (Davis et al., 2004). The link between altered executive functioning and the Behavioral Activation System has been recently explored (Kennis et al, 2013). The authors reviewed accumulating evidence pointing to a common personality dimension dominated by frontal brain systems, which mediate impulse inhibition, attentional management, and cognitive tasks requiring effortful control, such as task involving attention, decision making, or inhibitory control (Hofmann, Schmeichel, & Baddeley, 2012). They have suggested a fourth personality dimension, the "constraint system", to Grey & McNaughton's personality model; the "constraint system" is controlled by higher brain structures, i.e. the anterior cingulate cortex & prefrontal cortex, and it acts to inhibit impulses and provide attentional management and inhibitory control. However, this personality dimension has yet to officially be included in common questionnaires assessing Grey's BIS, FFFS, and BAS personality traits.

If we are to consider BED as an addictive disorder (Berridge et al., 2009), then evidence about substance abusers can teach us about possible relationships between impaired executive control, heightened behavioral approach and reward sensitivity to food in BED (Krmpotich et al., 2013). Compared with controls, substance dependent individuals who were free of drug use for a mean duration of 1.43 years showed greater behavioral activation score and higher resting-state activity in brain regions implicated in executive control, particularly the left dorsolateral prefrontal cortex.

2.2. The neurobiology of eating in BED

2.2.A. Functional brain imaging in BED

Evidence for a differential brain activation patterns in response to food cues in obese + BED participants compared with controls, is accumulating (Geliebter et al., 2006; Karhunen et al., 2000; Weygandt, Schaefer, Schienle, & Haynes, 2012; Wonderlich, Gordon, Mitchell, Crosby, & Engel, 2009). In comparison with healthy controls, obese + BED participants have shown greater activation in sub-regions of the amygdala, ventral striatum, and anterior cingulate cortex in response to palatable food stimuli (Weygandt et al., 2012). These structures are known to be involved in processing the 'incentive salience' of reward-related cues (Berridge, 2009; Mahler & Berridge, 2009). Animal studies indicate that the amygdala is responsible for converting learning into motivation by encoding 'incentive salience' into a particular food cue, thus making the cue more attractive and, in turn, triggering food intake (Mahler & Berridge, 2009). The anterior cingulate cortex has been noted as part of the brain network involved in food-cue processing (Berridge, 2009; Mahler & Berridge, 2009; Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; St-Onge, Sy, Heymsfield, & Hirsch, 2005), and it is postulated to reflect processes of attention to salient food-cues (Pelchat et al., 2004). The ventral striatum plays a major role in processing the incentive value of reward-related cues (Diekhof, Falkai, & Gruber, 2008), an activity directly connected to increase in the 'incentive salience' of food cues (Farooqi et al., 2007; Kelley, 2004).

In a recent study (Weygandt et al., 2012), left insular cortex and medial orbitofrontal cortex activation has been found elevated in obese + BED compared with control overweight participants while viewing high energy food stimuli. These differences could have been attributed to differences in food cravings (Garavan, 2010) and possibly occurred due to slight differences in BMI, in light of previous evidence pointing to positive relationships between BMI and anterior insula/frontal operculum activation in response to high energy food cues

(Ziauddeen, Farooqi, & Fletcher, 2012). Overweight controls in this study have also shown slightly but significantly greater activity in the ventral striatum and the anterior cingulate cortex in response to the high energy food visual cues, which the authors suggested could have been attributed to greater attention to the high energy food in the controls compared with the obese + BED group (Weygandt et al., 2012).

The right prefrontal cortex appears to play a critical role in behavioral restraint and moral self-control by keeping reward-generating mechanisms in check (Berthoud & Morrison, 2008). Successful dieters who have significantly higher dietary restraint compared with non-dieters have shown greater neural activity in the right dorsolateral prefrontal cortex in response to food consumption (DelParigi et al., 2007), demonstrating the importance of the right prefrontal cortex in executive functions related to eating behavior. Imbalanced executive functions in the prefrontal cortex could result in hyperactive reward mechanism (Berthoud & Morrison, 2008). Hence, studying neural correlates of general executive functions, such as conflict control and response inhibition, may assist in better understanding neurobiological deficits in BED. In a recent study, three groups of participants: obese, obese + BED, and lean controls, underwent functional brain imaging session while completing the Stroop color-word interference task, a neuropsychological test to assess their level of brain prefrontal systems functionality (Balodis et al., 2013). Compared with the other groups, the obese + BED showed differential hypoactivity in brain areas involved in self-regulation and impulse-control, including the ventromedial prefrontal cortex, inferior frontal gyrus, and insular cortex, during the test performance. Thus, the results of this study indicate impaired functioning of frontal brain regions in obese + BED, possibly relating to dysfunctional self-control over eating in this group.

2.2.B. Functional brain correlates of emotion dysregulation and anxiety

Until relatively recently, studies focusing on neural correlates of anxiety have mainly focused on emotional reactivity to a stimulus and the function of the amygdala (Etkin & Wager, 2007; Stein, Simmons, Feinstein, & Paulus, 2007), although the role of other brain regions, such as the ventrolateral prefrontal cortex, medial prefrontal cortex and insula, in this context, has also been noted. An active area of research is the functional inter-connection between affective and executive cognitive brain regions in response to an anxiety-inducing stimulus in individuals prone to anxiety. The finding that increased activity in affective brain regions disrupts activity in higher executive brain regions, resulting in cognitive impairment, is striking (Dolcos, Diaz-Granados, Wang, & McCarthy, 2008; Dolcos, Kragel, Wang, & McCarthy, 2006; Dolcos & McCarthy, 2006). This may be related to alterations in executive cognitive control in anxiety (Eysenck & Calvo, 1992; Eysenck, Derakshan, Santos, & Calvo, 2007). Studies have suggested a functional mechanism of under recruitment of dorsal executive cognitive regions, including the lateral prefrontal cortex, dorsolateral prefrontal cortex, and dorsal anterior cingulate cortex (Bishop, Duncan, Brett, & Lawrence, 2004; Bishop, 2009; Eysenck et al., 2007). For example, increased reactivity to emotional cue has been shown to distract anxious individuals from focusing on concurrent goal-relevant task, and this was positively correlated with under-recruitment of the lateral prefrontal cortex (Bishop et al., 2004). It is also possible that the influence of anxiety on cognitive-relevant brain regions in the face of emotionally-triggering stimuli is a result of impaired cognitive functioning to begin with, which may make the participants unable to cope well with emotional distraction (Dolcos et al., 2006). The evidence of impairment in executive brain regions in anxious individuals is in line with empirical research suggesting altered general executive functions and a disruption of dietary inhibition right before a binge in participants with BED.

Using an event-related fMRI design, a recent study has investigated brain mechanisms involved in mediating emotional and cognitive effects of transient anxiety-provoking images in

non-clinical participants performing a working memory task, and the role of individual variations in anxiety in influencing their sensitivity to this emotional distraction has been assessed (Denkova et al., 2010). This study has identified multiple sub-regions of the prefrontal cortex, i.e. dorsomedial prefrontal cortex and dorsolateral prefrontal cortex, in which reduced activity in response to the emotionally provoking stimuli was negatively correlated with trait anxiety scores. Thus, increased activity in emotion-processing areas in response to the emotionally-laden stimulus impaired participants' activity in brain regions responsible for active maintenance of goal-directed behavior, and this has been especially pronounced in highly anxious individuals. However, despite these findings, little is known about how anxiety can influence the emotion-cognition interaction in response to a threatening stimulus and during a cognitively demanding task (Phelps, 2006), and no study to date has checked this hypothesis in BED.

Another brain area responsive to psychologically threatening stimuli in highly anxious individuals is the orbitofrontal cortex. This brain area has been shown to be active following a negative affect induction and in the face of a high energy food stimulus in chronic dieters (Wagner et al., 2012). Furthermore, heightened orbitofrontal cortex and ventral striatum activation in response to the high energy food stimulus was positively correlated with participants' increased distress (i.e. reduced self-esteem) following the mood induction. This evidence may be indicative of up-stream regulation of higher brain areas, i.e. striatum and orbitofrontal cortex, by emotionally-responsive brain areas, i.e. amygdala, in response to a stimuli inducing anxiety and negative affect (Denkova et al., 2010), and of concurrent sensitization of reward circuits in the brain to a 'salient stimulus' (Ohla, Toepel, le Coutre, & Hudry, 2012; Wagner et al., 2012). Thus, it is plausible to hypothesize that obese + BED individuals are prone to anxiety in response to a trigger, and that this may influence the function of brain regions responsible for cognitive control and inhibition, contributing to binge-eating.

2.2.C. Functional brain correlates of brain activation system/ brain inhibition system (BAS/BIS)

It has been suggested that binge eaters have elevated sensitivity for primary rewards, such as food. Schienle, Schafer, Hermann, & Vaitl (2009) explored whether participants with BED have elevated food-reward sensitivity (i.e., score higher on the Behavioral Activation Scale) and have increased activation in reward processing brain areas while viewing high energy food images, following an overnight fast (Schienle et al., 2009). Four groups of female subjects who completed the BIS/BAS questionnaire were studied: BED, Bulimia Nervosa, and normal-weight and overweight controls. BED participants reported the greatest reward sensitivity and showed activation in the medial orbitofrontal cortex in response to the high energy food images. Also, they showed a positive correlation between the Behavioral Activation Scale score and the degree of medial orbitofrontal cortex activation. The authors noted that in binge eaters, heightened medial orbitofrontal cortex reactivity to highly palatable food cues might translate reward drive into binge eating. However, participants in this study were examined when fasted, thus hunger may have played a key role. Interestingly, medial orbitofrontal cortex has been noted for its involvement in decision making processes (Bechara, Tranel, & Damasio, 2000), and impairment in this system has been associated with deficits in executive functions (Bechara et al., 1998). This implies that individuals with BED may experience impaired executive control, which may possibly be one cause of binge-eating relapse.

Kennis et al. (2013) hypothesized that individual differences in behavior mediated by the Behavioral activation System are governed by activity in a functional brain network involving the ventral tegmental area-ventral pallidum-ventral striatum-prefrontal cortex. They have reviewed studies to date, examining correlation between personality traits and functional brain activity, and they concluded that a score on the Behavioral Activation System may be positively associated with activity in the ventral pre-frontal cortex, ventral striatum (i.e. nucleus accumbens), ventral pallidum (ventral globus pallidus), ventral tegmental area in the midbrain,

and possibly the amygdala, in response to rewarding stimuli or expectance of reward. Behavioral Activation Score may also be positively correlated with other brain areas in response to different stimuli, such as the dorsal anterior cingulate cortex during tasks with a cognitive aspect, ventral anterior cingulate cortex activity when stimuli signaling positive events are presented, and activity in the insular cortex in response to negative stimuli, such as when uncertain versus certain decision are made. Negative association between BAS score and the caudal anterior cingulate cortex in a working memory task with emotional induction has been found (Gray & Braver, 2002), and studies using functional connectivity analysis to examine how different factors may modulate the interaction between brain systems, have revealed positive correlations between behavioral activation score and *decreased* connectivity between regions of the cingulate cortex, including its' anterior and posterior parts, the pre-cuneate gyrus, and the prefrontal cortex, in response to a rewarding stimuli. These findings may indicate hyperactive brain networks implicated in processing rewarding stimuli and concurrent hypoactive brain networks involved in decision making and other cognitive executive tasks, both correlating positively with the behavioral activation score. Nevertheless, only one study to date examined the relationship between a score on the BAS scale and performance on cognitive executive tasks in obese + BED participants and controls. Svaldi et al (2010) examined obese + BED women and obese controls on a computerized Game of Dice Task (GDT), and assessed their score on the BAS subscales of 'Reward Responsiveness' and 'Fun Seeking', and on several other neuropsychological tests, to learn about possible differences in decision making under risk and prefrontal cortex functioning in the BED group versus controls. This study found significantly more risk taking and disadvantageous choices, and significantly poorer feedback processing, in the BED group compared with controls. Also, BED participants surprisingly showed to be less reward responsive and fun seekers, compared with controls, and to have weaker executive functioning, indicated by lower cognitive flexibility. Inappropriate use of feedback concerning their risky behaviors may be indicative of pre-frontal region malfunctioning, involving the

orbitofrontal cortex & ventromedial prefrontal cortex, which possibly mediated reward processing, decision making and reward learning.

2.2.D. Functional brain correlates of dietary restraint and disinhibition

The prefrontal cortex has been implicated in the cognitive control of appetitive behavior (DelParigi et al., 2007; Ochner, Green, van Steenburgh, Kounios, & Lowe, 2009). Compared to healthy adult non-dieters, successful dieters did not differ in disinhibition scores but had higher dietary restraint scores, lesser activity in the orbitofrontal cortex and greater activity in the dorsal prefrontal cortex, dorsal striatum and anterior cerebellum, while consuming a meal (DelParigi et al., 2007). Healthy adults with high dietary restraint have been compared to healthy adults with low dietary restraint on brain activation in response to food- and nonfood stimuli (Coletta et al., 2009). In response to the highly palatable food stimuli, restraint participants showed greater activation in orbitofrontal cortex, left dorsolateral prefrontal cortex, left insular cortex, and decreased activation in the cerebellum. In obese and overweight adults, disinhibition scores have predicted greater prefrontal cortex left-sided activation, indicating asymmetrical activity in this brain area, and increased insular cortex activity in response to highly palatable food stimuli (DelParigi et al., 2005). In obese adults who binge-eat (Boeka & Lokken, 2011), higher scores on numerous neurobehavioral traits associated with prefrontal cortex dysfunction may be associated with higher disinhibition scores and greater fronto-central electrical brain activity during resting state and while shown different stimuli (Tammela et al., 2010).

Dietary restraint plays a major role in a successful weight loss, but the coupling of high dietary restraint and high disinhibition may cause obese individuals to fail in weight loss attempts and increase the risk of binge-eating. Although research suggests that disinhibition mediates eating behavior in both fasted and fed states, it is unclear how the coupling of dietary restraint and disinhibition influences eating behavior in these states. In a community

sample of 112 healthy men and women, disinhibited eating and dietary restraint have shown significant positive correlation with each other, and cognitive restraint over eating significantly correlated with prefrontal brain systems dysfunction, disinhibition, and risky behaviors (Spinella & Lyke, 2004). In a recent study, obese, obese + BED, and lean controls have been examined while performing a neuropsychological task testing multiple constructs of cognitive and impulse control (i.e. attention, conflict monitoring, and response inhibition) in response to changing images of colors and words, while being brain scanned (Balodis et al., 2013), and their level of dietary restraint has been assessed. Not only the obese + BED group showed hypo-activity in brain areas involved in self-regulation and decision making (e.g. inferior frontal gyrus), but also, differently from the obese and lean control groups, dietary restraint scores in the obese + BED group negatively correlated with functional brain activity indicative of cognitive and inhibitory control. Hence, diminished activity in the right inferior frontal gyrus, ventromedial prefrontal cortex and the orbitofrontal cortex in the obese + BED group was negatively correlated with their dietary restraint scores. Moreover, reduced activity in the anterior insula in the obese + BED relative to the other groups may indicate low self-awareness during the cognitive challenge, as the insula is considered to integrate homeostatic with cognitive and affective signals, thereby influencing decision making (Craig, 2002). Thus, reduced engagement of self-regulatory mechanisms and dissociation from internal homeostatic signals have been associated with high dietary restraint in obese + BED participants, making it plausible to hypothesize that disnihibited eating may follow.

2.2.E. Brain activity in hunger versus satiety

Multiple brain areas are involved in the interaction between the hedonic aspect of food and current appetitive state. Activity in the orbitofrontal cortex (Morris & Dolan, 2001), anterior cingulate cortex, occipital lobe, and the amygdala (Fuhrer, Zysset, & Stumvoll, 2008) lights up in response to food, but not in response to nonfood items, when healthy participants are hungry. Heightened activity in both the orbitofrontal cortex and amygdala has been shown in

response to visual high energy food cues in hunger and to low energy food cues in satiety in normal-weight participants (Porubska, Veit, Preissl, Fritsche, & Birbaumer, 2006). Another study have found normal weight participants to have shown increased activity in posterior cingulate cortex, lateral and media orbitofrontal cortex, caudate nucleus, putamen, and fusiform gyrus, as well as the insular cortex, in response to the sight of highly palatable food images when hungry (Siep, et al., 2009), but decreased processing in these brain areas in response to the sight of low energy food when satiated. Goldstone et al (2009) compared food and nonfood stimuli in healthy non-obese adult participants on two days, after fasting or after breakfast. When fed, there was no significant difference in brain activation to high-calorie food vs. low-calorie food images. Activity in a number of brain reward areas (i.e., hippocampus, anterior cingulate cortex, and dorsolateral prefrontal cortex) was found in response to the high-calorie foods compared with the low-calorie foods in the fasted, but not the fed state. In another group of normal-weight participants, looking at images of high energy food was associated with activation in the dorsomedial frontal lobe and fusiform gyrus when hungry, but this effect was noticeable only in women and abated when they were satiated (Frank et al., 2010). Furthermore, hunger may interact with subjective attractiveness of food items. When hungry, healthy participants have shown heightened activity in the medial and lateral orbitofrontal cortex in response to food items previously rated by them as highly palatable (Piech et al., 2009). A recent meta-analysis of studies investigating brain activation in normal-weight participants in response to images of food versus nonfood items when hungry, have found activation in two brain clusters in response to images of foods: a region extending from the right parahippocampal gyrus to the amygdala, and the region of the left lateral orbitofrontal cortex (van der Laan, de Ridder, Viergever, & Smeets, 2011). However, the same study also found that body weight can modulate brain activation in response to images of food, thus conjunction maps of the brain activation contrasts "hunger versus satiety" and "normal-weight versus over-weight" should have been conducted to find overlapping brain regions activated in response to images of food in overweight participants, and how these may be different than normal-weight participants.

It is plausible that activation of the insular cortex is implicated in hunger and satiety. The insular cortex is acknowledged for its role in interoceptive awareness (Farb, Segal, & Anderson, 2013; Tataranni et al., 1999), including the integration of multisensory information, to establish an emotionally relevant context (Jabbi, Swart, & Keysers, 2007), such as the sight of food (Ohla, Toepel, le Coutre, & Hudry, 2012; Simmons, Martin, & Barsalou, 2005). These findings are in line with the alliesthesia phenomenon; that foods seem more attractive and palatable when hungry (Cabanac, 1979). To this may be responsible the insular cortex, whose reaction to sensory experiences of food may be affected by hunger (Del Parigi et al., 2002; Frank, Kullmann, & Veit, 2013; Frank et al., 2010). Insular cortex activity may be reduced following a meal, and this effect was enhanced in obese compared with lean participants (Gautier et al., 2000; Gautier et al., 2001). Also, obese participants have shown greater insular cortex activation in response to a liquid meal after prolong fast (DelParigi et al., 2005). Together with ventral prefrontal systems, including the orbitofrontal cortex, the insular cortex and operculum are involved in making neutral taste stimulus rated more palatable following exposure to visual images of high energy food cues, compared with a reaction to same taste stimulus after viewing images of low-energy food cues (Ohla, Toepel, le Coutre, & Hudry, 2012). Thus, the anterior insular cortex is highly responsive to anticipated and actual food intake, and this response may be more pronounced in obese individuals (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008).

Only a few studies have examined the difference in brain activation in hunger versus satiety, and in response to food versus nonfood items, in obese + BED. Karhunen et al. (2000) have shown obese + BED women to experience increased cerebral blood flow (rCBF) in the left frontal and prefrontal brain areas, compared with obese and normal weight control participants, and this activation in the obese + BED group was positively correlated with their hunger ratings when fasted and exposed to the sight and smell of a lunch meal . Thus, the evidence available indicates that multiple brain systems mediate our motivation to consume

food. Their function may differ in hunger versus satiety, and interact with multisensory systems activated in response to the sight, smell and taste of food items. When healthy participants are hungry and shown images of food, they are expected to show heightened activity in brain areas implicated in motivation, emotion and decision making, including the orbitofrontal cortex, frontal- and prefrontal brain areas (e.g. anterior/posterior cingulate cortex and caudate nucleus), insular cortex, amygdala, and parahippocampal gyrus. However, it is still not clear how activation of these and other brain areas is different during satiety, and how weight and binge-eating may modulate this activity. Since binge-eating in BED mostly occurs in the absence of hunger, the proposed study suggests examining brain functional response of obese versus obese + BED participants to two brain imaging modalities: 1. "foods versus nonfood", and 2. "high energy food versus low energy food", in the fed state. This would provide additional insight to compare obese versus obese + BED participants with previous studies examining lean participants and to better understand if and how binge eating disorder can modulate this brain response during a state of satiety. The proposed study is expected to shed light on how homeostatic and hedonic pathways in response to the sight of food interact in obese participants versus obese + BED.

CHAPTER THREE: Methods

3.1. Introduction

The project described in this dissertation paper was supplemental to a parent NIH funded study, "fMRI and Ghrelin in obesity and eating disorders" (Dr. Allan Geliebter: PI). The parent study examined neurobiological aspects of BED, using functional magnetic resonance imaging (fMRI) to assess brain activity in response to visual and auditory stimuli of high energy food, low energy food, and nonfood control items. Its main hypotheses were that: 1) for all participants, there will be greater activation in response to the two food groups than to the nonfood control items; 2) obese + BED participants will show greater brain activation in brain regions of interest, i.e., amygdala-hippocampal regions and orbitofrontal cortex, in response to the high energy foods, compared with the control obese group, and 3) the obese group will show a greater differential response between the fasted and the fed states to the two food groups, compared with the binge-eaters. Brain imaging protocol in the parent study included both visual and auditory stimuli, and the experiment was conducted over two days, when participants fasted versus when fed a liquid meal.

The present dissertation project is based on brain imaging data collected in the parent study over one experimental day, when participants were fed a liquid meal. Exposure to images of binge-type food in the absence of food deprivation was used to imitate a binge eating episode, which usually occurs in the absence of hunger. Analyzed in this dissertation project is brain imaging data collected during visual stimulation of food and nonfood items. This is consistent with multiple functional MRI studies of feeding behavior using visual stimuli as conditioned cues eliciting appetitive response (Rothemund et al., 2007; Leidy, Lepping, Savage, & Harris, 2011; Lowe, van Steenburgh, Ochner, & Coletta, 2009). The brain imaging analysis in this dissertation was exploratory in nature by using a whole-brain approach, rather than a “region of interest” analysis used in the parent study. This dissertation also adds to the parent study

multiple psycho-behavioral measures assessed via validated questionnaires. Brain regions found to be significantly different between obese + BED versus obese in response to food versus nonfood stimuli, and in response to high energy food versus low energy food stimuli, were then correlated with psycho-behavioral measures have been found to significantly differ between the groups, to examine possible associations. Thus, the present project compared functional brain imaging data obtained from obese versus obese + BED participants in response to high energy food, low energy food, and nonfood control visual images (office supplies), following a consumption of a liquid meal, and psycho-behavioral constructs were studied in both groups.

The proposed study had two stages; first, several psycho-behavioral measures were assessed and compared between obese + BED versus obese. These measures included behavioral activation [assessed using the behavioral activation system/behavioral inhibition system (BAS/BIS)], anxiety [assessed using the state trait anxiety inventory (STAI)], restraint eating and disinhibition [assessed using the three factor eating questionnaire (TFEQ)]. Most of these psycho-behavioral measures had been examined in the past in obese, but not in obese binge-eaters. Furthermore, no study to date assessed possible associations between these psycho-behavioral constructs and brain function in response to binge-type visual stimuli. The second part of this dissertation project included a brain imaging analysis: in a first level analysis, functional brain activation of all participants as one group, in response to food- versus nonfood items (step 1), and in response to high energy- versus low-energy food items (step 2), was analyzed. In a second level analysis, functional brain imaging data of each group, obese + BED versus obese, was averaged and the two groups compared. Behavioral measures found to be significantly different between obese + BED versus obese in the first part of this study were correlated with brain imaging data obtained in its second part. The main goal of this dissertation project was to generate new hypotheses about psycho-behavioral aspects implicated in BED and how these may be associated with neural mechanisms responsive to visual representation of binge-triggers in BED.

This chapter provides a description of methods employed in the parent study, followed by methodological steps conducted in the dissertation project.

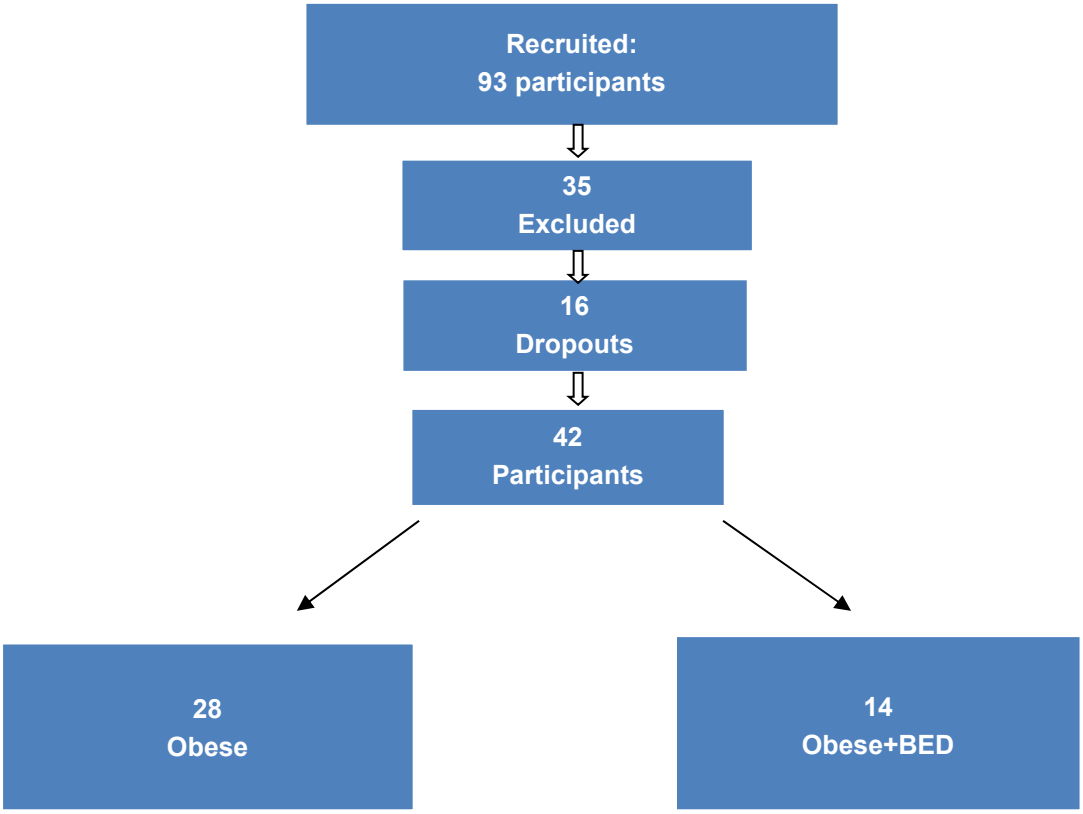
3.2. Study design

3.2.A. Parent study

The parent study investigated functional brain activity of the participants in response to three types of visual and auditory stimuli: high energy food (binge type foods) versus low energy food (non-binge type foods) versus nonfood (office supplies). Visual images were transmitted to the participants via goggles. The high energy food included images of pizza, cakes, ice cream, cookies, chips, and M & Ms. These types of food have been reported by binge-eaters to be consumed during a binge episode (Heaner & Walsh, 2013) and by rigid restraint eaters to be 'forbidden' (Haedt-Matt & Keel, 2011). Low energy food included images of raw vegetables and fruits such as cucumber, tomato, celery, apple, and lettuce. The nonfood stimuli consisted of office supplies, including tape, stapler, rubber bands, and paper clips. These images had been used in Dr. Allan Geliebter's preliminary studies and adopted from validated fMRI protocols matching images for volume, proportionality, colors, shades, and background (Schur et al., 2009). Functional brain imaging data were processed with SPM8. The realigned T2*-weighted brain imaging volumes were slice-time corrected, spatially transformed to a standardized brain (Montreal Neurologic Institute) and smoothed with 8-mm full-width half-maximum Gaussian kernel. These brain images were transferred to the author of the present dissertation project for image analysis (see section 3.4. "Data analysis plan" below). The parent study was conducted between December 2008 and December 2010. Consent form was obtained from each participant, and St.-Luke's Roosevelt Hospital Center's and Teachers College Columbia University's IRB committees approved the study.

3.2.B. Participants

For the dissertation study, we enrolled 42 right-handed (to prevent laterality from affecting brain imaging) obese participants, with a BMI of 30-50 (A BMI > 30 is generally defined as the cutoff for obesity) (National Institute of Health, 1998) and between the ages of 18-65. Participants were recruited by local newspaper advertising, flyer placement at designated areas on the Columbia University and St. Luke's-Roosevelt Hospital Campuses, and by referral from the NY obesity and nutrition research center (NYONRC) outpatient obesity clinic. Flow diagram 1 below shows participants' recruitment: out of 93 initially recruited, 58 were invited for initial consultation. Sixteen dropped out at different stages of the study, and 42 completed the study. Fourteen obese participants were diagnosed with BED (herein, obese + BED) using the Diagnostic and Statistical Manual for mental disorder edition V (DSM-V) (American Psychiatric Association, 2013), and 28 non-binge-eaters (herein, obese) were weight-matched, with male cases of 43% and 54%, respectively.



There were no children under 18 years-of-age involved in this study. Candidates with significant health problems, current and past (at least three months) use of certain prescribed medications, especially those that could affect body weight, such as antidepressants, stimulants, and oral contraceptives, as well as smoking, or excess alcohol (> 3 drinks/day), and those who vigorously exercised for more than 5 hours per week, were excluded. Also excluded were those with known claustrophobia for a scanner enclosure, who have metal implants, non-removable metallic dental retainers, pacemakers, or permanent eyeliner or large tattoos that contain metallic pigment. Women needed to have regular menstrual cycles (28 days +/- 5 d), not be pregnant or lactating, and be at least 1 year postpartum. Those meeting criteria for substance abuse or dependence within the last 6 months or current suicidal ideation were excluded. Candidates with a history of psychotic disorder or hospitalization for

psychiatric illness within the past one year were not eligible. Subjects could not be in treatment for obesity or currently receiving psychotherapy.

In the parent study, participants were stratified by gender before sequence assignment to the counterbalanced conditions of fed (meal) versus fasted (water). Participants were interviewed by phone with selected questions from the Questionnaire on Eating and Weight Patterns – Revised (QEWP-R; Spitzer et al., 1993) to screen for binge-eating disorder. Those who appeared to meet criteria for either obese + BED or obese controls, as assessed by the phone interview, were scheduled for an initial consultation to determine final eligibility. After signing an IRB approved consent form, participants were given the complete QEWP-R to diagnose BED initially, and they were then interviewed with the diagnostic Eating Disorder Examination (EDE) by a trained psychologist to confirm BED status. To be included in the BED group, candidates must have met the DSM-V criteria for binge-eating disorder: "…recurring episodes of eating significantly more food in a short period of time than most people would eat under similar circumstances, with episodes marked by feelings of lack of control. Someone with binge eating disorder may eat too quickly, even when he or she is not hungry. The person may have feelings of guilt, embarrassment, or disgust and may binge eat alone to hide the behavior. This disorder is associated with marked distress and occurs, on average, at least once a week over three months" (American Psychiatric Association, 2013). Those who reported no binge eating were assigned to the 'obese' control group. Based on Dr. Allan Geliebter's past studies, we estimated that about 30% would qualify to be included in the obese + BED group, 30% would report some binge eating, and 40% would report no binge eating.

3.2.C. Parent study procedures

Each participant visited the lab on one initial consultation day and two experimental days, separated by at least one, and no more than two, weeks apart. The first day of the experiment

took place in the lab at St Luke's-Roosevelt Hospital's NY Obesity and Nutrition Research Center (NYONRC) and was conducted over ~4 hours. Participants underwent an initial consultation (including signing consent forms) to confirm inclusion in the study, and a battery of psychological questionnaires (see section 3.2.D. “Psychological aspects” below), body composition assessment, physical exam by a physician, and a liquid meal taste test to determine their preferred flavor of chocolate, vanilla, or strawberry Boost (Novartis Nutrition), a nutritionally complete and palatable shake for the test meal intake on the "fed" experimental day. The experimental phase in the parent study consisted of the second and third visits of the participants to the lab in the morning, following a 12-hour fast. A detailed description of the experimental phase is separately provided below.

The parent study examined hormones implicated in binge eating disorder and possible association with brain function response to binge-triggers. Thus, on the two experimental days (i.e. "fed" versus "fasted" conditions, randomized and counterbalanced) ratings of appetite and blood draws were conducted every 10 minutes starting prior to and for 60 minutes after a 5-minutes ingestion of a 750 ml fixed liquid meal or an equivolumetric water control. Neuroimaging followed at 70 minutes to examine responses to food and nonfood stimuli. The timing of appetite ratings and blood draws is shown below:

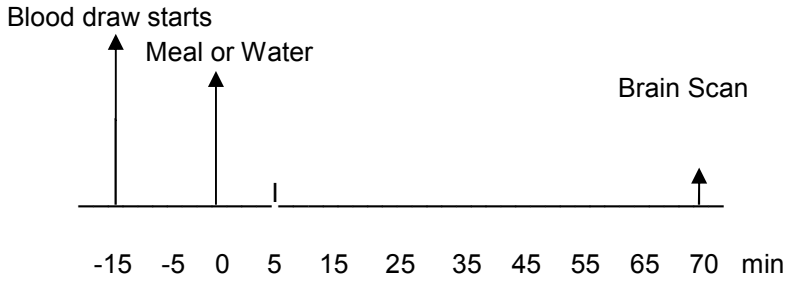


Figure 6: Experimental days schedule: appetite ratings and blood draws, followed by a brain scan

3.2.D. Psychological aspects

On initial consultation visit, participants completed several psychological scales, concerning binge eating, binge-related behaviors, and co-morbid psychopathology. The parent study included multiple questionnaires: the Gormally Binge Eating Scale (Gormally, Black, Daston, & Rardin, 1982), the Questionnaire on Eating and Weight Patterns-Revised (Celio, Wilfley, Crow, Mitchell, & Walsh, 2004), and measures of depression (Zung, 1965).

3.3. Data collection

3.3.A. Measures

The dissertation study added the following measures:

Behavioral Activation/Behavioral Inhibition was measured using the Behavioral Inhibition System/Behavioral Activation System instrument (BIS/BAS), a self-report scale based on a psychobiological model intended to assess BIS and BAS sensitivities, each associated with an independent neuro-physiological system (Carver, & White, 1994). The BIS scale includes items reflecting reactions to anticipation of punishment. The BAS scale is multi-dimensional and it includes three sub-scales: a *Drive* scale pertaining to a tendency to persistently pursue desired goals, a *Fun Seeking* scale reflecting a desire for new rewards and a willingness to approach a potentially rewarding event at a given moment, and a *Reward Responsiveness* scale, focusing on positive responses to the occurrence or anticipation of a reward.

Factor analysis of the BIS/BAS items was conducted on a sample of 732 college students, 374 women and 358 men (Carver and White, 1994), and in another sample of 2684 participants ages 18-79 (Jorm et al., 1998), and test-re-test reliability assessed on a sub-group of 113 college students. Convergent and discriminant validity were assessed using multiple other scales measuring closely related, but different, contrasts (Carver and White, 1994; Jorm et al., 1998), and correlations confirmed that the BIS/BAS is related to these measures but also somewhat distinguishable, as expected. Criterion validity was also conducted: the BIS

has been tested in response to a punishment cue (i.e. nervousness-provoking cue) in 69 college-age students and was found to be a reliable predictor of vulnerability to nervousness as a function of exposure to the proper cue. In another study, Carver and White (1994) exposed 90 college-age participants to a rewarding cue and correlated their level of reported happiness throughout the experiment with the BAS subscales. As expected, BAS sensitivity predicted positive emotional reactions to the cues impeding reward.

Dietary Restraint and Disinhibition were measured using the Three Factor Eating Questionnaire (TFEQ; Stunkard & Messick, 1985), a 51-item self-report inventory designed to assess three aspects of eating behavior: cognitive restraint, disinhibition, and hunger, which relates to BED and eating behavior (Karlsson, Persson, Sjostrom, & Sullivan, 2000). The TFEQ Disinhibition subscale is designed to assess overeating that occurs after exposure to various cognitive, social, and emotional triggers. Higher scores on the TFEQ Disinhibition subscale are associated with increased eating and overweight (Westenhoefer, 1991). The TFEQ Cognitive Restraint subscale is designed to measure the tendency to consciously restrict food intake either to prevent weight gain or to promote weight loss by controlling over energy intake or types of food eaten. The TFEQ has good psychometric properties (Stunkard & Messick, 1985) and good reliability and validity (Gorman & Allison, 1995), and the Disinhibition and Cognitive Restraint subscales demonstrate adequate internal consistency (Stunkard & Messick, 1985; Laessle, Tuschl, Kotthaus, & Pirke, 1989). The TFEQ is also called the Eating Inventory (EI; Stunkard & Messick, 1988), and a shorter version has been more recently developed (Karlsson, Persson, Sjostrom, & Sullivan, 2000; Angle et al., 2009; de Lauzon et al., 2004). In this 18-item version of the TFEQ, *Emotional Eating* has replaced the *Disinhibition* subscale, the latter which has been consistently shown to be associated with BED (Colles, Dixon, & O'Brien, 2008; Downe, Goldfein, & Devlin, 2009). Thus, in the dissertation study the original 51-item TFEQ has been used.

Anxiety was measured using the State Trait Anxiety Inventory (STAI), a self-report measure of trait anxiety (A-Trait) and state anxiety (A-State), which are highly correlated (Spielberger, Gorsuch, & Edward, 1970). The A-State consists of twenty statements that evaluate how respondents feel "*right now, at this moment*" and the A-Trait consists of twenty statements that assess how people "*generally feel*". In the dissertation study A-State has been used, since in this project the construct of anxiety was assessed on the initial consultation day, following a thorough assessment of binge-eating. Since our main goal was to assess anxiety in response to the presence of binge-triggers, we used A-State to reflect one's sensitivity to binge eating disorder psychopathological constructs. Moreover, the A-State not only assesses how people feel "*right now*", but it can also evaluate how they anticipate they would feel in a variety of hypothetical situations, such as when they encounter a binge-trigger.

Results of reliability, internal consistency and validity studies for the STAI fall as expected. A-Trait reliability for males and females varied between .86 and .73, while A-State varied between .54 and .27 for a retest period of 20 days and 104 days, respectively. This data is consistent with the theoretical notions of A-Trait and A-State, since A-Trait is a more stable measure of personality and A-State tests transitory anxiety. Internal consistency yielded coefficients between .83 and .92 for A-State and concurrent validity with other A-Trait measures, MAS and IPAT, yielded correlations between .75 and .85 for college students and psychiatric patients, respectively (Hedberg, 1972). Construct validity is demonstrated by the fact that the A-State items consistently vary with different experimental states of stress while A-Trait items do not.

3.3.B. Experimental phase (days 2 and 3)

For each participant the key experimental procedures took place on two non-consecutive days (at least a week, and maximum two weeks, apart), following a 12 hour overnight fast. The "fed" condition day is described below since it is the only experimental day relevant to this

dissertation project. The participants were called and reminded of their appointment the day before the experimental day took place. Participants were instructed to consume a pre-fast meal between 8 and 9 pm the night before the experiment, and to consume only water until the experiment. They were also instructed to consume a meal containing approximately 4180 kJ (1000 kcal), and to be free of alcohol and caffeine. On the morning of the experimental day, participants came to the fMRI Research lab at Columbia University Medical Center and filled out a standard questionnaire, confirming fasting status, hours of sleep, and ratings of wellness. If a subject reported not feeling well, the test day was postponed. Participants were asked to use the restroom and drink 1 cup of water to alleviate any thirst. Menstrual cycle day in women was tracked, although it has not affected our previous results. Participants then received a liquid drink of their preferred flavor of Boost, chosen on the initial consultation day (each 750 ml), and they were then escorted to the scanner. The schedule on the "fed" experimental day is detailed in Box 1 below:

-9:40-9:50 am: First appetite rating,

-9:50-10:50 am: fixed (750 ml) liquid meal (or water), followed by appetite ratings (60 min),

- 10:50-11:00 am: restroom break, positioning in scanner (10 min),

-11:00-11:45 am: functional brain imaging scan (45 min),

-11:45 am-12:15 pm: Questionnaires (30 min)

Box 1: “fed” experimental day schedule

Right before scanning, participants were asked to use the restroom. Metal objects and credit cards were stored in a locker. Each participant wore a headset and goggles and was positioned in the scanner with a head coil. Participants were exposed to three categories of visual stimuli during the fMRI scan: highly energy (binge type) food (HEF; ≥ 3.5kcal/g), healthy low energy food (LEF; < 1 kcal/g), and neutral nonfoods (office supplies). The images were transmitted to the goggles. For the baseline, participants were asked to fixate on a central

crosshair. To reduce boredom and motivate the participants to attend to the stimuli during the brain scan, they were asked to focus on the stimuli and try to remember them for a recognition test after the run.

3.3.C. Brain imaging scan

For each stimulation run, in a block design, participants were presented with 10 items, each for 4 seconds, for a total of 40 seconds. The stimulation epoch was preceded by a 52-seconds pre- and followed by a 40 seconds post-stimulus baseline (while crosshair centered in a black background), when no images were shown. For each category, i.e. HEF, LEF, and office supplies, there were two nonconsecutive runs of 10 stimuli of the same category. The two runs each had novel but similar stimuli to reduce habituation. The order of presentation varied across participants in a randomized block design. After each run, participants rated hunger and desire to eat, and as an independent measure of their attention, they were asked if they saw three particular stimuli during the run, of which two were correctly included. After the fMRI is complete, and while still in the scanner, participants rated each of the visual stimuli (colored printed pictures) for likeability and for (the food stimuli) the likelihood to binge-eat.

3.4. Data analysis plan

In the dissertation study, Excel version 2007 was used for psycho-behavioral data analysis, and, for the brain imaging analysis, SPM version 8. Questionnaires' scores were compared between obese + BED and obese participants using an independent sample t-test ($P < .05$), and brain imaging data was computed for the contrasts "food versus nonfood" and "HEF versus LEF" in a first level analysis, for all participants as one group. In a second level analysis, obese + BED versus obese were compared, for each contrast, to find differences in brain activation between the groups. A whole-brain exploratory analysis was used, and once results indicated brain areas significantly different between the groups, parameter estimates of

brain activation were extracted and averaged for each group. Results of behavioral measures found to be significantly different between obese + BED versus obese were correlated with parameter estimates of the brain imaging results to find the relationships between the behavioral measures and brain activation in response to binge-triggers.

3.4.A Data management

All participant charts with identifying information (e.g., names, dates of birth, etc.) were stored in locked file cabinets accessible only by authorized study personnel. The data sources were reviewed for accuracy and completeness immediately upon receipt, and an effort was made to obtain any missing data from the participant. Data was entered into a main network database, password protected for use by study personnel. The entered data was printed and then double checked by research assistants against the original sources.

3.4.B. Timetable and payments

Participants were recruited and enrolled on an ongoing basis. We expected exclusion of 30% during screening after the initial consultation and a 10% attrition rate in the study. In the parent study, participants visited three times over a 2-week period and received $350 and public transportation costs (round trip metro card) for participation. This payment was prorated for those who do not complete the study.

CHAPTER FOUR: Results

4.1. Introduction

Forty-two right handed men [n = 21] and women [n = 21] participated in the study. Fourteen were diagnosed with obese + BED and 28 were obese, according to the DSM-V criteria (Marek, R. J., Ben-Porath, Y. S., Ashton, K., & Heinberg, L. J., 2014). All were assessed using the Eating Disorder Examination interview (Fairburn & Copper, 1993). Both groups did not differ in BMI or age (table 1), and they were right-handed, weight-stable (±5%) ≥ 3 months, nonsmoking, premenopausal, not pregnant (urine pregnancy test), with no history of neurological, psychiatric, or medical conditions (e.g. diabetes) and not taking any medications or enrolled in obesity treatment (e.g. exercise > 5h/week). The protocol was approved by the Institutional Review Boards of Columbia University, St. Luke's Roosevelt Hospital Center, and Teachers College, Columbia University.

Table 1: **Participants' characteristics**

Groups (DSM-V)	**Average age (years)**	**Average BMI [Lbs/(inches)^2]**	**Percent Fat (BIA*)**	**Males (%)**	**Females (%)**
Obese + BED	38.29 (±11.08)	36.25 (±6.38)	40.04 (±6.63)	6 (43%)	8 (57%)
Obese	35.01 (±7.7)	35.76 (±5.37)	(±8.27)38.95	15 (54%)	13 (46%)
T-test (P ≤ .05)	1.12 (p = 0.27)	0.26 (p = 0.8)	0.38 (p = 0.71)		

*BIA = Body Impedance Analysis

On initial consultation, participants' height, weight, and percent body fat (via Body Impedance Analysis) were measures, and BMI was calculated. Participants selected their preferred flavor of milkshake (Boost; Novartis Nutrition): chocolate, strawberry, or vanilla, a nutritionally complete shake, to be consumed on the experimental day, prior to the brain scan. The participants also completed psycho-behavioral questionnaires assessing multiple parameters (Anxiety; Restraint; Disinhibition; BAS), and they went through physical testing to determine their eligibility to participate in the study.

4.2. Psycho-behavioral assessment

Results of comparing between the obese + BED versus obese on their scores on the psycho-behavioral questionnaires are detailed in table 2 below. The contrasts of 'Behavioral Inhibition System' (BIS) and 'Restraint' did not differ between the groups at $p \leq 0.05$, therefore it is not shown in the table below.

Table 2: Differences in scores of the behavioral measures (per DSM-V category)

	BAS (reward)	SD	Anxiety	SD	Disinhibition	SD
Obese + BED	15.86	3.48	39	13.75	10.57	3.13
Obese	18.36	2.00	29.92	9.49	6.96	3.37
P value	0.005***		0.02**		0.002***	
Cut-off point (adults)	16‴		39-40⁑		8θ	

**Significant at $p \leq 0.05$

***Significant at $p \leq 0.017$ (following Bonferroni correction for multiple comparisons)

⁑Dennis, Boddington, & Funnell, 2007

‴Davis et al., 2008

θ Marchesini et al., 2004

At a $p \leq 0.05$, the obese + BED group differed from the obese group on the 'anxiety (state)' and 'disinhibition' measures, with obese + BED scoring higher [Anxiety (state): 39 versus 29.92, respectively; $t = 2.43$, $p = 0.02$; Disinhibition: 10.57 versus 6.96, respectively; $t = 3.34$, $p = 0.002$]. The obese group scored significantly higher than the obese + BED group on the 'reward-responsiveness' subscale of the BAS (BAS-reward: 18.36 versus 15.86, respectively; $t = -2.96$, $p = 0.005$). Following Bonferroni correction for multiple comparisons, significance level changed to a $p \leq 0.017$, leaving 'disinhibition' and 'BAS (reward)' significantly different between the groups. Both measures were then correlated with the brain imaging data (see section "correlation of brain imaging with behavioral measures" below). The 'anxiety (state)' did not reach significance at $p \leq 0.017$, but it is of note that the Bonferroni correction method is relatively conservative (Perneger, 1998), thus it is plausible that with less rigid correction method the contrast of 'anxiety (state)' would have been significantly different between the groups. However, in the present dissertation project, Bonferroni correction method was selected due to the exploratory nature of this study, and the contrast of 'anxiety (state)' did not reach significance. Thereby, it was not correlated with the brain imaging results.

4.3. Brain imaging

On the evening prior to the experimental day, participants consumed a pre-fast meal of approximately 4180 KJ (1000 kcal) around 7-8 pm, followed by a 12-hour overnight fast. In the morning, they ingested 750 ml Boost (Mead Johnson; 24% protein, 55% carbohydrate, and 21% fat, 750 kcal) of their preferred flavor in the lab 95-minutes prior to the brain scan, and they were then escorted to the scanner. A 1.5-Tesla twin-speed fMRI scanner (General Electric) with quadrature RF head coil and 65cm bore diameter was used. Participants wore a head-set and goggles with their head placed in a passive restraint (pads and tape around the head) to minimize motion. Three-plane localization (x, y, & z) was used to verify head position. A head coil (MRI devices Corporation, Gainesville, FL) was used to improve the signal to

noise ratio. Total time in the scanner was about 60 minutes. In each run, 36 axial scans of the whole brain were acquired, consisting of 25 contiguous slices (4mm thick), with a 19 cm x 19 cm field of view, an acquisition matrix size of 128 x 128, and 1.5 mm x 1.5 mm in plane resolution. The first three scans of each ran (12 sec) were discarded to attain magnetic equilibrium. The axial slices were parallel to the AC/PC line. T2*-weighted images with a gradient echo pulse sequence (echo time = 60 ms, repetition time = 4sec, flip angle = 60°) were acquired with matched anatomic high resolution T1-weighted scans.

Brain imaging data were analyzed in two steps. Statistical Parametric Mapping version 8 (SPM8; Wellcome Department of Imaging Neuroscience, London, UK) was used for 1st and 2nd level analyses. Prior to statistical analyses, the realigned T2*-weighted volumes were preprocessed in a few steps, including slice-time correction, spatial transformation to a standard brain (Montreal Neurological Institute) and smoothing with an 8-mm full-width half-maximum Gaussian kernel. The six runs for each participant were concatenated together to create a single run per participant (i.e. 33 * 6 = 198 total time points). Block regressors were included in each participant's 1st level model to account for the mean of each run within each session. In this model additional covariates for motion, as well as global signal and spikes, were included to account for potential sources of noise. First level regressors of interest were created by convolving the onsets of each trial (high energy food, low energy food, office supplies) with the canonical Hemodynamic Response Function (HRF) with duration of 40 second. Given the specific hypotheses of this project, neural activation in response to food versus nonfood, as well as in response to high energy food versus low energy food, was examined. The specific contrasts submitted for a 2nd level analysis included: 1) food minus nonfood, 2) high energy food minus low energy food. Also submitted for a 2nd-level analysis were the effects of each stimulus type on BOLD signal response: 1) high energy food positive effect, 2) high energy food negative effect , 3) low energy food positive effect , 4) low energy food negative effect ,5) office supplies positive effect, and 6) office supplies negative effect.

The 2-nd level analysis was conducted to compare between the groups, i.e. obese + BED versus obese. The above 2 contrast maps and 6 effect magnitude maps were submitted to group random effects models using multiple regression analysis with binge-eating category (DSM-V) as a covariate of interest. First statistical map of binge-eating category (independent variable) and brain activation in response to visual images of food versus nonfood (dependent variable) was generated to find significant differences between the groups. A whole-brain analysis was conducted, with a threshold of $p \leq 0.005$, uncorrected, combined with a cluster-size threshold of $k \geq 50$ contiguous voxels. This analysis generated 17 significant clusters of brain activation, of which 11 were significant at a $p \leq 0.005$, combined with a cluster size of 88 continues clusters or above (i.e. $k \geq 88$) (table 3), after correction for multiple comparisons using the Monte Carlo multiple testing correction (URL: http://afni.nimh.nih.gov/sscc/gangc/mcc.html).

Table 3. Brain activation in response to visual cues of food versus nonfood (obese + BED > obese)

Region	Hemisphere	Cluster size	X	Y	Z	Peak Intensity
Insula*	Right	100	34	-4	12	4.11
Insula	Left	70	-38	-14	6	4.32
Cingulate cortex*	Right	312	8	8	44	4.75
Posterior cingulate*	Left	130	-38	-64	18	4.63
Posterior cingulate*	Right	313	24	-60	8	3.94
Middle temporal	Left	97	-38	-64	18	4.63

gyrus*						
Cuneate gyrus*	Left	90	-38	-64	18	4.63
Cuneate gyrus*	Right	214	16	-84	26	4.01
Lingual gyrus	Left	73	-38	-64	18	4.63
Lingual gyrus*	Right	126	24	-60	8	3.94
Middle occipital gyrus	Left	51	-38	-64	18	4.63
Pre-cuneate gyrus	Left	50	-38	-64	18	4.63
Brodmann area 30	Right	82	24	-60	8	3.94
Middle occipital gyrus	Right	51	24	-60	8	3.94
Inferior parietal lobule	Left	58	-34	-38	20	4.46
Postcentral gyrus*	Left	138	-66	-22	22	4.2
Brodmann area 19*	Right	89	16	-84	26	4.01
Inferior parietal lobule*	Right	97	54	-38	24	3.91
Brodmann area 32*	Right	118	8	8	44	4.75
Brodmann area 24	Right	53	8	8	44	4.75

*Significant at p ≤ 0.005 and k ≥ 88 (corrected with Monte Carlo multiple testing correction)

In another 2nd level analysis, the obese + BED and obese groups were compared using the contrast HEF versus LEF, to identify significant differences between the groups in BOLD signal in response to visual images of high energy food versus low energy food. A statistical map of binge-eating category as the independent variable and brain activation in response to HEF versus LEF as the dependent variable was generated in a whole-brain analysis, with a threshold of $p < 0.05$, uncorrected, combined with a cluster-size threshold of $k \geq 10$ contiguous voxels. Compared with the first contrast map (i.e. food versus nonfood), a larger p value and a smaller cluster size were used in this analysis (i.e. HEF versus LEF), since highly specific distinction within the food category was postulated to generate weaker BOLD signal, which would have been missed with a smaller threshold and/or larger cluster size, leading to failure to reject a false null hypothesis (Type II error). This analysis generated 33 significant clusters, of which three were significant at a $p < 0.01$ (corrected with Monte Carlo), combined with a cluster size of 119 continues voxels or above (i.e. $k \geq 119$, corrected with Monte Carlo) (table 4).

Table 4: Brain activation in response to visual cues of high energy food versus low energy food (obese + BED > obese)

Region	Hemisphere	Cluster size	X	Y	Z	Peak Intensity
Culmen	Right	97	34	-48	-36	Not found
Culmen	Left	10	-32	-44	-28	2.02
Fusiform gyrus	Right	15	42	-60	-14	2.76
Middle temporal gyrus	Right	11	62	-46	-16	2.5

Inferior parietal lobule	Left	46	-62	-30	36	2.44
Postcentral gyrus	Right	57	12	-38	66	3.52
Postcentral gyrus	Left	109	-20	-42	66	2.79
Brodmann area 2	Right	12	66	-26	40	2.11
Brodmann area 19	Left	47	-32	-82	32	2.53
Superior occipital gyrus	Left	37	-32	-82	32	2.53
Pre-cuneate gyrus	Right	63	18	-72	52	2.56
Pre-cuneate gyrus	Left	121	-18	-70	52	2.68
Middle frontal gyrus*	Left	427	-16	-8	50	3.57
Middle frontal gyrus	Right	81	32	-6	52	3
Brodmann area 40	Left	21	-62	-30	36	2.5
Brodmann area 2	Left	12	-62	-30	36	2.5
Brodmann area 8	Left	48	-16	-8	50	3.57
Brodmann area 6*	Left	198	-16	-8	50	3.57
Brodmann area 6	Right	55	8	-8	68	2.39

Superior frontal gyrus*	Left	152	-16	-8	50	3.57
Medial frontal gyrus	Left	88	-16	-8	50	3.57
Cingulate gyrus	Left	49	-16	-8	50	3.57
Brodmann area 24	Left	22	-16	-8	50	3.57
Superior parietal lobule	Right	13	18	-72	52	2.56
Superior parietal lobule	Left	51	-18	-70	52	2.68
Brodmann area 7	Left	83	-18	-70	52	2.68
Precentral gyrus	Left	18	-20	-24	52	1.95
Precentral gyrus	Right	31	32	-12	66	2.24
Paracentral lobule	Left	36	-4	-48	64	2.53
Paracentral lobule	Right	82	12	-38	66	3.52
Brodmann area 5	Left	36	-20	-42	66	2.79
Brodmann area 3	Left	12	-20	-42	66	2.79
Brodmann area 4	Right	24	12	-38	66	3.52

*Significant at $p < 0.01$ and $K \geq 119$ (corrected with Monte Carlo multiple testing correction)

Thus, eight different brain areas were found to be significantly different between the groups, obese + BED versus obese. These eight brain areas were identified using the Montreal Neurological Institute (MNI) atlas (Evans, Janke, Collins, & Baillet, 2012); a standardized brain space according to which each participant's brain was spatially normalized and registered. Spatial normalization was done by linear scaling to the x, y, and z axes (tables 3 and 4), to identify brain MNI coordinates for group analyses and identification of brain regions with significant differential activation between the groups. A 5 mm sphere was built around each of the eight MNI coordinates - seven for the contrast "food versus nonfood" and one for the contrast "HEF versus LEF". Some of the coordinates identified are junctions between multiple brain areas, thus some of the spheres included more than one brain area. For the 1st contrast, "food versus nonfood", seven brain coordinates significantly differred between the groups (table 3): 1) right insula, 2) right cingulate cortex and Brodmann area #32, 3) left posterior cingulate cortex, middle temporal gyrus and cuneate gyrus, 4) right posterior cingulate cortex and lingual gyrus, 5) right cuneate gyrus and Brodmann area #19, 6) left postcentral gyrus, and 7) right inferior parietal lobule. For the contrast HEF versus LEF, one significant MNI with three brain areas has been found: left middle frontal gyrus, Brodmann area #6, and the superior frontal gyrus.

Parameter Estimates of peak blood oxygen level dependent signal in each MNI tested were extracted for each participant. The parameter estimates of all participants in each group were averaged and plotted on a bar graph (figures 7-14). The parameter estimates were calculated using average blood oxygen level dependent signal in response to a stimulus, and participants' responses to each stimulus were separately plotted in order to understand neuronal activity fluctuations in response to each stimulus. Thus, parameter estimates were extracted, averaged and plotted for each group separately, in response to each type of stimulus. For each group, the food category consisted of the average parameter estimates in response to high energy food + low energy food, i.e. (HEF+LEF)/2, and the nonfood category included the averaged parameter estimates in response to office supplies.

Figures 7-14 (“a” series) show neuronal activity differences between the groups in response to food versus nonfood, and high energy food versus low energy food, in all MNI coordinates (x, y, & z) found to significantly differ between the groups. The “b” series shows neuronal activity fluctuations in response to each of the stimuli, in each group separately, and the “c” series shows graphical images of the brain with the location of each MNI identified to significantly differ between the groups.

The results of the significant differences ($p \leq 0.005$) between the groups in BOLD signal amplitude in the right insula (functions to integrate somatosensory experiences with internal state), in response to visual stimuli of food versus nonfood, are plotted below (figure 7a through figure 7c). The obese + BED group experienced an increase, while the obese group experienced a decrease, in BOLD signal in response to the contrast “food versus nonfood” (0.19 versus -0.09, respectively; $t = 3.53$, $p = 0.001$). Figure 7b shows the average BOLD signal of each group, in response to the food and nonfood stimuli. In response to images of food [i.e. (HEF + LEF)/2], there was a greater BOLD signal in the obese + BED group compared with the obese group, but this difference was not significant ($t = .69$, $p = 0.5$). However, in response to the images of OS, the BOLD signal of obese+ BED was significantly lower than that of obese (-0.09 versus 0.14, respectively; $t = -3.32$, $p = 0.002$).

Figure 7a: BOLD signal amplitude for "food versus nonfood" (per DSM-V category), in MNI: 34 -4 12 (right insula)

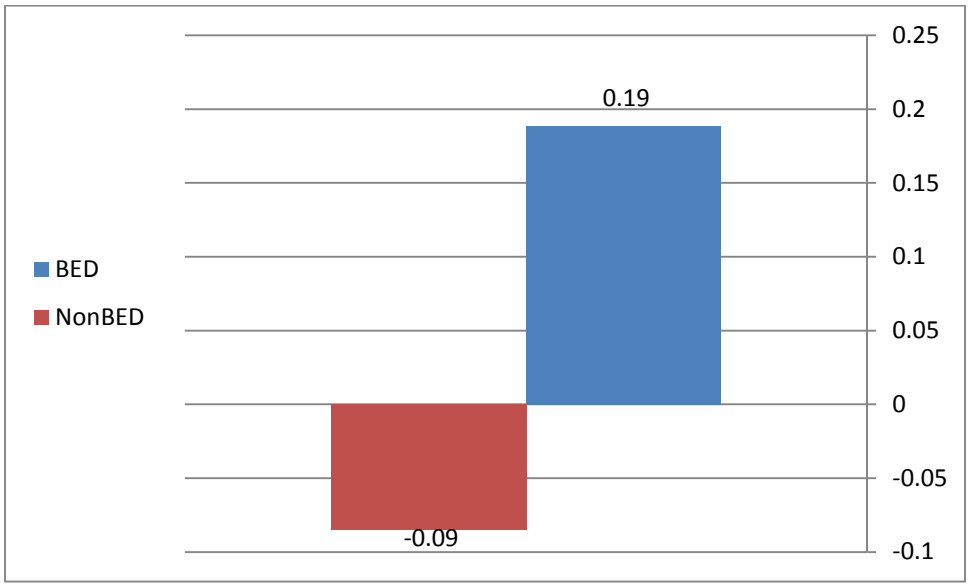


Figure 7b: Effect of food and nonfood (per DSM-V category), in MNI: 34 -4 12 (right insula)

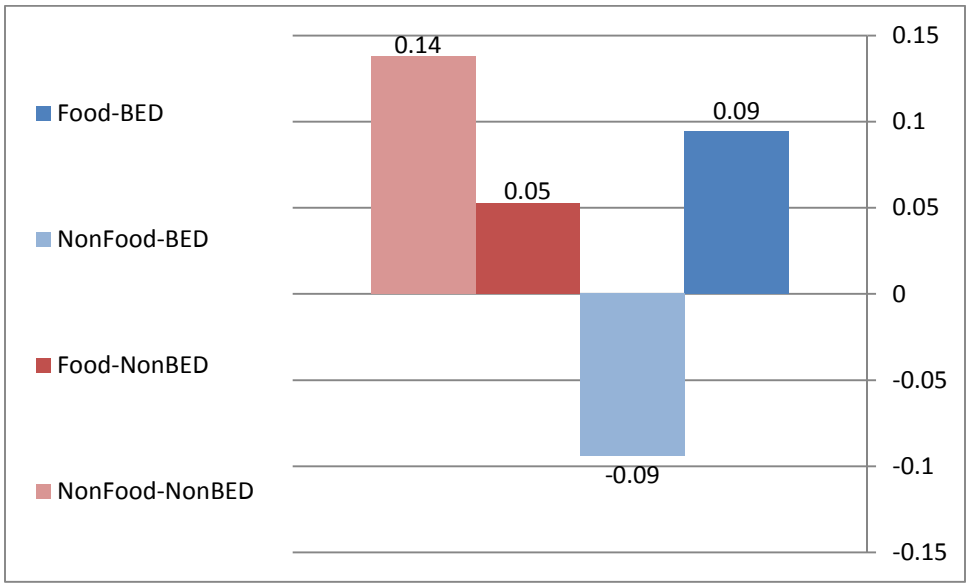
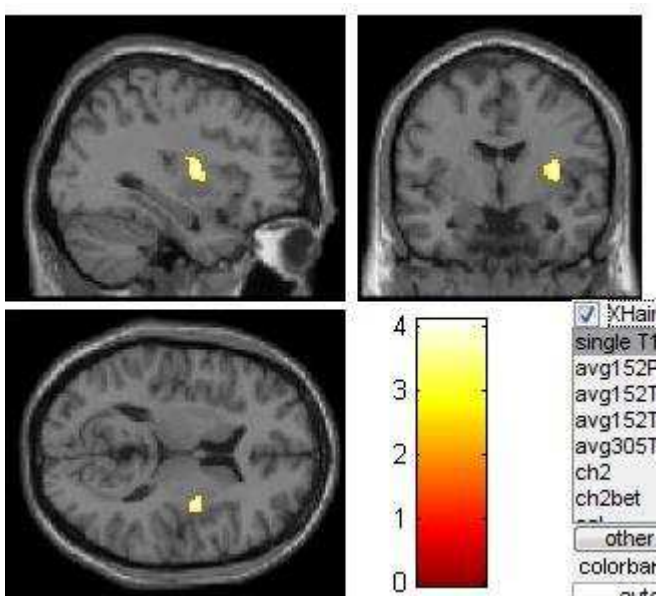


Figure 7c: Right insula activation in response to “food versus nonfood”



Figures 8a through 8c show the results of the comparison ($p \leq 0.005$) between obese + BED versus obese on their responses to “food versus nonfood” in the right cingulate cortex and Brodmann area #32 (function to process sensations, cognitions, thoughts and emotions). Obese + BED participants showed an increase, while the obese participants showed a decrease, in BOLD signal in this area (0.37 versus -0.11, respectively; $t = 4.06$, $p = 0.003$). In the right cingulate cortex and Brodmann area #32 positive effect of food [(HEF+LEF/2)] in obese + BED participants was low and not significantly different from the positive effect of food in the obese (0.02 versus 0.01, respectively; $t = .25$, $p = 0.8$). In contrast, obese + BED participants had significantly lower brain activation in response to nonfood images, compared with the obese (-.28 versus .12, respectively; $t = -3.28$, $p = 0.002$; figure 8b).

Figure 8a: BOLD signal amplitude for "food versus nonfood" (per DSM-V category), in MNI: 8 8 44 (right cingulate cortex-Brodmann area #32)

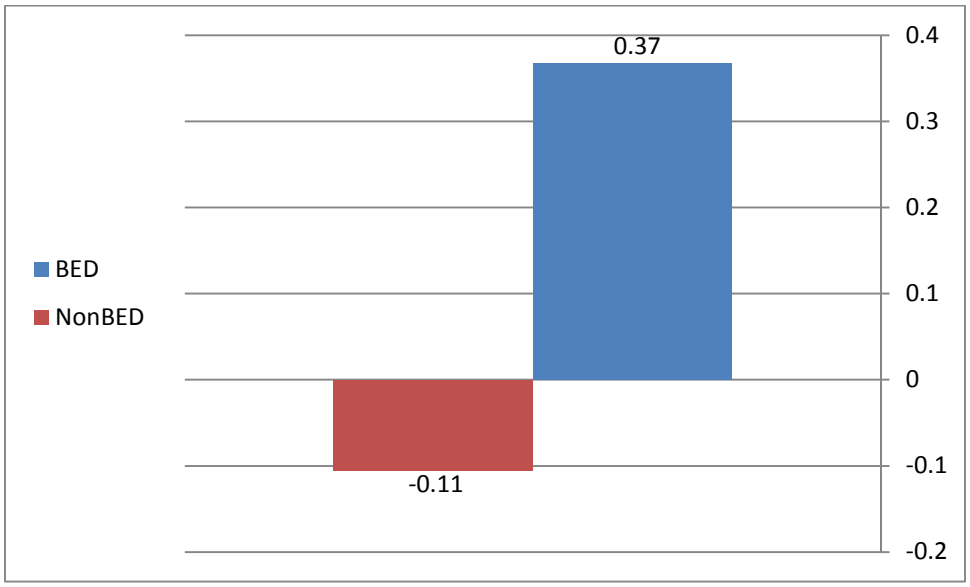


Figure 8b: Positive effect of food and nonfood (per DSM-V category), in MNI: 8 8 44 (right cingulate cortex-Brodmann area #32)

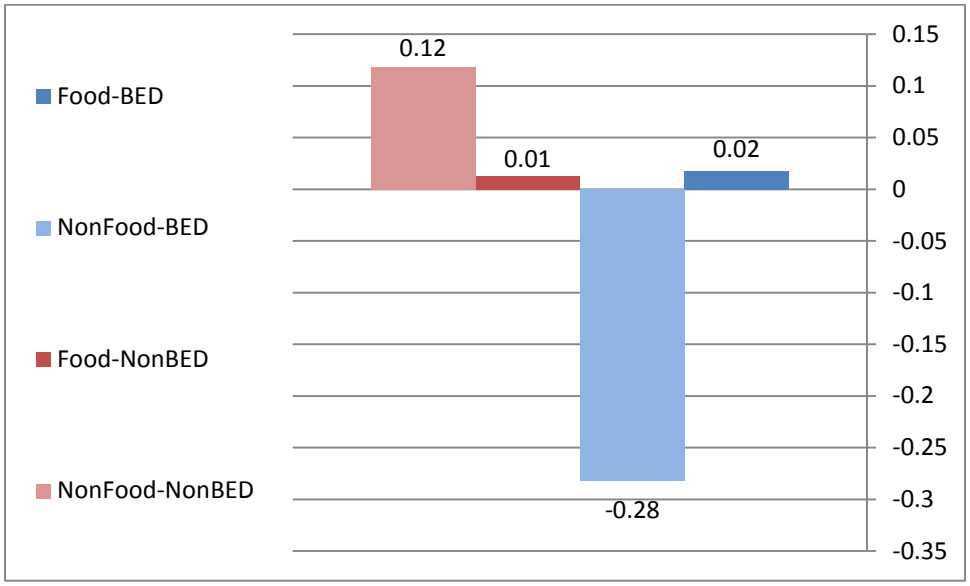
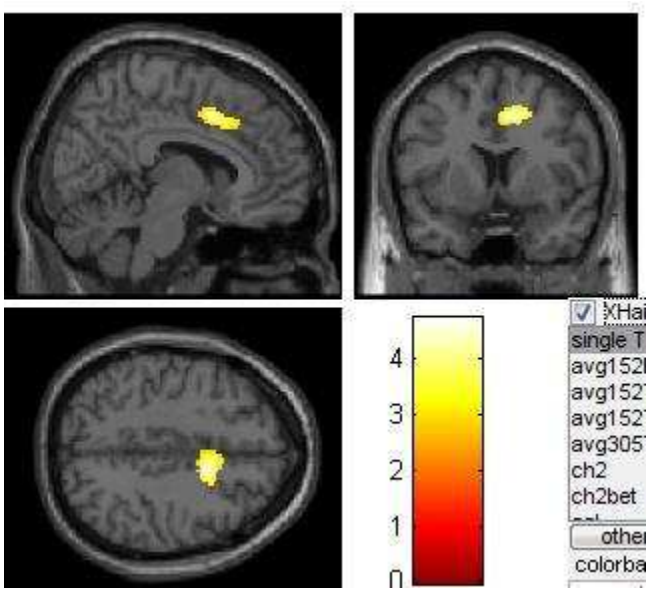


Figure 8c: Brain activation in the right cingulate cortex-Brodmann area #32 in response to "food versus nonfood"



In the left posterior cingulate cortex (functions as a higher order integration of sensory functions and memory), left middle temporal gyrus (higher order visual information), and left cuneate gyrus (processing of visual functions and somatosensation), BOLD response of obese + BED participants to "food versus nonfood" increased, while that of the obese decreased, and this was significant ($p \leq 0.005$; 0.12 versus -0.23, respectively; $t = 3.92$, $p = 0.000$; figure 9a). In both obese + BED and obese, BOLD signal in this MNI decreased in response to visual images of food (-0.06 versus -.13, respectively; $t = .87$, $p = 0.39$; figure 9b), while in response to nonfood images, BOLD signal decreased in obese + BED but increased in obese (-0.18 versus 0.09, respectively; $t = -2.3$, $p = 0.03$, figure 9b), but that was not significant.

Figure 9a: BOLD signal amplitude for "food versus nonfood" (per DSM-V category), in MNI: -38 -64 18 (left posterior cingulate cortex, middle temporal gyrus, cuneate gyrus)

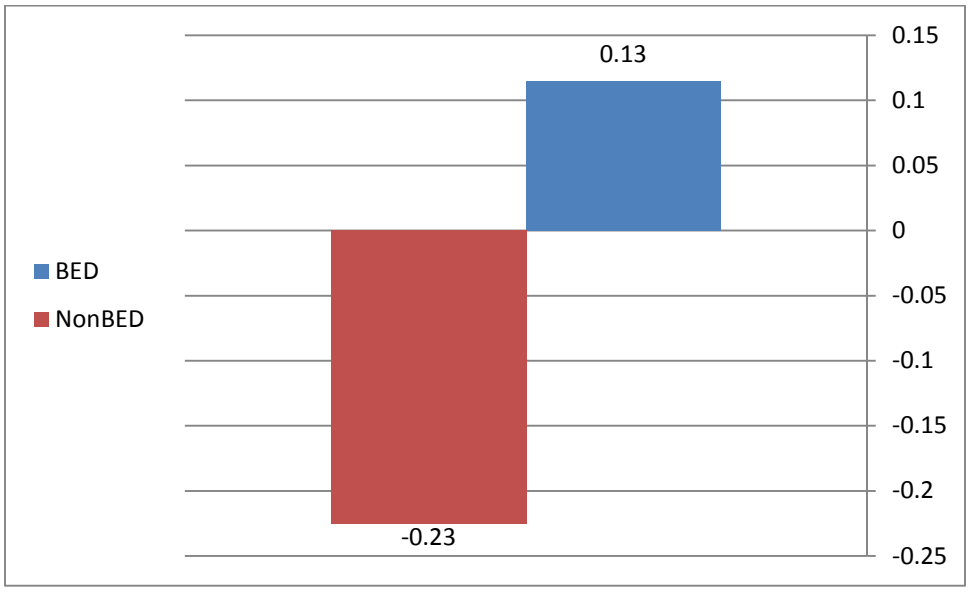


Figure 9b :Positive effect of food and nonfood (per DSM-V category), in MNI: -38 -64 18 (left posterior cingulate cortex, middle temporal gyrus, cuneate gyrus)

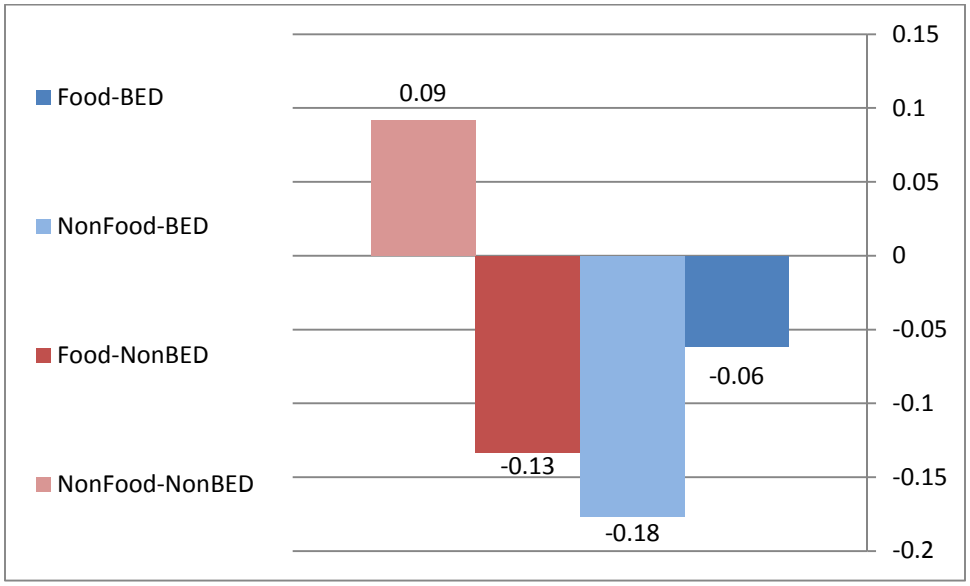
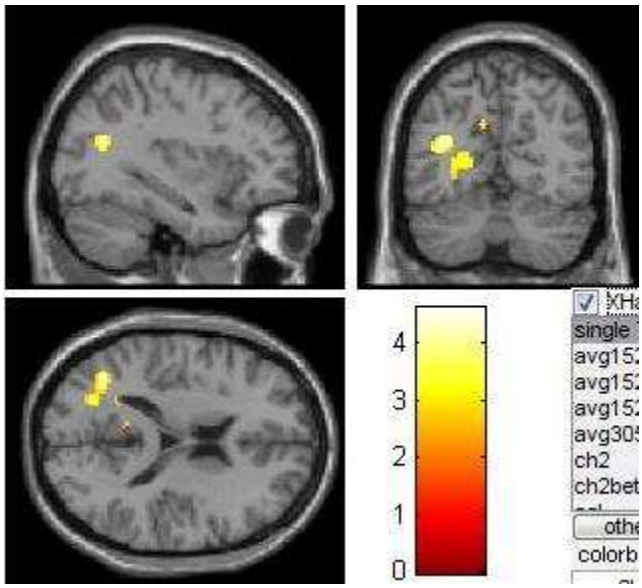


Figure 9c: Brain activation in the left posterior cingulate cortex, left middle temporal gyrus, & left cuneate gyrus in response to "food versus nonfood"



The BOLD signal response in the right posterior cingulate cortex (higher order integration of sensory functions and memory) and right lingual gyrus (visual area and somatosensation) in obese + BED participants increased in response to “food versus nonfood”, but in the obese it decreased, and these differences were significant ($p \leq 0.005$; 0.25 versus -0.17, respectively; $t = 3.5$, $p = 0.001$). As seen in figure 10b, in response to images of food, obese + BED participants showed an increase, while obese participants showed a decrease, in BOLD signal. However, these differences between the groups did not reach significance (0.06 versus -0.12, respectively; $t = 1.82$, $p = 0.08$). There was also a difference between the groups in their BOLD response to nonfood images, with obese + BED showing a decrease, and the obese showing an increase, in their BOLD signal, but this too did not reach significance (-.19 versus 0.06 for obese + BED and obese, respectively; $t = -1.86$, $p = 0.071$).

Figure 10a: BOLD signal amplitude for "food versus nonfood" (per DSM-V category), in MNI: 24 -60 8 (right posterior cingulate cortex, right lingual gyrus)

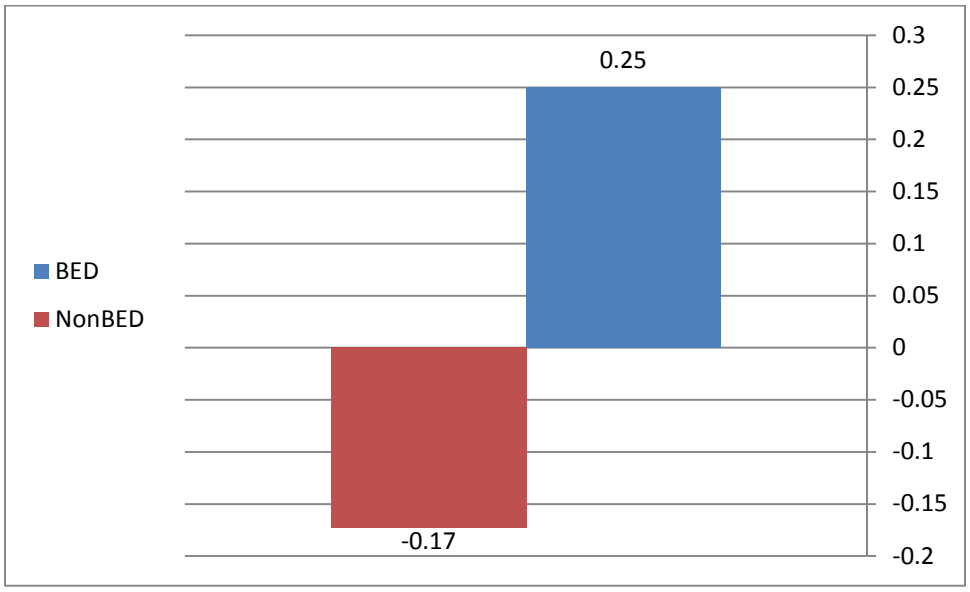


Figure 10b: Positive effect of food and nonfood (per DSM-V category), in MNI: 24 -60 8 (right posterior cingulate cortex, right lingual gyrus)

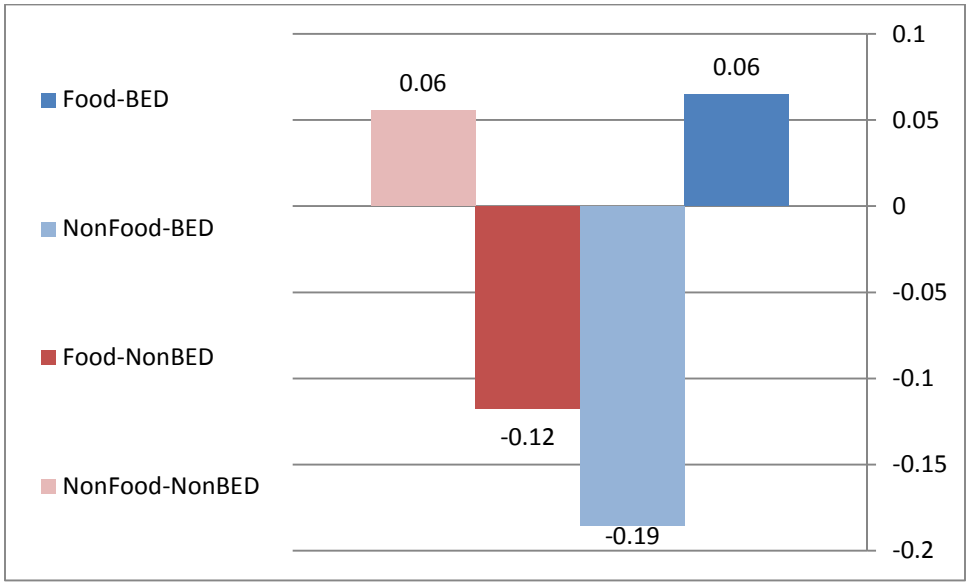
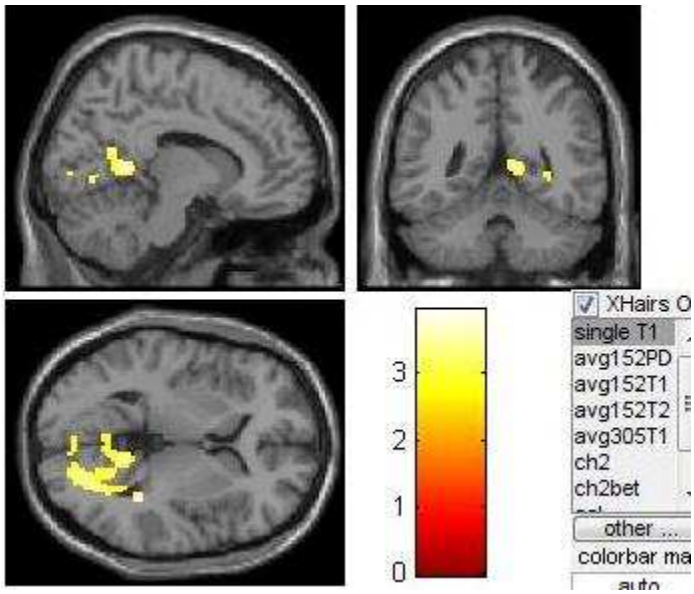


Figure 10c: Brain activation in the right posterior cingulate cortex & the right lingual gyrus in response to "food versus nonfood"



In the right cuneate gyrus (processing of visual information and somatosensations) and Brodmann area #19 (processing of visual information: color, motion, & depth), obese + BED participants experienced an increase, while obese experienced a decrease, in BOLD signal in response to "food versus nonfood", and this difference was significant ($p \leq 0.005$; 0.09 versus -0.31, respectively; $t = 3.45$, $p = 0.001$; figure 11a). Both obese + BED and obese showed a decrease in BOLD signal in response to images of food (-0.15 versus -0.19, respectively; $t = .23$, $p = 0.82$; figure 11b), while in response to nonfood stimuli, obese + BED showed a decrease, while the obese showed an increase, in BOLD signal, but the difference between the groups was not significant (-0.26 versus 0.12, respectively; $t = -2.13$, $p = 0.04$).

Figure 11a: BOLD signal amplitude for "food versus nonfood" (per DSM-V category), in MNI: 16 -84 26 (right cuneate gyrus-Brodmann area # 19)

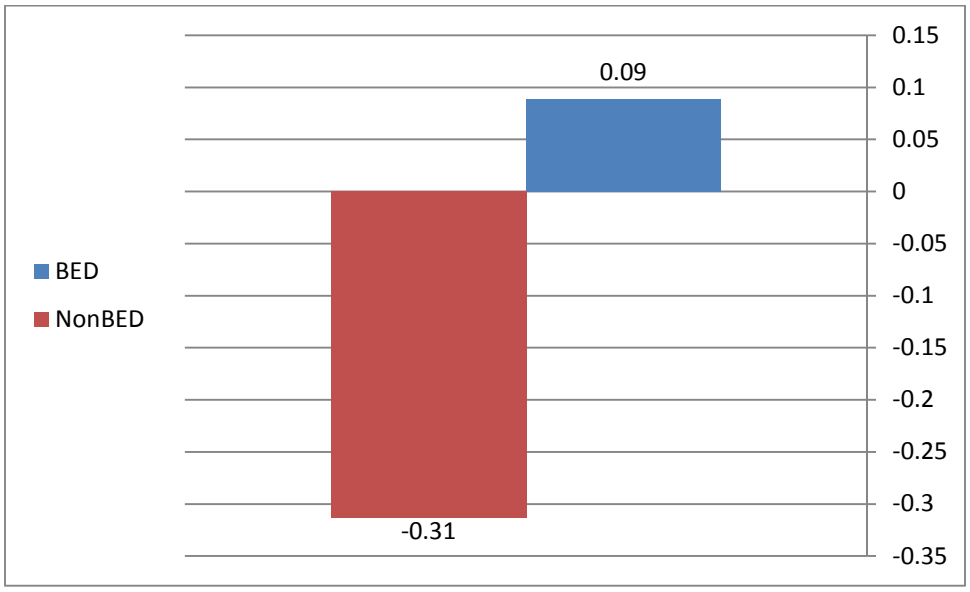


Figure 11b: Positive effect of food and nonfood (per DSM-V category), in MNI: 16 -84 26 (right cuneate gyrus-Brodmann area # 19)

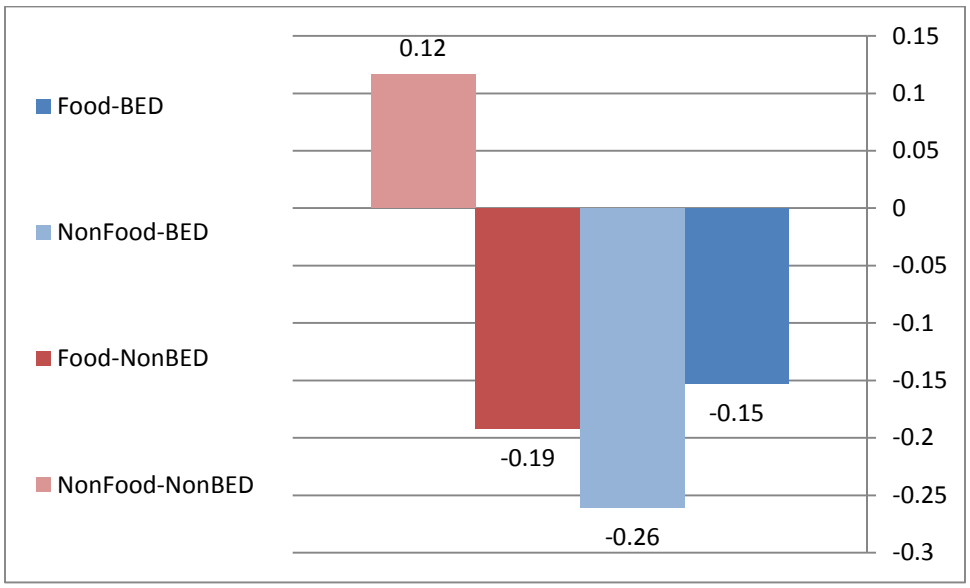
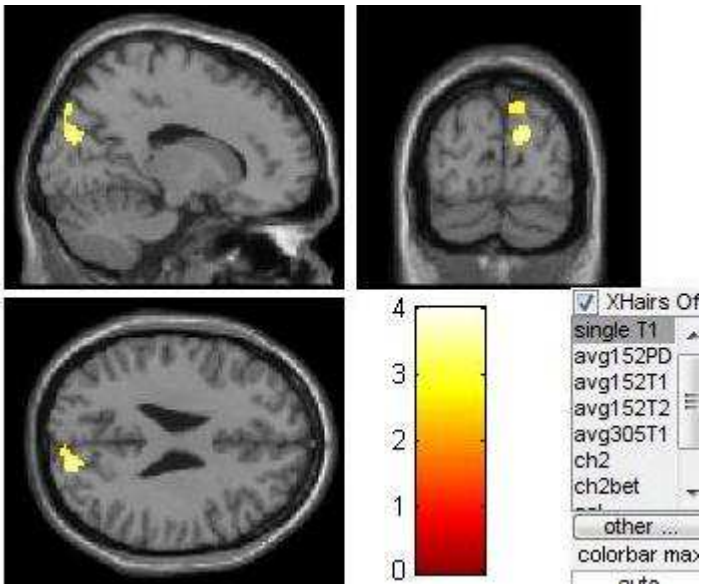


Figure 11c: Brain activation in the right cuneate gyrus-Brodmann area # 19 in response to "food versus nonfood"



In the left postcentral gyrus (primary somatosensory area), obese + BED showed an increase in BOLD signal in response to "food versus nonfood", while the obese showed a decrease, and this difference between the groups was highly significant ($p \leq 0.005$; 0.38 versus -0.12, respectively; $t = 3.42$, $p = 0.002$; figure 12a). Looking at the effect of each stimulus type separately (figure 12b), both obese + BED and obese showed a decrease in BOLD signal in response to images of food, ($t = -.13$, $p = .897$), but in response to images of nonfood there was a significant difference between the groups, with obese + BED showing a decrease in BOLD signal and the obese showing an increase (-0.47 versus 0.04, respectively; $t = -3.29$, $p = 0.002$).

Figure 12a: BOLD signal amplitude for "food versus nonfood", per DSM-V category, in MNI: 64 -10 36 (left postcentral gyrus)

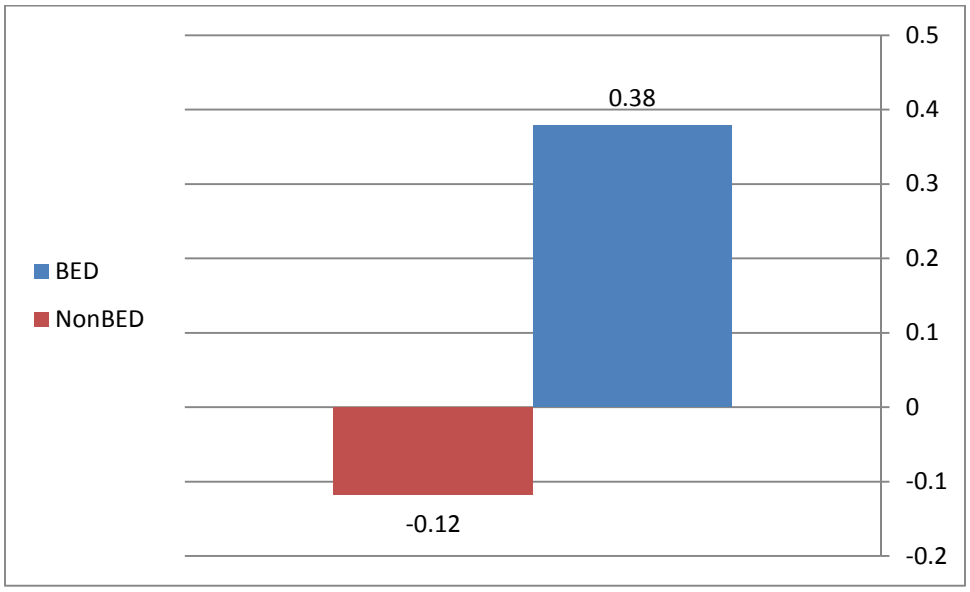


Figure 12b: Positive effect of food and nonfood, per DSM-V category, in MNI: 64 -10 36 (left postcentral gyrus)

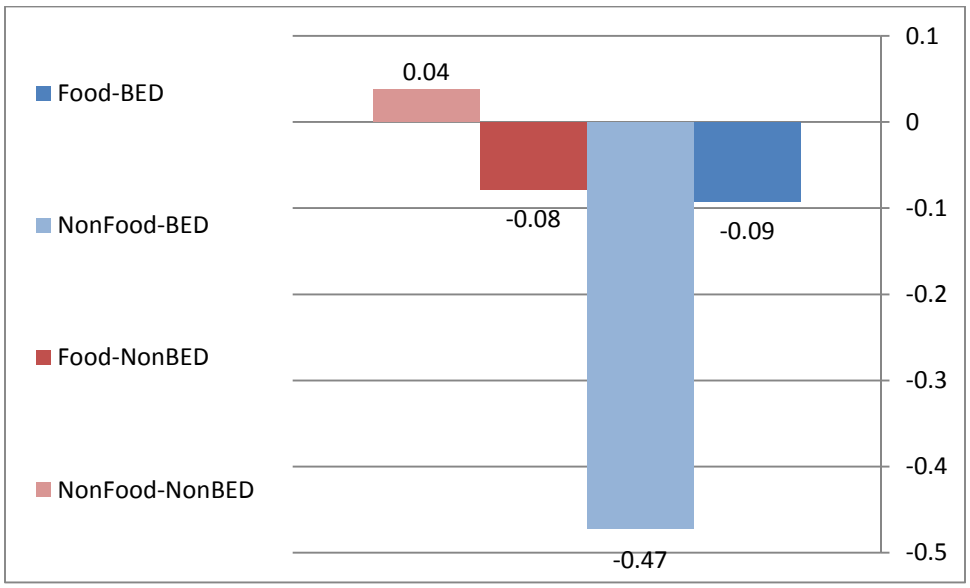
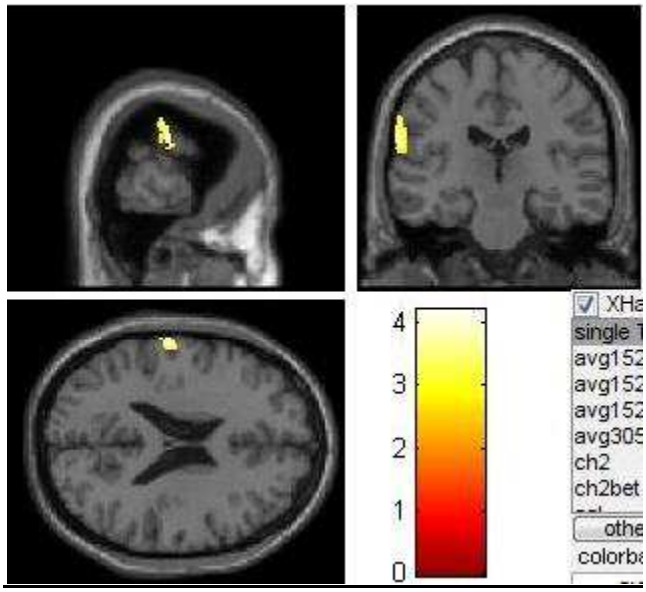


Figure 12c: Brain activation in the left postcentral gyrus in response to "food versus nonfood"



Lastly, participants' response to "food versus nonfood" significantly differed ($p \leq 0.005$) in the right inferior parietal lobule (MNI: 54 -38 24; part of somatosensory cortex, it functions to integrate diverse sensory information). In this brain region, obese + BED showed an increase in BOLD signal amplitude, while the obese showed a decrease (0.28 versus -0.11, respectively; $t = 3.54$, $p = 0.001$; figure 13a). Looking at each stimulus type separately (figure 13b), obese + BED and obese showed a decrease in BOLD signal amplitude in response to images of food ($t = .23$, $p = .82$), while in response to nonfood images there was a highly significant difference between the groups, with obese + BED showing a decrease in signal and the obese showing an increase (-0.32 versus 0.05, respectively; $t = -4.17$, $p = 0.000$).

Figure 13a: BOLD signal amplitude for "food versus nonfood", per DSM-V category, in MNI: 54 -38 24 (right inferior parietal lobule)

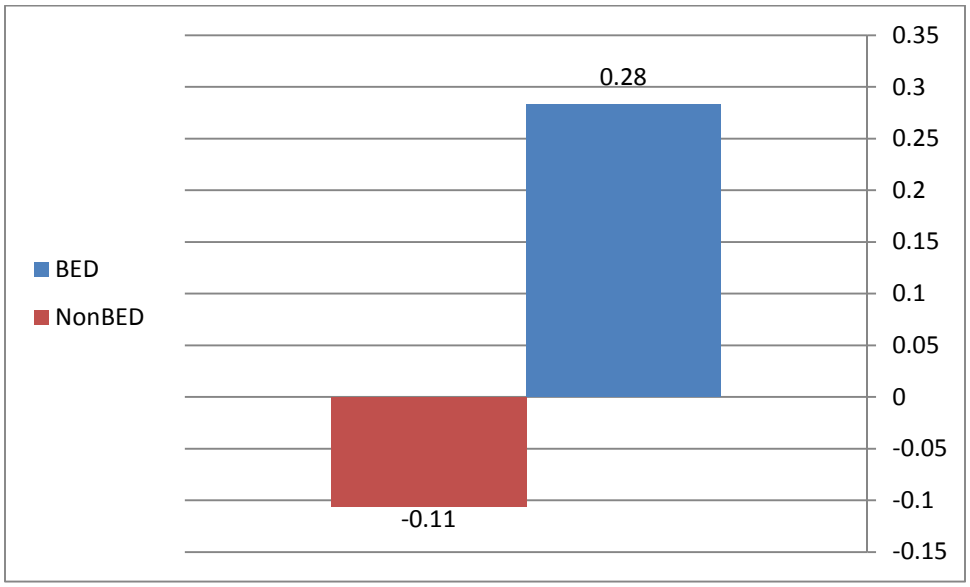


Figure 13b: Positive effect of food and nonfood, per DSM-V category, in MNI: 54 -38 24 (right inferior parietal lobule)

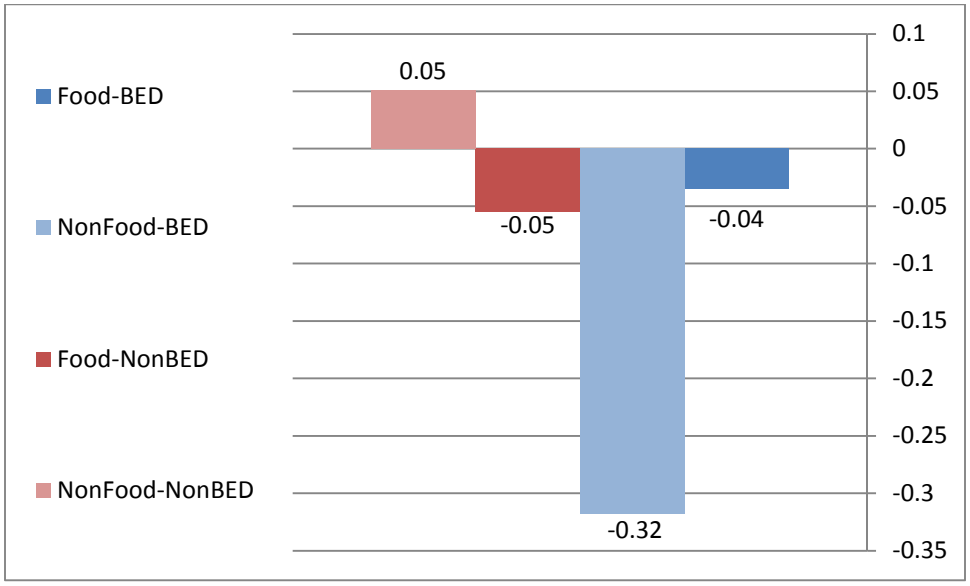
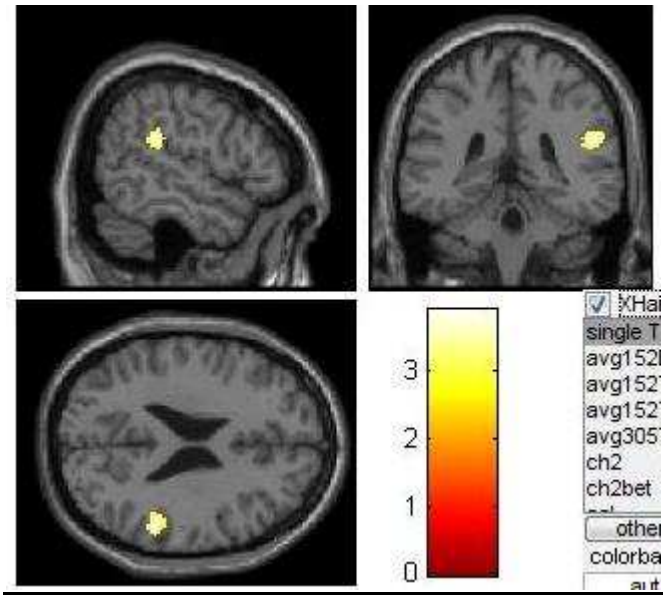


Figure 13c: Brain activation in the right inferior parietal lobule in response to "food versus nonfood"



In response to the contrast "HEF versus LEF", there was a significant difference between the groups in one MNI region: -16 -8 50, pertaining to the left middle frontal gyrus (part of the prefrontal association cortex, responsible for thought, cognition, movement, and planning), Brodmann area #6 (processing of motor behaviors that occur in response to emotions, drives, and movement planning), and left superior frontal gyrus (part of the prefrontal association cortex, responsible for thought, cognition, movement, and planning; figure 14a), with a $p \leq 0.01$ and a cluster size of $k \geq 119$, adjusted for multiple comparisons. In these brain regions, obese + BED showed an increase in BOLD signal amplitude and the obese showed a decrease (0.14 versus -0.075, respectively; $t = 3.17$, $p = 0.003$; figures 14a & 14c). Similarly, the groups differed in their response to each type of stimuli, with obese + BED showed an increase, while the obese showed a decrease, in BOLD signal amplitude in response to images of HEF (0.1 versus -0.03, respectively; $t = 2.03$, $p = 0.05$). In response to LEF, obese + BED showed a decrease, while the obese experienced an increase, in signal amplitude;

however, these differences were not significant (-0.04 versus 0.04, respectively; t = -1.5, p = 0.141).

Figure 14a: BOLD signal amplitude for "HEF versus LEF", per DSM-V category, in MNI: -16 -8 50 (left middle frontal gyrus, Brodmann area #6, and left superior frontal gyrus)

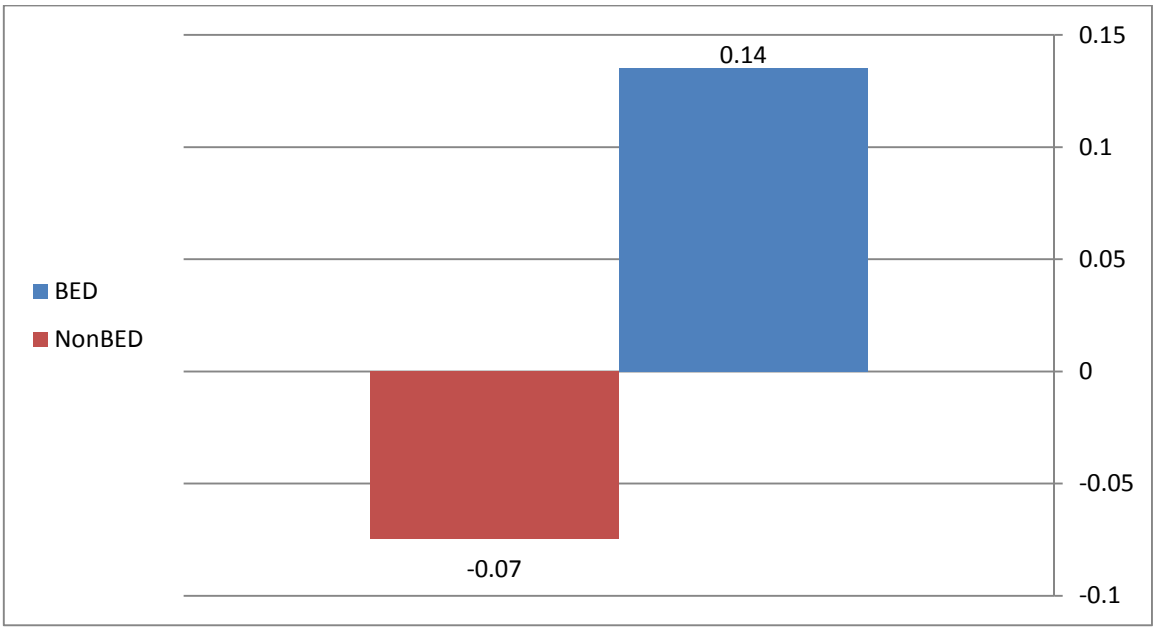


Figure 14b: Positive effect of HEF and LEF, per DSM-V category, in MNI: -16 -8 50 (left middle frontal gyrus, Brodmann area #6, and left superior frontal gyrus)

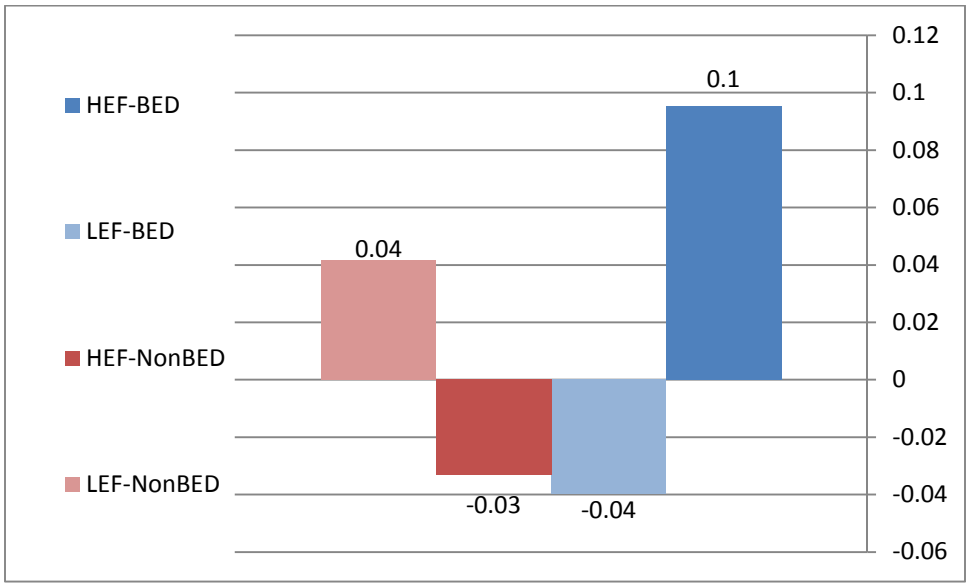
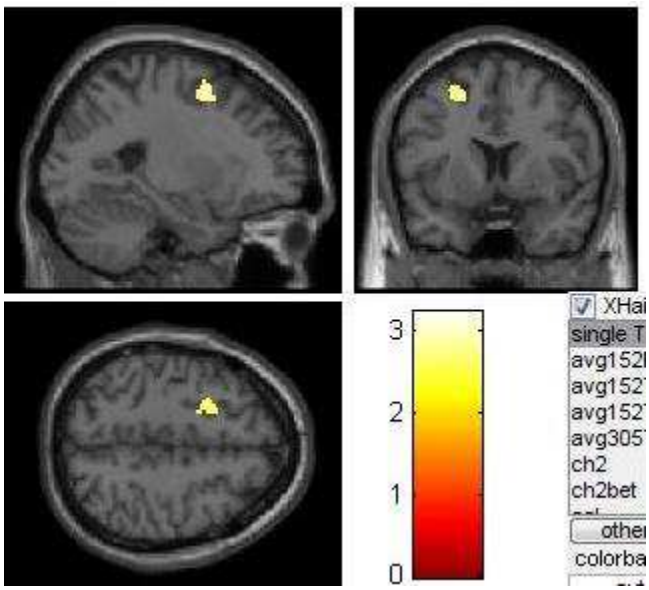


Figure 14c: Brain activation in the left middle frontal gyrus, Brodmann area #6, & left superior frontal gyrus in response to "HEF versus LEF"



4.4. Correlation between brain imaging and psycho-behavioral measures

For each of the eight significant regions of interest detailed above (seven for the contrast "food versus nonfood", and one for the contrast "HEF versus LEF") parameter estimates of each region of interest were correlated with 'disinhibition' scores in each group of participants (table 5). Pearson's correlation coefficients were calculated and converted into a z distribution scores using an online calculator (http://vassarstats.net/rdiff.html) to assess the significance of the difference between the two independent samples in the relationships between brain activation and psycho-behavioral measures in each group. The two sample groups were assumed to have a normal distribution, thus a 2-taled significance test between the z values (corresponding to the correlation coefficients of the two groups) was chose, and thereby an alpha of 0.05 was used. The results of the calculations are detailed in table 5 below: the correlation between brain activation in the right anterior cingulate cortex - Brodmann area #32 and disinhibition scores was negative (-.49) in the obese + BED group and significantly different ($p = .018$) from the positive correlation (0.32) between the same two variables in the

obese group. Similarly, the correlation between brain activation in the left postcentral gyrus and disinhibition scores was negative (-0.54) in the obese + BED group and significantly different (p = 0.008) from the positive (0.37) correlation between the two variables in the obese group.

Table 5: Correlation between brain activation and 'disinhibition' scores

Brain area (region of interest)	**Pearson's r & direction of relationships in obese + BED**	**Pearson's r & direction of relationships in obese**	**Difference between groups***
Right insula	-0.33 negative	0.3 positive	p = 0.08 z = -1.75
Right ACC*-BA[a]32**	**-0.49** **negative**	**0.32** **positive**	**p = 0.018** **z = -2.36**
Left PCC***, cuneate gyrus, MTG**	-0.06 negative	0.35 positive	p = 0.254 z = -1.14
Right PCC***, lingual gyrus	0.07 positive	0.37 Positive	p = 0.379 z = -0.88

Right cuneate gyrus-BA[a]19	-0.03 negative	0.3 Positive	p = 0.363 z = -0.91
Left postcentral gyrus	**-0.54** **negative**	**0.37** **Positive**	**p = 0.008** **z = -2.66**
Right IPL***	-0.33 negative	0.25 Positive	p = 0.112 z = -1.59
Left MFG***-BA[a]6-SFG***	-0.11 negative	0.01 Positive	p = 0.764 z = -0.3

* P ≤ 0.05 for the difference between the groups in the correlation of 'Disinhibition' and brain activation, using a Z distribution with 2 tales

** ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; MTG = middle temporal gyrus; IPL = inferior parietal lobule; MFG = middle frontal gyrus; SFG = superior frontal gyrus

[a] BA = Brodmann area

Figures 15 and 16 below show correlations between disinhibition scores in each group and brain activation in the anterior cingulate gyrus-Brodmann area #32 and the left postcentral gyrus, respectively.

Figure 15: Correlation between 'disinhibition' scores and right cingulate cortex–Brodmann area #32 activation in response to “food versus nonfood”, per DSM-V category

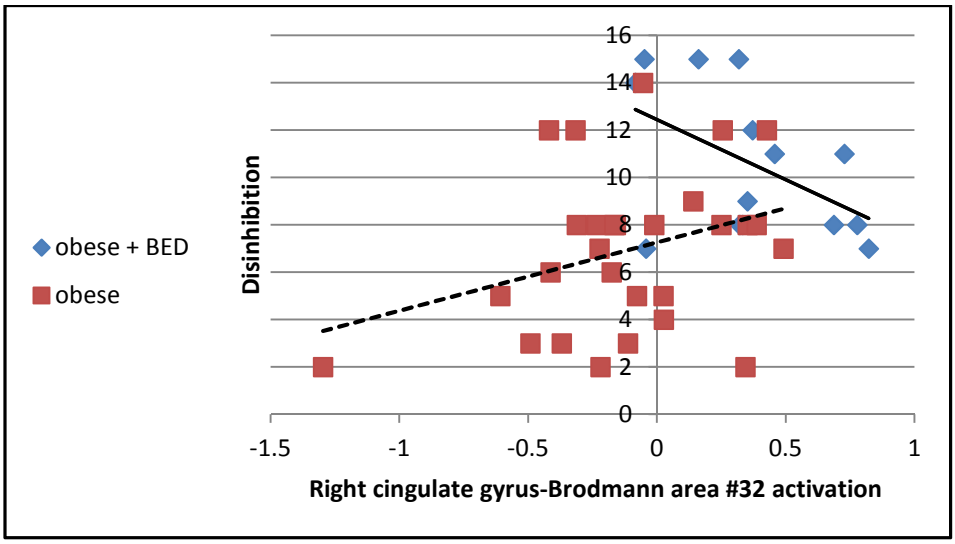


Figure 16: Correlation between 'disinhibition' scores and brain activation in the left postcentral gyrus in response to “food versus nonfood” (per DSM-V category)

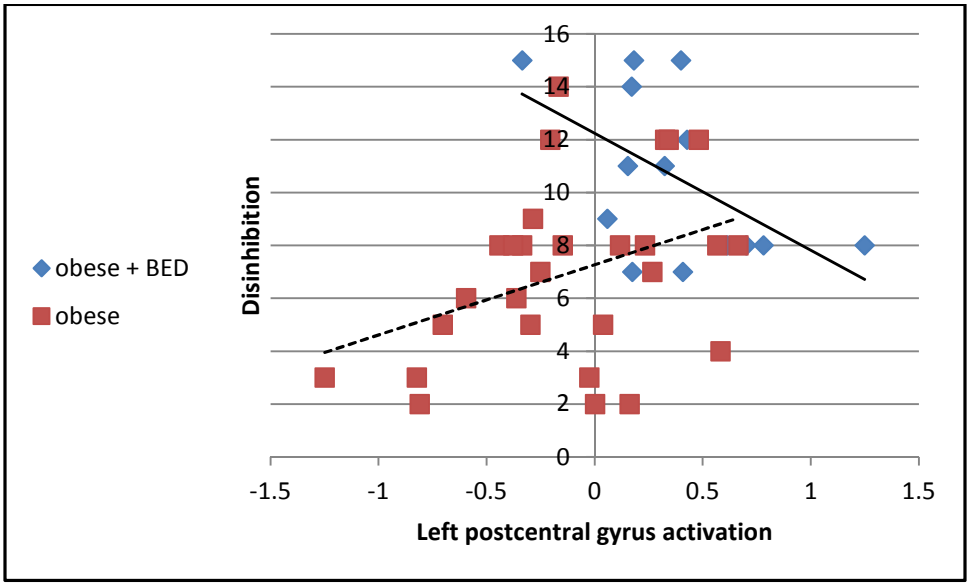


Table 6 below shows the correlation between brain activation of the eight regions of interest above and ‘BAS(reward)’ scores in each group, as well as the differences in z scores

(corresponding to the correlation coefficient) between the groups and their significance. Table 6 can attest to weak correlations between 'BAS(reward)' scores and brain activation in either group. Furthermore, no significant differences were detected between the groups in the correlation between brain activation in any of the brain regions examined and 'BAS(reward)' scores.

Table 6: Correlation between brain activation and 'BAS(reward)' scores

Area	**Pearson's r & direction of relationships in obese + BED**	**Pearson's r & direction of relationships in obese**	**Difference between groups (P ≤ 0.05)***
Right insula	-0.06 negative	0.02 positive	p = 0.803 z = -.25
Right ACC***	-0.36 negative	0.18 positive	p = .134 z = -1.5
Left PCC***, cuneate gyrus, MTG***	-0.06 negative	0.35 positive	p = 0.254 z = -1.14
Right PCC***, lingual	-0.07 negative	0.07 positive	p = 0.711 z = -0.37

gyrus			
Right cuneate gyrus, BA[a]19	0.1 positive	0.06 positive	p = 0.92 z = 0.1
Left postcentral gyrus	-0.3 negative	0.11 positive	p = .267 z = -1.11
Right IPL***	-0.17 negative	-0.03 negative	p = 0.704 z = -0.38
Left MFG***, BA[a]6, SFG***	0.19 positive	-0.09 negative	p = 0.453 z = 0.75

* P value for the difference between the groups in the correlation between 'BAS(reward)" and brain activation

***ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; MTG = middle temporal gyrus; IPL = inferior parietal lobule; MFG = middle frontal gyrus; SFG = superior frontal gyrus

[a] BA = Brodmann area

CHAPTER FIVE: Discussion

In the present project, two groups of obese individuals, obese + BED and obese controls, were scanned in an fMRI machine while shown images of food- and nonfood items, and their brain activation in response to the images examined. Participants were brain scanned an hour following a consumption of a pre-load meal, such that participants' drive for eating in the absence of hunger, common in BED (De Zwaan, 2001; Marcus & Kalarchian, 2003; Zocca et al., 2011), can be studied. On a different day, the participants answered questionnaires related to the psychopathology of BED, and differences between obese + BED versus obese were examined. An analysis of their answers to the questionnaires revealed significant differences between the groups and clinically significant findings. Out of the four behavioral measures studied, the construct of 'disinhibition' was significantly greater in obese + BED, while 'restraint' was high for both groups but did not significantly differ between them. Second in the level of significance of the difference between the groups was the construct of 'reward responsiveness', measured via the Behavioral Activation Scale. It is of note that the construct of 'anxiety' was significant at $p \leq 0.05$ but not at $P \leq 0.017$, following a Bonferroni correction for multiple comparisons. It is likely that with less conservative correction method the 'anxiety' construct would have reached statistical significance. However, since this is an exploratory study, the more conservative Bonferroni correction method was chosen. Possible loss of power due to this reason may be a limitation of this dissertation study. Striking is the findings that the obese + BED showed clinically-significant anxiety level, reaching the cut-off score of 39 on this scale, while the obese did not reach a clinically significant score. Considering the fact that both groups were exposed to the same controlled setting during the time of filling-out the questionnaires (over the initial consultation day), it is plausible that obese + BED in this study suffer from clinical anxiety, which may be prevalent in binge eating disorder. Despite the differences between the groups not reaching significance in this study, further research with a greater sample size is warranted to investigate the clinical significance of these findings.

Since ‘disinhibition’ tends to co-occur with rigid dietary ‘restraint’ (Gallant et al., 2012; Stunkard & Messick, 1985; Williamson et al., 1995), the finding that both groups showed high ‘restraint’, concurrently with significantly higher ‘disinhibition’ in the obese + BED, should be noted, since disinhibiting behaviors related to food, co-occurring with rigid dietary restraint, may be a hallmark of BED. Disinhibiting behaviors related to food may be linked to trait disinhibition in BED: in line with the “Escape Theory” (Heatherton & Baumeister, 1991), and supported by our brain imaging data suggesting emotional processing of food-related cues in obese + BED greater than in the obese, BED may be a disorder whereby trait disinhibition meets negative emotional state in the face of a binge-trigger. Further support for this hypothesis comes from data showing obese + BED having difficulties staying engaged in goal-directed behavior when exposed to binge-triggers (Gianini et al., 2013), at that point possibly neglecting cognitive dietary restraint and engaging in disinhibited eating.

In the present study the obese + BED showed an average score of disinhibition above the clinically significant cut-off score of 8, while the obese group showed a score below this cut-off. Thus, there is a clinically meaningful difference between the groups in trait disinhibition, suggesting that further attention should be given to this psycho-behavioral trait in BED. Reducing disinhibition concurrently with increasing cognitive dietary restraint for the treatment of BED has shown success in the short-, but not in the long-term (Downe, Goldfein, & Devlin, 2009). Thus, it is plausible that addressing ‘disinhibition’ is an invaluable component in the treatment of BED, but it may not be enough. As a preventive measure, it is likely that the assessment of obese individuals for high ‘disinhibition’ co-occurring with high rigid dietary restraint can help identify obese individuals free of BED, but prone to developing it. According to the present study, it is likely that addressing disinhibiting behaviors related to food intake in a treatment program for BED can assist in recovery, but further clinical research is necessary to understand how disinhibition of dietary restraint should be addressed in BED, and how trait

disinhibition should be treated in this disorder. It is of note that the co-occurrence of anxiety and disinhibiting behaviors in a subset of individuals has been previously suggested (Fowles, 1987), as well as a link between disihibition, anxiety, and psychopathology related to substance abuse (Iacono, Carlson, Taylor, Elkins, & McGue, 1999). In light of obese + BED showing high rates of substance abuse (Yanovski, Nelson, Dubbert, & Spitzer, 1993; Holderness, Brooks□Gunn, & Warren, 1994), this psychopathological link may be of clinical significance and should be further explored in BED.

Of note is the direction of the differences between the groups: while 'disinhibition' was significantly higher in the obese + BED group, as expected, the construct of 'reward responsiveness' was significantly higher in the obese group, and this was not expected based on previous literature (Davis, 2013; Dawe & Loxton, 2004), despite one study confirming this finding (Svaldi, Brand, & Tuschen-Caffier, 2010). Clinically, reward responsiveness in the obese + BED almost reached the cut-off score, but the score of the obese group was much higher. Despite significant differences between the groups, this confirms previous findings of clinically significant reward responsiveness in both groups compared with healthy adults, suggesting that high reward responsiveness is a disorder of all obese, regardless of psychopathological subgroups (Davis et al., 2008).

The direction of the relationship between 'reward responsiveness' and BED may be explained with the contrast of 'disinhibition' in mind: in obese + BED, disinhibition may be a contributing factor to the development and maintenance of BED (Downe, Goldfein, & Devlin, 2009), by reflecting the "all or nothing" response to food, especially to 'forbidden' foods (Kales, 1990; Guertin, 1999). Individuals with BED tend to rigidly restrain their eating and avoid consuming high energy foods, since they believe that this can contribute to their weight gain. They also tend to eat very little throughout the day. When experiencing intense negative emotions, coupled with the availability of food and the absence of dominant-enough

distractions (usually at home and in the evening) (Loxton, Dawe, & Cahill, 2011; Carrard, Crépin, Ceschi, Golay, & Van der Linden, 2012; Agras & Telch, 1998), these individuals disinhibit their rigid food restriction and binge on the foods available, dominantly on 'forbidden' foods (Haedt-Matt & Keel, 2011), according to their beliefs. Thus, despite eventually consuming food high in energy in large amounts, coupled with loss of control, these individuals are not consciously responsive to the rewarding properties of food, i.e. they experience very little conscious 'liking' response, and therefore it is possible that they barely enjoy the food they binge on (Cambridge et al., 2013). Conversely, obese individuals with no BED do experience a 'liking' response to food (Davis et al., 2007; Stroebe, van Koningsbruggen, Papies & Aarts, 2013). They may often try to restrict their food intake, but they do not engage in binge-fast cycles. They like to eat and they may allow themselves to enjoy the taste of food (Pérez-Cueto et al., 2010), possibly contributing to their increased reward responsiveness to food. Thus, obese participants with no BED may experience greater reward responsiveness when they are confronted with a cue representing rewarding food, possibly since they are used to enjoying consuming this food. Moreover, the behavioral constructs 'reward responsiveness' and 'reward sensitivity' have been interchangeably used in the literature, however they may not mean the same. Individuals with obesity + BED may be sensitive to cues impeding reward, but in the same time they may show lower reward responsiveness to food relative to other groups. Thus, these two constructs should be further explored for differences and similarities in future studies.

5.1. Brain activation

Several hypotheses were examined in relation to participants' brain activation in response to visual images of food and nonfood items. Compared with the obese group, the obese + BED were expected to experience greater activation in brain areas related to emotions, cognition, memory and motivation. Table 7 below summarizes anatomical location and known functions of each brain area significantly activated in obese + BED greater than in obese, in response to

food versus nonfood stimuli, and high energy food versus low energy food stimuli, in the present study.

Table 7: Anatomical location and functions of brain areas activated in obese + BED > obese

Brain area*	**Anatomical location***	**Relevant Function***	**Studies in BED***
Right insula	-Part of the cerebral cortex, located beneath the frontal, parietal, and temporal lobes	-Via connectivity with the postcentral gyrus and secondary sensory areas in the parietal lobe, the insula functions to cognitively integrate somatosensory stimulation (including sensory representations of taste), with internal state, in order to form a percept. -Together with the claustrum, which is located more medially (i.e. toward the center of the	1/Cambridge et al., 2013 (in this study, fasted men, mildly binge eaters were tested) 2/Woolley et al., 2007 (in this study, fed participants who binge-eat and have the behavioral variant of front-temporal dementia (FTD), were tested and found to have aberrant right

		brain), the insula is involved in multisensory experiences and the orchestration of the cerebral cortex (i.e. information processing between the two hemispheres, as well as within the hemispheres). By that, the insula is contributing to the experience of consciousness and to attentional processes (Smith & Alloway, 2010; Crick & Koch, 2005).	insular integrity) 3/ Schienle, Schäfer, Hermann, & Vaitl, 2009; Weygandt, Schaefer, Schienle, & Haynes, 2012 (in this study food-deprived females were tested) 4/Dodds et al., 2012 (this study examined both genders with a BMI ≥ 27, following a 15-hour fast, and used “region of interest” analysis of seven brain structures determined *a*

			priory, among which is the bi-lateral insula)
Right cingulate cortex-Brodmann area #32	-Cingulate gyrus: a C-shaped structure in the pre-frontal cortex, encompassing sections of the frontal and parietal lobes, on the medial side of the brain -Brodmann area #32 is located adjacent to the frontal part of the cingulate cortex -Both are part of the limbic lobe -The lower part of the cingulate cortex is adjacent to the parahippocampal gyrus and other	-As part of the limbic lobe and the association network, these structures are important for processing sensations, cognitions, thoughts and emotions -The cingulate cortex has three parts: frontal, middle and posterior. The anterior (frontal) part is responsible for motor control, arousal/drive, affect regulation, and cognition. The middle portion is responsible for movement driven by emotions and reward. For	1/Cambridge et al., 2013 2/ Weygandt, Schaefer, Schienle, & Haynes 2012 (in this study food-deprived females were tested)

	internal limbic structures, including the amygdala and the hypothalamus	information about the posterior part, see “Left posterior cingulate cortex” below. -The cingulate cortex is involved in the formation and retrieval of emotional memories, and its’ activation signals an emotional load	
Left posterior cingulate cortex	See above	-The posterior part of the cingulate cortex is involved in higher order integration of sensory functions and memory. This is part of the visual association area, helping integrate an emotional value with a sensory stimulus, such as a visual stimulus, mediating	Studies not found

		motivation and expectancy for future outcomes	
Left middle temporal gyrus	-Located on the lateral temporal lobe	-Important for higher visual functions, especially object recognition -Involved in the perception of visual motion	
Left cuneate gyrus	-Located in the occipital lobe	-This is a structure in the primary visual area -Part of the somatosensory system, it mediates mechanosensations	Studies not found
Right posterior cingulate cortex	See above for “left posterior cingulate cortex”	See above for “left posterior cingulate cortex”	Studies not found
Right lingual gyrus	-Located in the occipital lobe, adjacent to the cuneate gyrus	-See “Left cuneate gyrus”	Geliebter et al., 2006 (female participants with BED as well as

			sub-threshold BED were tested 3 hours following a meal)
Right cuneate gyrus	-Located in the occipital lobe	-See “Left cuneate gyrus”	Geliebter et al., 2006
Brodmann area #19	-Located in the occipital lobe	-This is another structure in the higher order visual area, working together with the middle temporal visual area, responsible for vision, color, motion, and depth	Studies not found
Left postcentral gyrus	-Located in the parietal lobe	- This area is the primary somatosensory center responsible for mechanosensation from several areas in the body, as well as cognitive	Studies not found

		integration of sensory stimulus outside of the body	
Right inferior parietal lobule	-Located in the parietal lobe	-This area encompasses the inferior part of the somatosensory center -It is involved in integrating diverse sensory information for perception and language, and visuo-spatial cognition	Studies not found
Left middle frontal gyrus	-Located in the frontal lobe	-This is the prefrontal association cortex, responsible for thought, cognition, movement, and planning	Studies not found
Left superior frontal	-Located in the frontal lobe	-See “Left middle frontal gyrus”	Studies not found

gyrus			
Brodmann area #6	-This is part of the cingulate motor area adjacent to the precentral gyrus, on the medial portion of the limbic lobe	-This area is yet to be fully understood, but it is postulated to be responsible for motor behaviors that occur in response to emotions, drives, and movement planning	Geliebter et al, 2006

*References: (Martin, 2012; Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2012).

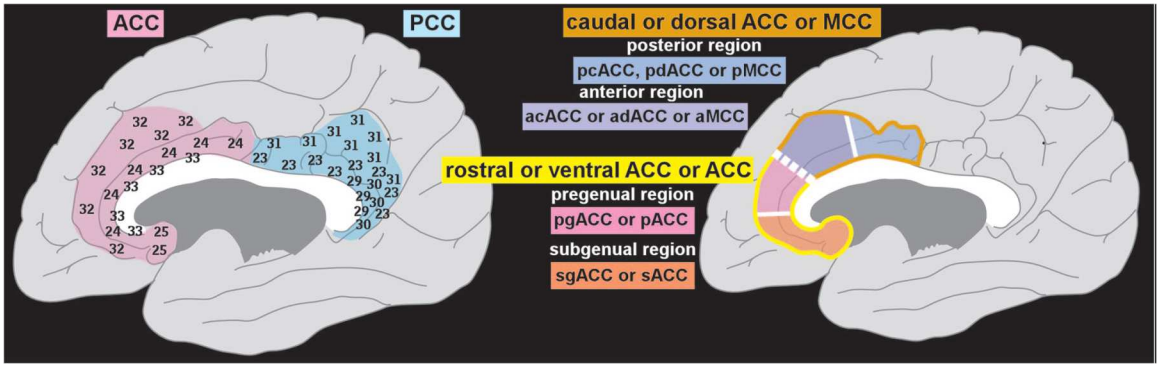


Figure 17: Anatomical divisions of the cingulate cortex, with Brodmann areas (Stevens, Hurley, & Taber, 2011). In this sagittal view of the brain (i.e. as if the brain is cut vertically, from top to bottom – anterior to posterior, dividing the brain into right and left halves; see appendix for definition of brain sections and planes), the pink area is called the anterior cingulate cortex (ACC) (also called the anterior cingulate gyrus; function: integration of motor control, motivation, and cognitive messages) and the blue area is called the posterior cingulate cortex (PCC) (also called the posterior cingulate gyrus; functions: integration of

sensory experiences and memory) (Palomero-Gallagher N, Vogt BA, Schleicher A, et al., 2009).

Greater activation of the cingulate cortex in obese + BED more than in obese, in response to the contrast “food versus nonfood”, is of significance. Sub-areas of the cingulate cortex which were activated include the anterior cingulate cortex, encompassing Brodmann area #32 (figure 17), on the right side, and the posterior cingulate cortex on both sides (bilateral). In the posterior cingulate cortex, slight differences were seen between the two sides: peak intensity of activation was greater on the left side, while greater number of voxels were activated on the right side. The cingulate cortex is a brain region with high metabolic needs, and it is involved in many functions including *mediation of cognitive control over emotions*. The anterior cingulate cortex is of special note for its integration of neural activity for *affect regulation*, and this is especially relevant to BED participants in the present experiment, as escape from negative emotions is a driving force to engage in binge eating behavior, taken in an attempt to avoid or control painful emotional states (Stevens, Hurley, Hayman, & Taber, 2011). The anterior cingulate cortex has been suggested to have the unique function of translating intentions into action, by integrating motor control, motivational drive/arousal state, and cognitive messages (Paus, 1999).

The cingulate cortex has special anatomy and cell topography, serving it in its functions. The anterior cingulate cortex contains special neurons called “spindle neurons”, found in humans and great apes and present only in the insula and cingulate cortex. These neurons are much larger compared with other types of neurons in the cerebral cortex, suggesting faster transmission of messages and greater connections with other brain regions. This has been suggested to help humans and great apes communicate quickly with the anterior insula as part of the salience network (Craig, 2009; Menon & Uddin, 2010), as well as to efficiently react to instinctual/intuitive messages about the external environment. The anterior cingulate

cortex has extensive connections with areas known to be important for emotions (e.g. amygdala), memory (e.g. hippocampus), and reward (e.g. orbitofrontal cortex, ventral striatum). The right anterior cingulate cortex is thought to have a role in monitoring for conflicts and errors (MacDonald, Cohen, Stenger, & Carter, 2000; Gehring, & Knight 2000), and detecting and signaling the need for cognitive control to increase self-regulatory efforts, such as needed for resisting temptations (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Kerns et al., 2004; Peterson et al., 1999; Paus, 2001). A group we can learn from is smokers, whom right anterior cingulate cortex was activated to a greater extent when they were asked to resist cravings for cigarettes compared with when they were asked not to resist cravings (Brody et al. 2007). Thus, tasks requiring *conflict monitoring, emotional assessment and self-control, emotion-related learning, and conditioned learning,* are all activating the anterior cingulate cortex (Etkin, Egner & Kalisch, 2011; Shackman et al., 2011; Beckmann, Johansen-Berg, & Rushworth, 2009; Vogt , 2005).

Another sub-area of the cingulate cortex differentially activated in the obese + BED group is the bilateral posterior cingulate cortex, functionally implicated in the *control of frontal-parietal messages, sensorimotor activity, and evaluation of salience* (Leech, Braga, & Sharp, 2012; Leech, Kamourieh, Beckmann, & Sharp, 2011). Of relevance to the present project is posterior cingulate's dominant participation in *cognitive tasks*, *attention,* and *evaluation of salience*. The posterior cingulate cortex is responsible for cognitive tasks, including the making of a perceptual decision and about the appropriate motor response (Leech & Sharp, 2014).The posterior cingulate cortex, together with multiple other brain regions, is taking part in a *top-down control of visual attention*, in a network called the 'dorsal attentional network' (Corbetta, Patel & Shulman, 2008), functioning as an executive control system. The posterior cingulate cortex, together with other parts of the cingulate cortex (e.g. the anterior cingulate cortex), the presupplementary motor area, the anterior insula, and the Inferior parietal lobule, are part of another functional brain network called the 'fronto-parietal control network' (FPCN), activated when *executive control* and *decision making* is needed (Leech & Sharp, 2014). A sub-

network of the FPCN is termed the ‘salience network’, since it is involved in rapidly responding to transient behaviorally salient events. The three networks described above, i.e. the ‘dorsal attentional network’, the FPCN, and the ‘salience network’, work together in coordination to produce an appropriate cognitive function.). The bilateral activation of the posterior cingulate cortex in the present study reduces the likelihood of findings by chance, thereby increasing its power. These results point to a biological process involving impaired executive functioning and an emotionally-relevant dilemma when facing a binge-type cue, in obese + BED.

The dorsal (i.e. upper) part of the posterior cingulate cortex is postulated to exhibit a ‘transitional’ pattern of connectivity, linking between the different networks to produce an efficient cognitive function (Vincent et al, 2006; Margulies et al, 2009). The posterior cingulate cortex integrates the consequences of behavior over time, and it provides a signal for strategic behavioral change if the consequences of previous actions are suboptimal (Hayden, Nair, McCoy, & Platt, 2008; Pearson, Hayden, Raghavachari, & Platt, 2009). Posterior cingulate cortex activity has been shown to increase during *attentional bias* to targets that are of high motivational value, and this was accompanied by increase in functional connectivity to parietal areas involved in spatial attention (Leech & Sharp, 2014).

The posterior cingulate cortex can further be functionally subdivided. The structure of the posterior cingulate cortex is intermediate between and resembling both, higher order structures within the cortex and more primitive limbic and hypothalamic lower-brain regions that are primarily involved in *internal homeostasis*. In accordance, the posterior cingulate cortex has multiple anatomical and functional sub-areas, and it can code complex patterns of neural activity from largely remote brain areas, functioning as *a brain hub* involved in integrating multiple sources of information (figure 18). In accordance with current theories (Leech & Sharp, 2014), the dorsal (i.e. upper) and ventral (i.e. bottom) fractions of the posterior cingulate cortex are involved in integrating messages from the cortex and more primitive lower regions, respectively, for an evaluation of a situation and production of

appropriate response (Leech, Kamourieh, Beckmann, & Sharp, 2011). It is very likely that this is what happened in the obese + BED group to a greater extent than in the obese group: when shown images of food (compared with images of nonfood), the obese + BED group showed greater activation in areas responsible for the integration of sight, memory, salience, spatial attention & attentional bias toward the food images, motivation to attain reward, emotional conflict, and cognitive evaluation about the consequences of their behavior (Svaldi, 2014

Heightened visual processing of a stimulus can attest to attentional processes in the brain (Small et al., 2005; Engelmann, Damaraju, Padmala, & Pessoa, 2009). The differential activation of the bilateral cuneate gyrus and right lingual gyrus in obese + BED is not surprising in light of the function of these brain areas in high-level visual associations (Parker, Zalusky, & Kirbas, 2014). Obese + BED participants' cue-induced heightened activity in visual association areas, as described above, reflects their high attention to the food stimuli, and these findings are unlikely due to chance, supported by the bi-laterality of the activation. Once stimulus-reward (salience) association has been established, it can influence sensory processing at an early stage of stimulus presentation, by establishing preferential-coding mechanisms that increase attention to the specific stimulus has been associated with the reward. This mechanism is advantageous to the survival of humans by maximizing reward when interacting with the environment (Schultz, 2002; Wise, 2004), but often the reward predicted via the associated stimulus becomes irrelevant, and the reward salience is "transferred" to the stimulus itself (Krebs, Boehler, Egner, & Woldorff, 2011). It is likely that this is what happened in the obese + BED when they saw images of food: the stimulus saliency may have attracted their attention at an early stage of visual processing, engaging visual association areas i.e. the bilateral cuneate gyrus and right lingual gyrus. In the obese, the behavioral effect of such, often involuntary, early attentional processing, is engagement of key reward regions, such as the ventral striatum (e.g. the nucleus accumbens), and regions signaling about increased motivation (e.g. orbitofrontal cortex) and evaluation of saliency of the stimulus (e.g. ventromedial prefrontal cortex) (Schienle, Schäfer, Hermann, & Vaitl, 2009;

Hare, Camerer, & Rangel, 2009). Indeed, it is of note that no differential activation in obese + BED was seen in these brain areas, e.g. the nucleus accumbens, orbitofrontal cortex, and ventromedial prefrontal cortex, most often discussed in the context of reward attainment (Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004; Bjork & Hommer, 2007; Knutson, Adams, Fong, & Hommer, 2001; Knutson, Fong, Adams, Varner, & Hommer, 2001; O'Doherty et al., 2004). This implies that it is the *processing* of salient cues, previously had been primed with highly rewarding food (Corwin, Avena, & Boggiano, 2011), via integration of multiple pathways, which may be malfunctioning in obese + BED, and this may have clinical implications. Since this network of functionally-related sub-areas, processing a rewarding sensory stimulus with an emotional load, and evaluating conflicting solutions to the environmental 'problem' and the consequences of such a behavior, was activated to a larger extent in the obese + BED, compared with the obese , it is possible that BED is a disorder of hyperactivity of this highly sensitized (due to frequent food deprivation, or a long history of dieting and binging) brain network (Corwin, Avena, & Boggiano, 2011; Bressler & Menon, 2010).

The left postcentral gyrus was activated to a greater extent in the obese + BED group, compared with the obese, in response to images of food. The postcentral gyrus is the primary somatic-sensory area, and it's working together with the inferior parietal lobule to form the "secondary somatic sensory area" and to analyze mechanosensory information from the body. Each subdivision of the primary somatic sensory cortex contains a complete "map" of the contralateral sensory surface. One primary responsibility of the somatic sensory cortices is to create a "schema" of the somatic self, based on integration of somatic sensory and visual inputs. This is what we often refer to as "body image" (Purves et al., 2012). Also, the postcentral gyrus and inferior parietal lobule are connected with limbic structures, *thus somatic sensory information is integrated with emotional signals and memory traces*. In mammals, sensory exposure to food, without ingestion of any food, leads to an early miniature version of postprandial release of various digestive and metabolic components, like saliva, gastric acid,

pancreatic enzymes and insulin (Mattes, 1997). This response is considered to be preparatory for ingestion, and it adaptively affects both metabolism and behavior. For example, the sight and smell of a food can lead to increased glucose clearance (Verhagen, 2007). Thus, the postcentral gyrus, via its' connections to visual areas and other association areas in the parietal lobe, such as the cuneate gyrus, the inferior parietal lobule, and the insular cortex (which is connected to the inferior parietal lobule) (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2012), is responsible for cognitive integration of sensory information with body scheme, memory and emotions (figure 18).

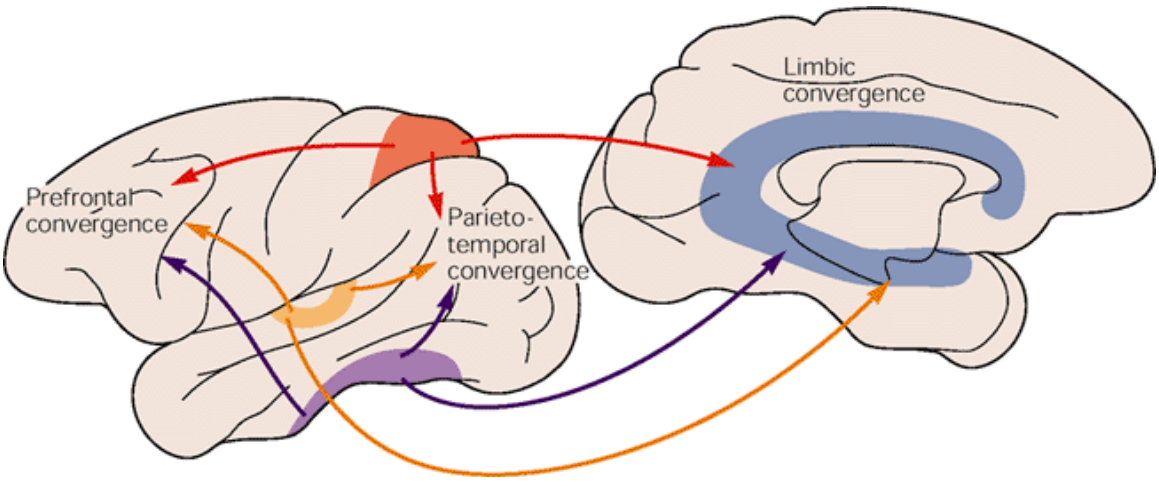


Figure 18: Unimodal sensory inputs converge on multimodal association areas in the prefrontal, the parieto-temporal, and the limbic cortices (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2012). Image on the left shows a lateral view of the left half of the brain; image on the right shows a sagittal (vertical cut from anterior to posterior end of the brain; see appendix for brain sections and planes) view of the same left half of the brain.

In the obese + BED there was greater activation in a number of functionally related brain areas, i.e. the insula, cingulate cortex, inferior parietal lobule, cuneate gyrus, lingual gyrus, and the postcentral gyrus. These areas are all part of the "multimodal association integration system" (figure 18), where signals from several areas, such as visual areas (e.g. cuneate gyrus) and limbic areas involved in processing of emotions and reward (e.g. cingulate gyrus)

are integrated in the visual association area, i.e. the inferior parietal lobule, to create an internal representation of the sensory stimulus concerned with a specific aspect of behavior (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2012). Furthermore, the inferior parietal lobule plays a central role in body representation, prediction of, and preparation for, motor action (Blakemore & Sirigu, 2003), such as in 'motor imagery' related to a behavioral action to attain a reward associated with a cue with incentive salience (Mendelson, Pine, & Schiller, 2014). The differential activation of this brain region in the obese + BED in the present study may thus indicate attentional arousal in response to food cues carrying a salient value, in preparation for mental imagery related to reward attainment and outcomes (Pelchat, 2002; Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Robinson & Berridge, 2008).

In response to images of high energy food, compared with images of low energy food, obese + BED participants showed increased activation in prefrontal areas, collectively referred to as "multimodal association areas" (figure 18), concerned with planning of motor strategies (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2012.). The superior and middle frontal gyri are part of the prefrontal association cortex, working together with visual, parietal and limbic areas to help plan and execute a motor behavior, such as satisfy hunger by eating. The prefrontal association area weighs the consequences of future actions and processes planning and organization of actions accordingly. To select the appropriate motor response, this area of the brain must integrate sensory information from the outside world, as well as from the body. This area is also responsible for finding solutions to novel problems, and it is concerned with the sequencing of behaviors over time. Thus, it is possible that in response to high energy food, compared with low energy food, obese + BED participants responded with a motor planning action associated with the salient cue they saw.

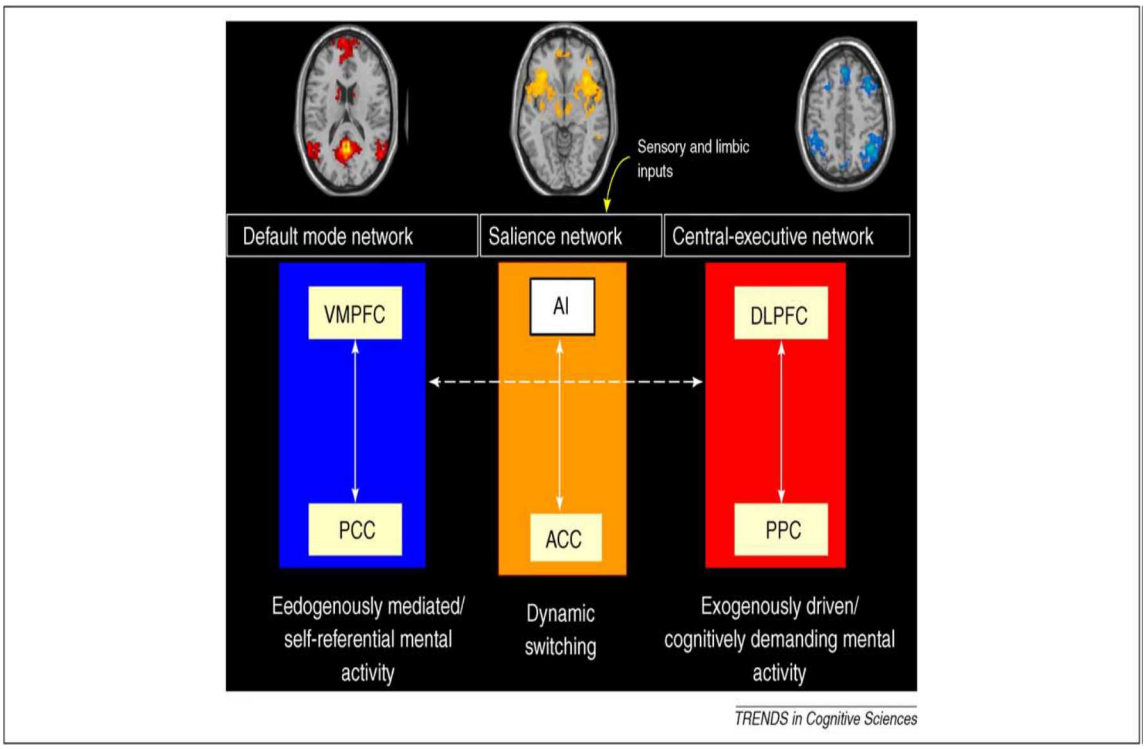


Figure 19: Multi-network switching initiated by the salience network (Bressler & Menon, 2010). Images of the brain in this figure have been obtained via a horizontal cut through the brain (see appendix for definition of brain sections and planes); VMPFC = ventromedial prefrontal cortex (self-regulation, decision making); PCC = posterior cingulate cortex (higher order integration of sensory functions and memory); AI = anterior insula (integration of somatosensory experiences with internal state); ACC = anterior cingulate cortex (integration of motor control-motivation and drive-cognitive control over emotions); DLPFC = dorsolateral prefrontal cortex (sustained self-control)

Out of five main brain networks, each consisting of multiple brain areas working together to perform a certain function (Mesulam, 1990; Bressler & Menon, 2010; figure 19), three could be relevant to our understanding of BED. The default mode network (DMN) consists of the posterior cingulate cortex (PCC) and the ventromedial prefrontal cortex (VMPFC), and it is activated at rest and de-activated during cognitively demanding tasks; the central executive network (CEN) is comprised of two main cortical areas – the prefrontal cortex (PFC) and the

posterior parietal cortex (PPC), and it is activated during cognitively-demanding and executive planning tasks; and the salience network (SN) consists of the right anterior insula (AI) and anterior cingulate cortex (ACC), and it is a key player when switching from rest to cognitively demanding task is needed (Sridharan, Levitin,& Menon, 2008; Menon & Uddin, 2010). Since brain areas including the posterior cingulate cortex, anterior insula, anterior cingulate cortex, and some areas of the prefrontal cortex were differentially activated in obese + BED compared with obese, in response to a task demanding attention and processing of a visual stimuli, one may hypothesize that the ventromedial prefrontal cortex and dorsolateral prefrontal cortex are hypoactive, while the posterior parietal cortex, anterior insula and anterior cingulate cortex are hyperactive, in BED. To confirm this hypothesis one may study brain activation of BED during rest and during switching from rest to a cognitively-demanding task. Support for this hypothesis comes from neuropsychological testing of differences in neural substrates underlying sustained cognitive control in obese and obese+ BED; obese + BED participants showed hypo-activity in frontal brain areas sub-serving inhibitory control (Balodis et al, 2013; Svaldi et al., 2014). However, considering the functional roles of the dosrolateral prefrontal cortex and the ventromedial cortex (inhibition of an action brought about by the motivation to consume food, and evaluation of proper action, respectively), while understanding that participants in this study did not have the opportunity to act on their food cravings and access the foods the viewed in the pictures, it is reasonable to postulate that the participants did not have to recruit these two brain areas to control their food intake.

It should be noted that in the present study differences between obese versus obese + BED were found to be unidirectional; the contrast of “food versus nonfood” in obese versus obese + BED did not show any significant results indicating neural deactivation, indicating that obese + BED participants did not show significantly reduced activation compared with the obese group in any area of the brain detected to be differently activated between the groups. Thus, it is plausible that the dorsolateral prefrontal cortex & the ventromedial prefrontal cortex are similarly weak in both groups, but other brain networks are hyperactive in obese + BED.

Another possibility is that both groups did not have to recruit these two brain areas since the food stimuli was not available for consumption, These hypotheses, however, requires further studying.

Comparing obese + BED participants' brain activation to that of the obese, all together, shows greater activation of brain areas responsible for vision, reward saliency, attention, memory, emotion, sensory-associations and planning of motor actions and behaviors associated with the visual cues. It is plausible that the obese + BED engaged in some motor-plan imagery to obtain the reward associated with the saliency of the images. In response to food cues and following a pre-load meal, obese + BED participants showed a heightened attentional response to an emotionally-relevant stimulus, which may have translated into a drive to reach out for the reward associated with the saliency of the cue. Obese + BED participants did not show differential brain activation in areas signaling pure reward, such as the nucleus accumbens in the striatum, but it is possible that both groups, obese + BED and obese, had elevated brain activity in the striatum in response to cues signaling rewarding food, in line with previous findings reporting impaired dopamine receptors, reduced dopamine signaling, and high functional activation in these brain areas in the obese, regardless of BED, in response to rewarding food stimuli (Wang et al., 2001). The present study adds to current knowledge that obese + BED may suffer from hyperactive food-related reward association system in the brain, which is possibly co-occurring with reduced self-control over the motivation to obtain this reward (Balodis et al., 2014). Obese + BED participants did not have a differential activation in brain areas responsible for self-control *per se*, e.g. the dorsolateral prefrontal cortex, and the ventromedial prefrontal cortex (Hare, Camerer, & Rangel, 2009), although inhibitory control in response to food in BED has been reported to be impaired (Svaldi, Naumann, Trentowska, & Schmitz, 2014). This suggests that obese individuals, regardless of BED diagnosis, may experience poor self-control (He et al., 2014). To sustain cognitive control and resist temptations, activation of the dorsolateral prefrontal cortex is needed (Mitchell et al. 2007). Furthermore, energy resources of the cognitive system are

finite, and cognitive load from one brain network may compete with the others for energy allocation (Heatherton, 2011; Baumeiser & Heatherton 1996). Thus, controlling impulse or emotional load may deplete brain energy and by that weaken cognitive control (Hoffman et al. 2007; Wagner & Heatherton, 2010). In accordance, hyperactivation of the right anterior cingulate cortex in BED may deplete cognitive energy resources, weakening executive functions, thereby loosening self-control, and disinhibiting food restraint, bringing on a binge. Differently from obese participants, however, the hyperactive reward-association in obese + BED, coupled with emotional regulatory failures to control it and weakened self-control, may bring those affected by BED to excessively "want" binge-type foods and binge on them as a coping mechanism to escape unbearable negative affect (Heatherton & Baumeister, 1991). The co-occurrence of behavioral and biological markers, i.e. differences in disinhibition & reward responsiveness and heightened arousal in response to emotionally-laden stimulus, respectively, may indicate that it may be worth studying the value that obese + BED versus obese attach to food, as well as biological parameters, such as heart rate, in response to the presentation of food stimuli; one hypothesis may be that obese + BED would regard food as an enemy, while the obese with no BED would regard it as a friend (Corwin, Avena, & Boggiano, 2011).

Studies on functional brain activity in BED are scarce. As few as one study have looked at functional brain imaging in fed obese + BED participants (Geliebter et al., 2006), despite a growing understanding about differential brain activation between hunger and satiety in healthy individuals, as well as in obesity and disordered eating (García-García et al., 2013; Stice, Burger, & Yokum, 2013; Wang et al., 2009), and the understanding about "eating in the absence of hunger" as a behavioral construct in BED (De Zwaanm, 2001; Marcus & Kalarchian, 2003). Similarly to the present study, albeit using different methodology, several studies have found brain activation in the right insula (Cambridge et al., 2013; Schienle, Schäfer, Hermann, & Vaitl, 2009; Dodds et al., 2012; Woolley et al., 2007), the anterior cingulate cortex (Cambridge et al., 2013; Weygandt, Schaefer, Schienle, & Haynes 2012), the

precentral gyrus, Brodmann area #6, Brodmann area # 19, and the lingual gyrus, in response to food cues in binge eaters (Geliebter et al, 2006). The present study differs in its methodology from the studies above in multiple aspects: 1/it includes both males and females, whose functional brain activation in response to images of food has been shown to differ (Geliebter et al., 2013; Wang, 2009), and 2/it scanned the participants one hours after a liquid meal, which is a shorter time period compared with Geliebter et al. (2006), who studied functional brain activation of obese + BED participants three hours post-meal. In the present project, males and females were equally stratified to both groups, thus results can be generalized to both genders, Furthermore, the shorter postprandial time period in the present study was intended to imitate eating in the absence of hunger, while a three hour window between the meal and the brain scan may be long enough for the participants to be hungry again. Another related study of note was conducted by Karhunen et al. (2000), who found greater left-sided cerebral blood flow (rCBF) in energy deprived obese + BED women, versus an obese group, in response to the sight and scents of a freshly cooked lunch meal (Karhunen et al., 2000). Differently from the present project, however, this study used SPECT (single photon emission computed tomography), a direct method to trace blood flow in the brain, using an injected radioactive isotop, This relatively inexpensive method is often used in clinical practice to examine brain damage from stroke or for early Alzheimer, but it does not provide high spatial resolution as can be obtained using functional MRI.

Of note is a clinical syndrome called fronto-temporal dementia (FTD). Patients who suffer from FTD demonstrate behavioral symptoms of hyperphagia and uncontrollable binge-eating, similarly to individuals with BED. In these patients, the fronto-temporal loop is malfunctioning, and they show similar brain activation response when faced with food cues (i.e. functional activation in frontal and temporal areas, such as the insula and middle temporal gyrus, respectively). Furthermore, these individuals suffer from impaired brain executive network function (Torralva, Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009). Therefore, individuals

with fronto-temporal dementia share common features with individuals with BED, and it may be beneficial to study common neurobehavioral aspects of the two disorders.

The interpretation of the brain imaging data has some limitations which should be noted. Seven brain regions of interest showed greater activity in obese + BED, compared with the obese group, in response to the contrast "food versus nonfood", and one region of interest in response to the contrast "high energy food versus low energy food". The contrast "food versus nonfood" is used below to illustrate the limitation of fMRI analysis in contrasting modalities. Due to the nature of contrasts, the end value is a result of subtraction of two values: A) parameter estimates of peak brain activation in a certain region of interest in response to images of food, minus B) parameter estimates of peak brain activation in the same region of interest in response to control images, i.e. office supplies. Multiple scenarios could happen here, ending in a positive value, according to which we conclude about differential activation in the experimental group in the region of interest studied. For example, both "A" and "B" may show negative values relative to baseline (i.e. when the subjects are presumably at rest since they do not engage in any task), meaning deactivation in the peak voxel for the region of interest investigated. However, if the contrast examined is "food versus nonfood", we subtract parameter estimates of "nonfood" (i.e. condition "B") from parameter estimates of "food" (i.e. condition "A"). If "A" > "B", but both are negative values, then the total value for the contrast (i.e. "C") is positive (i.e. "A" -["B"] = "A" + "B" = "C"). The end results is a positive value "C", which is the product of the contrast "A"-"B" = "C", and the interpretation of "C" is activation in the region of interest investigated in response to condition "A" greater than to condition "B". An example for this methodology in question can be seen in four out of the eight regions of interest reported to be significantly activated in obese + BED participants greater than the obese, in response to the contrast "food versus nonfood" (see figures: 9b, 11b, 12b, 13b). It can be seen in the figure that obese + BED participants showed deactivation in the respective regions of interest in response to both food and nonfood images. However, the average parameter estimates value of all BED participants for nonfood images was more negative than

the value for food images [i.e. (parameter estimates for “food”) > (parameter estimates for “nonfood”)], thus the overall value of the contrast “food versus nonfood” becomes positive. Differently, the obese participants showed a positive average parameter estimates value in response to food images and a negative value in response to images of nonfood. The result of the contrast “food versus nonfood” in the obese for the regions of interest studied is a negative value, leading to a conclusion that obese + BED participants had greater brain activation in response to images of food, versus images of nonfood, compared with the obese, in this region of interest.

Hemodynamic changes in neurons are influenced by both metabolic and vascular processes, but are also sensitive to the biomechanical, structural, and physiological state of the brain. Fluctuations in neuronal signals are incompletely understood in the brain imaging literature, but these are common in light of continues and co-occurring inhibitory and excitatory activity of billion of neurons in the brain. Despite this limitation, comparison of dynamic vascular models between different brain imaging modalities has shown insignificant differences between fMRI and other, more conservative (but also necessitating the use of a radioactive tracer), brain imaging techniques (Huppert, Allen, Diamond, & Boas, 2009). Thus, it can be concluded with relative confidence that in the present study, participants with obese + BED, compared with the obese, showed greater activity in several brain regions, i.e. right insula, right cingulate cortex and Brodmann area #32, and right posterior cingulate cortex, in response to images of food, and left middle and superior frontal gyri and Brodmann area #6 in response to images of high energy food (see figures 7b, 8b, 10b, 14b). In these figures it can be clearly seen that the differences between brain activation in response to the stimulus in question (i.e. food, or high energy food) compared with a control stimulus (i.e. office supplies) originated from a positive parameter estimate values, i.e. increase in activation in the region of interest investigated, in the obese + BED group in response to the experimental manipulation.

5.2. Correlation between psycho-behavioral measures and brain activation

Scores on the behavioral measures of ‘disinhibition’ and ‘BAS(reward)’ were correlated with parameter estimate values of brain activation obtained using both contrasts, “food versus nonfood” & "high energy food versus low energy food", and differences between the groups on these relationships were studied. This produced multiple observations, novel to the field of eating behavior. In the obese + BED group, the greater the disinhibition score, the weaker the brain activation in the anterior cingulate cortex-Brodmann area #32 in response to food (versus nonfood) stimuli. However, in the obese group the opposite direction of relationships between these two variables was identified: the greater the disinhibition scores, the stronger the brain activity in the anterior cingulate cortex-Brodmann area #32 in response to food versus nonfood stimuli. Despite these findings lack a cause and effect analysis, based on these significant differences between the groups multiple explanations may be hypothesized: in obese + BED, frequent disinhibition of dietary restraint may desensitize the anterior cingulate cortex and weaken its functioning. This may be associated with both reduced ability of obese + BED to effectively switch from one brain network to the other, as shown in figure 19, and their reduced cognitive control over emotions as well as uncontrollable drive for approaching binge-triggers. Since the obese + BED showed a clinically-significant disinhibition score, a possible link between weak anterior cingulate cortex functioning and disinhibiting behaviors in BED may be postulated. Supporting evidence comes from a study investigating patients suffering from fronto-temporal degeneration and healthy controls, linking poor executive functioning, behavioral disinhibition, and eating abnormalities in this population, with impaired functioning of several brain regions, including the anterior cingulate cortex, during neuropsychological testing (Raczka et al., 2010). Thus, this possible link of disinhibition of dietary restraint and poor executive control functioning, with weak anterior cingulate cortex in obese + BED, should be further explored in future studies. Furthermore, it may be beneficial to study adults with bulimia nervosa, to learn if high disinhibition of dietary restraint in this group is associated with the same neuronal substrates as in obese + BED. Similarities and distinctions between obese + BED and adults with bulimia nervosa may help reveal if the

association found in this study between increased disinhibition scores and weakened function of the anterior cingulate cortex-Brodmann area #32 in response to binge-triggers is associated with binge-eating with- versus without compensatory behaviors.

The relationships between scores on the disinhibition scale and brain activation in the left postcentral gyrus in response to binge-triggers were significantly different between the groups. In the obese + BED this association was negative, while in the obese group these relationships were positive. These differences should be discussed considering the role of the postcentral gyrus in mechanosensation and cognitive integration of sensory stimulation with the body's internal state, emotions and memory. The negative association between disinhibition scores and brain activation in the postcentral gyrus (in response to images of binge-triggers) in obese + BED may attest to their reduced ability to sense physiological hunger and satiety cues as the disinhibition score increases. At the moment of disinhibited eating one dampens rigid restraint over food intake (Herman & Polivy, 1980). Thus, in light of the postcentral gyrus function in evaluating sensory information related to food, it is plausible that reduced evaluation of sensory experiences takes place with more disinhibited eating. Similarly to the relationships found between brain activation in the anterior cingulate gyrus-Brodmann area #32 and disinhibition scores, causal relationships between brain activation in the left postcentral gyrus and disinhibition scores cannot be determined by these findings. However, further research may test the hypothesis that disinhibiting behaviors related to food intake in obese + BED desensitize physiological sensations of hunger and satiety, and whether this indeed is related to reduced functioning of the left postcentral gyrus in this group, differently from obese controls.

The correlation between scores on ‘BAS(reward)’ and brain activation in all eight regions of interest was weak, and no significant differences between the groups were observed. The behavioral construct of ‘BAS(reward)’ has been associated with activation in brain areas such

as the ventral striatum, the dorsolateral prefrontal cortex, and the medial orbitofrontal cortex (Pizzagalli, Sherwood, Henriques, & Davidson, 2005), and these brain areas were not observed to be significantly different between obese + BED versus obese, in the present study. It is possible that differences in brain activation between obese + BED versus obese in areas reflecting reward responsiveness are too small to detect when participants are not food deprived. This postulation is based on multiple previous studies using brain imaging paradigm in participants who are food-deprived, where brain activation patterns reflecting reward responsiveness have been identified (Stice, Spoor, Bohon, Small, 2008; Stice, Burger, & Yokum, 2013). In sum, more studies are warranted to examine possible distinction between the constructs of 'reward responsiveness' versus' reward sensitivity', and their brain activation correlates in different homeostatic states. Differences between obese + BED versus obese can then be more clearly identified.

It should be noted that the correlations mentioned above between brain activation in response to binge triggers and 'disinhibition' scores are somewhat counter-intuitive. Brain activation in the right anterior cingulate cortex - Brodmann area #32 and the left postcentral gyrus, separately, were negatively correlated with 'disinhibition' scores in the obese + BED group, thus the higher the 'disinhibition' score, the lower the brain activation in these two brain regions in this group. In obese, however, the direction of these relationships was positive. This pattern of correlation is of note, since the obese + BED group, compared with the obese, scored significantly higher on the behavioral construct of 'disinhibition' and showed greater brain activation in the right anterior cingulate cortex – Brodmann area #32 and left postcentral gyrus, separately, in response to the contrast "food versus nonfood". Therefore, findings about the relationships between 'disinhibition' and brain activation in these two brain areas, in the obese + BED group, were postulated to be positive. Furthermore, participants were brain scanned following a meal, in the absence of hunger, when individuals with obese + BED are expected to experience disinhibition (Gill, Chen, D'Angelo, & Chung, 2014). It may be possible that the higher the disinhibition tendency and the more often it is practiced, the lesser the

sensitivity of the right anterior cingulate cortex –Brodmann area #32 and the left postcentral gyrus to cues of rewarding food, but this speculation should be investigated. Future studies may continue to explore these relationships between dietary disinhibition and brain activation in response to food cues in obesity and BED, to find out whether neuro-modulation of these two key brain areas may be of a therapeutic value. It is possible that subtypes of BED may show different relationships between brain activation and disinhibition tendencies (Carrard, Crépin, Ceschi, Golay, & Van der Linden, 2012), and this should be further explored.

The results of the present study clearly point to a "wanting" reaction in obese + BED when exposed to binge cues. The fact that this group of participants showed differential brain activation in response to the food images, despite being unable to taste the food (represented by the images) at- or immediately after the scan, points to their attentional response to the cues representing binge-triggers, but not to the actual reward associated with the consumption of these binge-type foods. Furthermore, neuronal substrates in brain reward areas previously have been identified during of a 'liking' reaction to food, i.e. the striatum, were not differentially activated between the groups. Instead, brain areas functionally pointing to an early attentional bias toward the food images, and other areas functionally responsible for controlling emotional load and cognitively monitoring decisions about motor behavior, were differentially activated in the obese + BED, pointing to their strong 'wanting' reaction in response to the binge-triggers.

Several methodological issues of the present project should be discussed. Small sample size of the groups made it challenging to find clinically- and statistically-significant results. It would be beneficial to conduct a similar study using a larger sample size in each group to increase the power size. Nevertheless, clinically-relevant differences between the groups were found, with significant implications to the field of obesity and binge eating disorder. Another methodological challenge of the present project is the external validity of its findings: the population studied was strictly selective to exclude confounding variables and to ensure that

participants are suitable to go inside an fMRI machine. It still remains a question whether obese + BED who receive psychotherapy, or who currently are working on their weight loss, show similar behavioral traits and neurobiological correlates when viewing images of binge-triggers. Furthermore, it is not clear to what extent other individuals on the binge-eating spectrum, such as obese individual with some binge-eating behavior, who are missing one or more criteria for the official DSM-V diagnosis of binge-eating disorder, differ in their behavioral traits and neurobiological underpinnings, compared with the population studied in the present project. Thus, future research may investigate psycho-neurobiological correlates of binge-eating in different sub-groups over the binge-eating spectrum. Moreover, despite stratifying males and females to both groups, obese and obese + BED, it is notable that the final representation of each gender was slightly different in each group after some drop-out: there were more women in the obese + BED group (57%) and more men in the obese group (54%). Based on previous research showing gender differences in neural responses to images of food (Frank et al., 2010; Geliebter et al., 2013; Wang et al.,2009), the possibility that these small differences in the ratio of women to men between the groups skewed the results, should be raised. However, since analysis of functional brain imaging data involves tens of thousands of voxels averaged between participants, it is unlikely that these small gender differences between the groups introduce a problem to the validity of the results. Nevertheless, further study of gender differences on psycho-neurobehavioral parameters related to obesity and BED may be of clinical significance and should be pursued.

5.3. Summary

In the present study the obese + BED group showed greater dietary disinhibition and less reward responsiveness, compared with the obese group, and brain activation differences were detected in brain areas implicated in visual attention, emotional, motivational and cognitive evaluation of reward, as well as mechanosensation and motor planning of future actions, in response to images of binge-triggers. Furthermore, differences were detected between obese

+ BED versus obese in the relationships between 'disinhibition' scores and brain activation in two brain areas: the right anterior cingulate gyrus – Brodmann #32, and the left postcentral gyrus. It is possible that frequent 'yo-yo' dieting and emotional eating in the obese population with BED produce heightened attention and somatosensory responses to binge-triggers. Coupled with blunted internal awareness of mechanosensory cues, such as physiological sensations of hunger and satiety, this may weaken the obese + BED's control over the drive to initiate a binge and curtail their efforts to stop it when they are full.

The etiology of binge eating disorder is complex. Emotional coping difficulties with everyday life, beliefs about 'forbidden' foods and misconceptions about proper dietary behavior are at the core of this eating disorder. Physiological, structural and neurochemical changes are associated with disturbed dietary behaviors (Corwin, Avena, & Boggiano, 2011), but cause and effect relationships are still unknown. A dietary, cognitive and emotional therapy to target these behaviors and beliefs may help support healthier relationships with food. The present study is novel in its contribution to the understanding of functional brain substrates of binge-eating behavior in the absence of hunger in BED. Furthermore, it points to three behavioral traits (anxiety; reward responsiveness; disinhibition of dietary restraint) with clinical significance to the field of obesity and BED, and to a possible link between these psycho-behavioral constructs and their neurobiological underpinnings. These findings should be further studied to help find the best approach for prevention of, and treatment for, BED.

5.4. Implications for research and practice

It would be of a great value if future studies focus on the distinction and similarities between the constructs of 'reward responsiveness' versus 'reward sensitivity', and on their neurobiological underpinnings in obese adults and in obese with binge eating disorder. Also, replication of several aspects of the present project are indicated: greater 'reward responsiveness', reflected in the BAS(reward) subscale, in obese versus obese + BED should

be reexamined to confirm the findings of significant differences between the groups. Reduced 'liking' and increased 'wanting' responses to a visual presentation of binge-triggers in obese + BED has clinical implications. Clinicians may address the automatic 'wanting' response experienced by obese + BED when they encounter binge-triggers, since this group may be practicing this automatic response for years, building on a functional brain system supporting this reaction to binge-triggers. With practice, this automatic 'wanting' response may attenuate, and new, healthier, habits may be established, supported by normalized functional brain responses to cues of high energy food. It would be of great value to study a group of obese + binge before and after such a learning process.

Secondly, the construct of anxiety – trait and state - in obesity and obesity + BED should be explored to a greater depth. The present project points to possible relationships between these two constructs, but it has not provided a clear understanding in this regard. Based on previous studies pointing to greater psychopathology in obese + BED compared with obese controls, it is plausible that anxiety may contribute to obese + BED's response to binge-triggers. Thus, future studies may look at the functional neurobiological correlates of anxiety in these two groups, in general and in response to encountering binge-triggers, and possible link between anxiety, trait disinhibition, and substance abuse, should be explored.

Several other research questions can be explored, based on the findings of the present project: 1/ does the executive control system of the brain play a role in abnormal function of the anterior cingulate cortex and disinhibited eating in obese + BED, and how this may be different in obesity? Do obese versus obese + BED have problems with sustained attention and cognitive control in response to binge-triggers? These questions could be studied using similar methodology as used in the present project, and by adding clinical neuropsychological tests to examine executive control functioning in these two populations. Also, it would be beneficial to study functional brain activity of obese versus obese + BED at rest and during

switching to a cognitively-demanding task, to identify brain regions with abnormal functioning. Other questions to explore are whether adults with other sub-types of binge-eating, i.e. binge-eaters who do not conform to the DSM-V definition of BED, show similar psycho-neurobiological findings to obese + BED. The answer to this could help clarify if the results of the present project can be generalized to other binge-eaters, such as people who suffer from binge-eating as part of "eating disorders not otherwise specified", or bulimics, thereby increasing the external validity of the results. Lastly, comparing eating behavior in patients with fronto-temporal dementia versus eating behavior in participants with obesity + BED could help shed light on our understanding of neurobiological correlates of binge-eaters.

Clinically, disinhibition of rigid dietary restraint plays a role in the etiology of obesity with BED. It was clearly indicated in the present study that disinhibition of rigid dietary restraint differentiates between obese adults versus obese + BED, and, in response to pictures of binge-triggers, this was correlated with reduced activity in key brain areas responsible for somatosensation and emotional evaluation of, and salience attribution attached to, a stimulus. Thus, clinicians are encouraged to use this information to treat their obese + BED patients: reducing rigid, while increasing flexible, dietary restraint, concurrently with changing the "all or nothing" attitude of binge-eaters to high energy food, is expected to reduce binge-eating episodes, and, if practiced for long enough, normalize brain function in response to the sight of a binge-eating stimulus.

REFERENCES CITED

-American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (5th Ed.). Arlington, VA: American Psychiatric Publishing.

-American Psychiatric Association. (2013). Feeding and Eating Disorders. American Psychiatric Publishing: Arlington, VA. Retrieved from: http://www.dsm5.org/documents/eating%20disorders%20fact%20sheet.pdf

-Abraham, S. F., & Beumont, P. J. (1982). How patients describe bulimia or binge eating. Psychol Med, 12(3), 625-635.

-Adam, T. C., & Epel, E. S. (2007). Stress, eating and the reward system. Physiol Behav, 91(4), 449-458.

-Agras, W. S., Telch, C. (1998). The effects of caloric deprivation and negative affect on binge eating in obese binge-eating disordered women. . Behavior Therapy, 29, 491-503.

-Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. Clin Psychol Rev, 30(2), 217-237.

-Alegria, M., Woo, M., Cao, Z., Torres, M., Meng, X. L., & Striegel-Moore, R. (2007). Prevalence and correlates of eating disorders in Latinos in the United States. Int J Eat Disord, 40 Suppl, S15-21.

-Alonso-Alonso, M., & Pascual-Leone, A. (2007). The right brain hypothesis for obesity. JAMA, 297(16), 1819-1822.

-Alpers, G. W., & Tuschen-Caffier, B. (2001). Negative feelings and the desire to eat in bulimia nervosa. Eat Behav, 2(4), 339-352.

-Angle, S., Engblom, J., Eriksson, T., Kautiainen, S., Saha, M. T., Lindfors, P., . . . Rimpela, A. (2009). Three factor eating questionnaire-R18 as a measure of cognitive restraint, uncontrolled eating and emotional eating in a sample of young Finnish females. Int J Behav Nutr Phys Act, 6, 41.

-Aragona, B. J., & Carelli, R. M. (2006). Dynamic neuroplasticity and the automation of motivated behavior.Learn Mem, 13(5), 558-559.

-Arnow, B., Kenardy, J., & Agras, W. S. (1992). Binge eating among the obese: a descriptive study. J Behav Med, 15(2), 155-170.

-Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. Nat Rev Neurosci, 10(6), 410-422.

-Augustine, J. R. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. [Review]. Brain Res Brain Res Rev, 22(3), 229-244.

-Balodis, I. M., Grilo, C. M., Kober, H., Worhunsky, P. D., White, M. A., Stevens, M. C., ... & Potenza, M. N. (2014). A pilot study linking reduced fronto–Striatal recruitment during reward processing to persistent bingeing following treatment for binge-eating disorder. International Journal of Eating Disorders, 47(4), 376-384.

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

-Baumeister, R. F. (1997). Esteem threat, self-regulatory breakdown, and emotional distress as factors in self-defeating behavior. Review of General Psychology, 1(2), 145-174.

-Baumeister, R. F., & Heatherton, T. F. (1996). Self-regulation failure: An overview. Psychological inquiry, 7(1), 1-15.

-Bechara, A., Damasio, H., Tranel, D., & Anderson, S. W. (1998). Dissociation Of working memory from decision making within the human prefrontal cortex. J Neurosci, 18(1), 428-437.

-Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. Brain, 123(Pt 11), 2189-2202.

-Beckmann, M., Johansen-Berg, H., & Rushworth, M. F. (2009). Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. The Journal of neuroscience, 29(41), 175-1190.

-Berns, G. S., McClure, S. M., Pagnoni, G., & Montague, P. R. (2001). Predictability modulates human brain response to reward. J Neurosci, 21(8), 2793-2798.

-Berridge, K. C. (2001). Reward learning: reinforcement, incentives, and expectations. In D. L. Medin (Ed.), The psychology of Learning and Motivation (Vol. 40, pp. 223-278). Waltham, Massachusetts: Academic Press.

-Berridge, K. C. (2007). The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl), 191(3), 391-431.

-Berridge, K. C. (2009). 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. Physiol Behav, 97(5), 537-550.

-Berridge, K. C., & Aldridge, J. W. (2008). Decision Utility, the Brain, and Pursuit of Hedonic Goals. Soc Cogn, 26(5), 621-646.

-Berridge, K. C., Ho, C. Y., Richard, J. M., & DiFeliceantonio, A. G. (2010). The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. Brain Res, 1350, 43-64.

-Berridge, K. C., & Kringelbach, M. L. (2008). Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl), 199(3), 457-480.

-Berridge, K. C., Robinson, T. E., & Aldridge, J. W. (2009). Dissecting components of reward: 'liking', 'wanting', and learning. Curr Opin Pharmacol, 9(1), 65-73.

-Berthoud, H. R., & Morrison, C. (2008). The brain, appetite, and obesity. Annu Rev Psychol, 59, 55-92.
-Bishop, S. J. (2009). Trait anxiety and impoverished prefrontal control of attention. Nat Neurosci, 12(1), 92-98.

-Bishop, S., Duncan, J., Brett, M., & Lawrence, A. D. (2004). Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. Nat Neurosci, 7(2), 184-188.

-Bjork, J. M., Hommer, D. W. (2007). Anticipating instrumentally obtained and passively received rewards: a factorial fMRI investigation. Behavioral Brain Research, 177(1), 165–170.

-Blakemore, S. J., & Sirigu, A. (2003). Action prediction in the cerebellum and in the parietal lobe. Experimental Brain Research, 153(2), 239-245.

-Bochicchio, G. V., Guzzo, J. L., & Scalea, T. M. (2006). Percutaneous endoscopic gastrostomy in the supermorbidly obese patient. JSLS, 10(4), 409-413.

-Boeka, A. G., & Lokken, K. L. (2011). Prefrontal systems involvement in binge eating. Eat Weight Disord, 16(2), e121-126.

-Bonelli, R. M., & Cummings, J. L. (2007). Frontal-subcortical circuitry and behavior. Dialogues Clin Neurosci, 9(2), 141-151.

-Borg, P., Fogelholm, M., & Kukkonen-Harjula, K. (2004). Food selection and eating behaviour during weight maintenance intervention and 2-y follow-up in obese men. Int J Obes Relat Metab Disord, 28(12), 1548-1554.

-Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. Psychological review, 108(3), 624.

-Branson, R., Potoczna, N., Kral, J. G., Lentes, K. U., Hoehe, M. R., & Horber, F. F. (2003). Binge eating as a major phenotype of melanocortin 4 receptor gene mutations. N Engl J Med, 348(12), 1096-1103.

-Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. Trends in cognitive sciences, 14(6), 277-290.

-Brody, A. L., Mandelkern, M. A., Olmstead, R. E., Jou, J., Tiongson, E., Allen, V., ... & Cohen, M. S. (2007). Neural substrates of resisting craving during cigarette cue exposure. Biological psychiatry, 62(6), 642-651.

-Brunstrom, J. M., Yates, H. M., & Witcomb, G. L. (2004). Dietary restraint and heightened reactivity to food. Physiol Behav, 81(1), 85-90.

-Bryant, E. J., King, N. A., & Blundell, J. E. (2008). Disinhibition: its effects on appetite and weight regulation. Obes Rev, 9(5), 409-419.

-Bulik, C. M., Sullivan, P. F., & Kendler, K. S. (2002). Medical and psychiatric morbidity in obese women with and without binge eating. Int J Eat Disord, 32(1), 72-78.
-Bulik, C. M., Sullivan, P. F., & Kendler, K. S. (2003). Genetic and environmental contributions to obesity and binge eating. [Twin Study]. Int J Eat Disord, 33(3), 293-298.

-Burgess, E. E., Turan, B., Lokken, K. L., Morse, A., & Boggiano, M. M. (2014). Profiling motives behind hedonic eating. Preliminary validation of the Palatable Eating Motives Scale. Appetite, 72, 66-72.

-Caballero, B. (2001). Introduction. Symposium: Obesity in developing countries: biological and ecological factors. [Review]. J Nutr, 131(3), 866S-870S.

-Cabanac, M. (1971). Physiological role of pleasure. Science, 173(4002), 1103-1107.
-Cabanac, M. (1979). Sensory pleasure. Q Rev Biol, 54(1), 1-29.

-Cabeza de Vaca, S., & Carr, K. D. (1998). Food restriction enhances the central rewarding effect of abused drugs. J Neurosci, 18(18), 7502-7510.

-Cambridge, V. C., Ziauddeen, H., Nathan, P. J., Subramaniam, N., Dodds, C., Chamberlain, S. R., ... & Fletcher, P. C. (2013). Neural and behavioral effects of a novel mu opioid receptor antagonist in binge-eating obese people. Biological psychiatry, 73(9), 887-894.

-Campbell, B. C., & Eisenberg, D. (2007). Obesity, attention deficit-hyperactivity disorder and the dopaminergic reward system. Coll Antropol, 31(1), 33-38.

-Cardinal, R. N., Parkinson, J. A., Hall, J., & Everitt, B. J. (2002). Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci Biobehav Rev, 26(3), 321-352.

-Carr, K. D. (2002). Augmentation of drug reward by chronic food restriction: behavioral evidence and underlying mechanisms. Physiol Behav, 76(3), 353-364.

-Carrard, I., Crépin, C., Ceschi, G., Golay, A., & Van der Linden, M. (2012). Relations between pure dietary and dietary-negative affect subtypes and impulsivity and reinforcement sensitivity in binge eating individuals. Eating behaviors, 13(1), 13-19.

-Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. J Pers Soc Psychol, 67(2), 319-333.

-Celio, A. A., Wilfley, D. E., Crow, S. J., Mitchell, J., & Walsh, B. T. (2004). A comparison of the binge eating scale, questionnaire for eating and weight patterns-revised, and eating disorder examination questionnaire with instructions with the eating disorder examination in the assessment of binge eating disorder and its symptoms. Int J Eat Disord, 36(4), 434-444.

-Chua, J. L., Touyz, S., & Hill, A. J. (2004). Negative mood-induced overeating in obese binge eaters: an experimental study. Int J Obes Relat Metab Disord, 28(4), 606-610.

-Chudler, E.H. (2012). Neuroscience for kids. Retrieved from https://faculty.washington.edu/chudler/slice.htm

-Cloninger, C. R. (1994). Temperament and personality. Curr Opin Neurobiol, 4(2), 266-273.
-Colantuoni, C., Schwenker, J., McCarthy, J., Rada, P., Ladenheim, B., Cadet, J. L., . . . Hoebel, B. G. (2001). Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. Neuroreport, 12(16), 3549-3552.

-Colditz, G. A. (1999). Economic costs of obesity and inactivity. Med Sci Sports Exerc, 31(11 Suppl), S663-667.

-Coletta, M., Platek, S., Mohamed, F. B., van Steenburgh, J. J., Green, D., & Lowe, M. R. (2009). Brain activation in restrained and unrestrained eaters: an fMRI study. J Abnorm Psychol, 118(3), 598-609.

-Colles, S. L., Dixon, J. B., & O'Brien, P. E. (2008). Loss of control is central to psychological disturbance associated with binge eating disorder. Obesity (Silver Spring), 16(3), 608-614.

-Contento, I. R., Zybert, P., & Williams, S. S. (2005). Relationship of cognitive restraint of eating and disinhibition to the quality of food choices of Latina women and their young children. Prev Med, 40(3), 326-336.

-Cottone, P., Sabino, V., Steardo, L., & Zorrilla, E. P. (2008). Opioid-dependent anticipatory negative contrast and binge-like eating in rats with limited access to highly preferred food. Neuropsychopharmacology, 33(3), 524-535.

-Coutinho, W. F., Moreira, R. O., Spagnol, C., & Appolinario, J. C. (2007). Does binge eating disorder alter cortisol secretion in obese women? Eat Behav, 8(1), 59-64.

-Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. Neuron, 58(3), 306-324.

-Corwin, R. L., Avena, N. M., & Boggiano, M. M. (2011). Feeding and reward: perspectives from three rat models of binge eating. Physiology & behavior,104(1), 87-97.

-Covington, H. E., 3rd, & Miczek, K. A. (2005). Intense cocaine self-administration after episodic social defeat stress, but not after aggressive behavior: dissociation from corticosterone activation. Psychopharmacology (Berl), 183(3), 331-340.

-Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci, 3(8), 655-666.

-Craig, A. D. (2003). Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol, 13(4), 500-505.

-Craig, A. D. (2009). How do you feel—now? the anterior insula and human awareness. Nature Reviews Neuroscience, 10, 59–70.

-Crick, F., & Koch, C. (2005). "What is the function of the claustrum?". Philosophical Transactions of the Royal Society B: Biological Sciences, 360(1458), 1271–1279.

-Cromwell, H. C., & Berridge, K. C. (1993). Where does damage lead to enhanced food aversion: the ventral pallidum/substantia innominata or lateral hypothalamus? Brain Res, 624(1-2), 1-10.
-Dallman, M. F., Pecoraro, N., Akana, S. F., La Fleur, S. E., Gomez, F., Houshyar, H., . . . Manalo, S. (2003). Chronic stress and obesity: a new view of "comfort food". Proc Natl Acad Sci U S A, 100(20), 11696-11701.

-Dalton, M., Blundell, J., & Finlayson, G. (2013). Effect of BMI and binge eating on food reward and energy intake: further evidence for a binge eating subtype of obesity. Obes Facts, 6(4), 348-359.
-Davis, C. (2013). From passive overeating to “food addiction”: a spectrum of compulsion and severity. ISRN obesity, 2013.

-Davis, C., & Carter, J. C. (2009). Compulsive overeating as an addiction disorder. A review of theory and evidence. Appetite, 53(1), 1-8.

-Davis, C., Levitan, R. D., Kaplan, A. S., Carter, J., Reid, C., Curtis, C., . . . Kennedy, J. L. (2007). Dopamine transporter gene (DAT1) associated with appetite suppression to methylphenidate in a case-control study of binge eating disorder. Neuropsychopharmacology, 32(10), 2199-2206.

-Davis, C., Levitan, R. D., Kaplan, A. S., Carter, J., Reid, C., Curtis, C., ... & Kennedy, J. L. (2008). Reward sensitivity and the D2 dopamine receptor gene: A case-control study of binge eating disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 32(3), 620-628.

-Davis, C., Levitan, R. D., Muglia, P., Bewell, C., & Kennedy, J. L. (2004). Decision-making deficits and overeating: a risk model for obesity. Obes Res, 12(6), 929-935.

-Davis, C. A., Levitan, R. D., Reid, C., Carter, J. C., Kaplan, A. S., Patte, K. A., . . . Kennedy, J. L. (2009). Dopamine for "wanting" and opioids for "liking": a comparison of obese adults with and without binge eating. Obesity (Silver Spring), 17(6), 1220-1225.

-Davis, C., Patte, K., Levitan, R., Reid, C., Tweed, S., & Curtis, C. (2007). From motivation to behaviour: a model of reward sensitivity, overeating, and food preferences in the risk profile for obesity. Appetite, 48(1), 12-19.

-Dawe, S., & Loxton, N. J. (2004). The role of impulsivity in the development of substance use and eating disorders. Neuroscience and Biobehavioral Reviews, 28(3), 343-351.

-de Araujo, I. E., Rolls, E. T., Kringelbach, M. L., McGlone, F., & Phillips, N. (2003). Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. Eur J Neurosci, 18(7), 2059-2068.

-Deen, B., Pitskel, N. B., & Pelphrey, K. A. (2011). Three systems of insular functional connectivity identified with cluster analysis. Cereb Cortex, 21(7), 1498-1506.

-DelParigi, A., Chen, K., Salbe, A. D., Hill, J. O., Wing, R. R., Reiman, E. M., & Tataranni, P. A. (2007). Successful dieters have increased neural activity in cortical areas involved in the control of behavior. Int J Obes (Lond), 31(3), 440-448.

-DelParigi, A., Chen, K., Salbe, A. D., Reiman, E. M., & Tataranni, P. A. (2005). Sensory experience of food and obesity: a positron emission tomography study of the brain regions affected by tasting a liquid meal after a prolonged fast. Neuroimage, 24(2), 436-443.

-Del Parigi, A., Gautier, J. F., Chen, K., Salbe, A. D., Ravussin, E., Reiman, E., & Tataranni, P. A. (2002). Neuroimaging and obesity: mapping the brain responses to hunger and satiation in humans using positron emission tomography. Ann N Y Acad Sci, 967, 389-397.

-Dennis, R. E., Boddington, S. J. A., & Funnell, N. J. (2007). Self-report measures of anxiety: Are they suitable for older adults?. Aging & mental health,11(6), 668-677.

-Denkova, E., Wong, G., Dolcos, S., Sung, K., Wang, L., Coupland, N., & Dolcos, F. (2010). The impact of anxiety-inducing distraction on cognitive performance: a combined brain imaging and personality investigation. PLoS One, 5(11), e14150.

-De Zwaan, M. (2001). Binge eating disorder and obesity. International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity, 25, S51-S55.

-Diekhof, E. K., Falkai, P., & Gruber, O. (2008). Functional neuroimaging of reward processing and decision-making: a review of aberrant motivational and affective processing in addiction and mood disorders. Brain Res Rev, 59(1), 164-184.

-DiLeone, R. J., Taylor, J. R., & Picciotto, M. R. (2012). The drive to eat: comparisons and distinctions between mechanisms of food reward and drug addiction. Nat Neurosci, 15(10), 1330-1335.

-Dodds, C. M., O'Neill, B., Beaver, J., Makwana, A., Bani, M., Merlo-Pich, E., ... & Nathan, P. J. (2012). Effect of the dopamine receptor antagonist GSK598809 on brain responses to rewarding food images in overweight and obese binge eaters. Appetite, 59(1), 27-33.

-Dolcos, F., Diaz-Granados, P., Wang, L., & McCarthy, G. (2008). Opposing influences of emotional and non-emotional distracters upon sustained prefrontal cortex activity during a delayed-response working memory task. Neuropsychologia, 46(1), 326-335.

-Dolcos, F., Kragel, P., Wang, L., & McCarthy, G. (2006). Role of the inferior frontal cortex in coping with distracting emotions. Neuroreport, 17(15), 1591-1594.

-Dolcos, F., & McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. J Neurosci, 26(7), 2072-2079.

-Downe, K. A., Goldfein, J. A., & Devlin, M. J. (2009). Restraint, hunger, and disinhibition following treatment for binge-eating disorder. Int J Eat Disord, 42(6), 498-504.

-Drewnowski, A., Krahn, D. D., Demitrack, M. A., Nairn, K., & Gosnell, B. A. (1995). Naloxone, an opiate blocker, reduces the consumption of sweet high-fat foods in obese and lean female binge eaters. Am J Clin Nutr, 61(6), 1206-1212.

-Engelmann, J. B., Damaraju, E., Padmala, S., Pessoa, L. (2009). Combined effects of attention and motivation on visual task performance: transient and sustained motivational effects. Frontiers in Human Neuroscience , 3.

-Epel, E., Lapidus, R., McEwen, B., & Brownell, K. (2001). Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behavior. Psychoneuroendocrinology, 26(1), 37-49.

-Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. Trends in cognitive sciences, 15(2), 85-93.

-Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry, 164(10), 1476-1488.

-Evans, A.C., Janke, A.L., Collins, D.L., Baillet, S. (2012). Brain templates and atlases. Neuroimage, 62(2):911-22.

-Eysenck, M. W., Calvo, M.G. (1992). Anxiety and Performance: The Processing Efficiency Theory. Cognition & Emotion, 6(6), 409-434.

-Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. Emotion, 7(2), 336-353.

-Fairburn, C.G., Cooper, Z. The Eating Disorder Examination. In: Fairburn, C. G., Wilson, G. T., & Schleimer, K. (1993). Binge eating: Nature, assessment, and treatment (pp. 333-360). New York: Guilford Press.

-Farb, N. A., Segal, Z. V., & Anderson, A. K. (2013). Mindfulness meditation training alters cortical representations of interoceptive attention. Soc Cogn Affect Neurosci, 8(1), 15-26.

-Farooqi, I. S., Bullmore, E., Keogh, J., Gillard, J., O'Rahilly, S., & Fletcher, P. C. (2007). Leptin regulates striatal regions and human eating behavior. Science, 317(5843), 1355.

-Flagel, S. B., Watson, S. J., Akil, H., & Robinson, T. E. (2008). Individual differences in the attribution of incentive salience to a reward-related cue: influence on cocaine sensitization. Behav Brain Res, 186(1), 48-56.

-Fowles, D. C. (1987). Application of a behavioral theory of motivation to the concepts of anxiety and impulsivity. Journal of research in personality, 21(4), 417-435.

-Francis, L.S., Robin, A.H., Katherine, H.T. (2011). Anterior Cingulate Cortex: Unique Role in Cognition and Emotion. The Journal of Neuropsychiatry Clinical Neuroscience , 23(2), 121-125.

-Frank, S., Kullmann, S., & Veit, R. (2013). Food related processes in the insular cortex. Front Hum Neurosci, 7, 499.

-Frank, S., Laharnar, N., Kullmann, S., Veit, R., Canova, C., Hegner, Y. L., . . . Preissl, H. (2010). Processing of food pictures: influence of hunger, gender and calorie content. Brain Res, 1350, 159-166.

-Friston, K. J., Holmes, A. P., Poline, J. B., Grasby, P. J., Williams, S. C., Frackowiak, R. S., & Turner, R. (1995). Analysis of fMRI time-series revisited. Neuroimage, 2(1), 45-53.

-Finlayson, G., King, N., & Blundell, J. E. (2007). Liking vs. wanting food: importance for human appetite control and weight regulation Neurosci Biobehav Rev, 31(7), 987-1002.

-French, S. A., Epstein, L. H., Jeffery, R. W., Blundell, J. E., & Wardle, J. (2012). Eating behavior dimensions. Associations with energy intake and body weight. A review. Appetite, 59(2), 541-549.

-Fuhrer, D., Zysset, S., & Stumvoll, M. (2008). Brain activity in hunger and satiety: an exploratory visually stimulated FMRI study. Obesity (Silver Spring), 16(5), 945-950.

-Gorman, B.S., & Allison, D.B. Measures of restrained eating. (1995). In: Allison, DB., editor. Handbook of assessment for eating behaviors and weight-related problems. Thousand Oaks, CA: Sage Publishing, Inc., 149-184.

-Gormally, J., Black, S., Daston, S., & Rardin, D. (1982). The assessment of binge eating severity among obese persons. Addict Behav, 7(1), 47-55.

-Galanti, K., Gluck, M. E., & Geliebter, A. (2007). Test meal intake in obese binge eaters in relation to impulsivity and compulsivity. Int J Eat Disord, 40(8), 727-732.

-Gallant, A. R., Tremblay, A., Pérusse, L., Després, J. P., Bouchard, C., & Drapeau, V. (2012). Past dieting is related to rigid control and disinhibition in adolescents from the Quebec Family Study. British Journal of Nutrition,108(11), 1976-1979.

-Garcia-Garcia, I., Jurado, M. A., Garolera, M., Segura, B., Sala-Llonch, R., Marques-Iturria, I., . . . Junque, C. (2013). Alterations of the salience network in obesity: a resting-state fMRI study. Hum Brain Mapp, 34(11), 2786-2797.

-García-García, I., Narberhaus, A., Marqués-Iturria, I., Garolera, M., Rădoi, A., Segura, B., ... & Jurado, M. A. (2013). Neural responses to visual food cues: insights from functional magnetic resonance imaging. European Eating Disorders Review, 21(2), 89-98.

-Garavan, H. (2010). Insula and drug cravings. Brain Struct Funct, 214(5-6), 593-601.

-Gautier, J. F., Chen, K., Salbe, A. D., Bandy, D., Pratley, R. E., Heiman, M., . . . Tataranni, P. A. (2000). Differential brain responses to satiation in obese and lean men. Diabetes, 49(5), 838-846.

-Gautier, J. F., Del Parigi, A., Chen, K., Salbe, A. D., Bandy, D., Pratley, R. E., . . . Tataranni, P. A. (2001). Effect of satiation on brain activity in obese and lean women. Obes Res, 9(11), 676-684.

-Gehring, W. J., & Knight, R. T. (2000). Prefrontal–cingulate interactions in action monitoring. Nature neuroscience, 3(5), 516-520.

-Geiger, B. M., Haburcak, M., Avena, N. M., Moyer, M. C., Hoebel, B. G., & Pothos, E. N. (2009). Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity. Neuroscience, 159(4), 1193-1199.

-Geliebter, A., Gluck, M. E., & Hashim, S. A. (2005). Plasma ghrelin concentrations are lower in binge-eating disorder. J Nutr, 135(5), 1326-1330.

-Geliebter, A., Hashim, S. A., & Gluck, M. E. (2008). Appetite-related gut peptides, ghrelin, PYY, and GLP-1 in obese women with and without binge eating disorder (BED). Physiol Behav, 94(5), 696-699.

-Geliebter, A., Ladell, T., Logan, M., Schweider, T., Sharafi, M., Hirsch, J. (2006). Responsivity to food stimuli in obese and lean binge eaters using functional MRI. Appetite, 46(1), 31–35.

-Geliebter, A., Pantazatos, S. P., McOuatt, H., Puma, L., Gibson, C. D., & Atalayer, D. (2013). Sex-based fMRI differences in obese humans in response to high vs. low energy food cues. Behavioural brain research, 243, 91-96.

-Geliebter, A., Yahav, E. K., Gluck, M. E., & Hashim, S. A. (2004). Gastric capacity, test meal intake, and appetitive hormones in binge eating disorder. Physiol Behav, 81(5), 735-740.

-Gianini, L. M., White, M. A., & Masheb, R. M. (2013). Eating pathology, emotion regulation, and emotional overeating in obese adults with Binge Eating Disorder. Eat Behav, 14(3), 309-313.

-Gill, R., Chen, Q., D'Angelo, D., & Chung, W. K. (2014). Eating in the absence of hunger but not loss of control behaviors are associated with 16p11. 2 deletions. Obesity.
-Gluck, M. E., Geliebter, A., Hung, J., & Yahav, E. (2004). Cortisol, hunger, and desire to binge eat following a cold stress test in obese women with binge eating disorder. Psychosom Med, 66(6), 876-881.

-Goldfein, J. A., Walsh, B. T., LaChaussee, J. L., Kissileff, H. R., & Devlin, M. J. (1993). Eating behavior in binge eating disorder. Int J Eat Disord, 14(4), 427-431.

-Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry, 159(10), 1642-1652.

-Gray, J. A. (1994). Three fundamental emotion systems. In P. Ekman & R. J. Davidson (Eds.), The nature of emotion: Fundamental questions (pp. 243-247). New York: Oxford University Press.

-Gray, J. R., & Braver, T. S. (2002). Personality predicts working-memory-related activation in the caudal anterior cingulate cortex. Cogn Affect Behav Neurosci, 2(1), 64-75.

-Gray, J. A., & McNaughton, N. (2000). The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system. Oxford: Oxford University Press.

-Greeno, C. G., Wing, R. R., & Shiffman, S. (2000). Binge antecedents in obese women with and without binge eating disorder. J Consult Clin Psychol, 68(1), 95-102.

-Gross, J. J. (2007). Handbook of emotion regulation. New York, NY: Guildford Press.

-Gluck, M. E., Geliebter, A., Hung, J., & Yahav, E. (2004). Cortisol, hunger, and desire to binge eat following a cold stress test in obese women with binge eating disorder. Psychosom Med, 66(6), 876-881.

-Grucza, R. A., Przybeck, T. R., & Cloninger, C. R. (2007). Prevalence and correlates of binge eating disorder in a community sample. Compr Psychiatry, 48(2), 124-131.

-Guss, J. L., Kissileff, H. R., Devlin, M. J., Zimmerli, E., & Walsh, B. T. (2002). Binge size increases with body mass index in women with binge-eating disorder. Obes Res, 10(10), 1021-1029.

-Haedt-Matt, A. A., & Keel, P. K. (2011). Revisiting the affect regulation model of binge eating: a meta-analysis of studies using ecological momentary assessment. Psychological Bulletin, 137(4), 660–681.

-Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. Science,324(5927), 646-648.

-Harvey, K., Rosselli, F., Wilson, G. T., Debar, L. L., & Striegel-Moore, R. H. (2011). Eating patterns in patients with spectrum binge-eating disorder. Int J Eat Disord, 44(5), 447-451.

-Hasler, G., Pine, D. S., Gamma, A., Milos, G., Ajdacic, V., Eich, D., . . . Angst, J. (2004). The associations between psychopathology and being overweight: a 20-year prospective study. Psychol Med, 34(6), 1047-1057.

-Hawkins, R. C., Clement, P. F. (1984). Binge-eating: measurement, problems and a conceptual model. In R. C. Hawkins, Fremouw, W. J., Clement, P. F. (Ed.), The binge purge syndrome: Diagnosis, treatment, and research (pp. 229-251). New York, NY: Springer.

-Hayden, B. Y., Nair, A. C., McCoy, A. N., Platt, M. L. (2008). Posterior cingulate cortex mediates outcome-contingent allocation of behavior. Neuron, 60(1), 19-25.

-He, Q., Xiao, L., Xue, G., Wong, S., Ames, S. L., Schembre, S. M., & Bechara, A. (2014). Poor ability to resist tempting calorie rich food is linked to altered balance between neural systems involved in urge and self-control. Nutrition journal, 13(1), 92.

-Heaner, M. K., & Walsh, B. T. (2013). A history of the identification of the characteristic eating disturbances of Bulimia Nervosa, Binge Eating Disorder and Anorexia Nervosa. Appetite, 65, 185-188.

-Heatherton, T. F. (2011). Neuroscience of self and self-regulation. Annual review of psychology, 62, 363.

-Heatherton, T. F., & Baumeister, R. F. (1991). Binge eating as escape from self-awareness. Psychol Bull, 110, 186-108.

-Hedberg, A. G. (1972). Review of State-Trait Anxiety Inventory. Prof Psychol, 3(4), 389-390.

-Herman, C. P., & Mack, D. (1975). Restrained and unrestrained eating. J Pers, 43(4), 647-660.

-Herman, C. P., & Polivy, J. (1975). Anxiety, restraint, and eating behavior. J Abnorm Psychol, 84(6), 66-72.

- Herman CP, Polivy J. Restrained Eating. W.B. Saunders: Philadelphia, 1980.

-Hetherington, M. M., & MacDiarmid, J. I. (1993). "Chocolate addiction": a preliminary study of its description and its relationship to problem eating. Appetite, 21(3), 233-246.

-Higgs, S., & Eskenazi, T. (2007). Dietary restraint and disinhibition are associated with increased alcohol use behaviours and thoughts in young women social drinkers. Eat Behav, 8(2), 236-243.

-Hofmann, W., Schmeichel, B. J., & Baddeley, A. D. (2012). Executive functions and self-regulation. Trends Cogn Sci, 16(3), 174-180.

- Holderness, C. C., Brooks-Gunn, J., & Warren, M. P. (1994). Co-morbidity of eating disorders and substance abuse review of the literature. International Journal of Eating Disorders, 16(1), 1-34.

-Howard, C. E., & Porzelius, L. K. (1999). The role of dieting in binge eating disorder: etiology and treatment implications. Clin Psychol Rev, 19(1), 25-44.

-Hudson, J. I., Hiripi, E., Pope, H. G., Jr., & Kessler, R. C. (2007). The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry, 61(3), 348-358.

-Huppert, T. J., Allen, M. S., Diamond, S. G., & Boas, D. A. (2009). Estimating cerebral oxygen metabolism from fMRI with a dynamic multicompartment Windkessel model. Human brain mapping, 30(5), 1548-1567.

-Isnard, P., Michel, G., Frelut, M. L., Vila, G., Falissard, B., Naja, W., . . . Mouren-Simeoni, M. C. (2003). Binge eating and psychopathology in severely obese adolescents. Int J Eat Disord, 34(2), 235-243.

-Jabbi, M., Swart, M., & Keysers, C. (2007). Empathy for positive and negative emotions in the gustatory cortex. Neuroimage, 34(4), 1744-1753.

-Jorm, A. F., Christensen, H., Henderson, A.S., Jacomb, P.A., Korten, A.E., Rodgers, B. (1998). Using the BIS/BAS scales to measure behavioural inhibition and behavioural activation: Factor structure, validity and norms in a large community sample. Pers Individ Dif, 26(1), 49-58.

-Kandel, E. R., Schwartz, J.H., Jessell, T.M. (2000). Principles of Neural Science. New York, NY: McGraw-Hill Health Professions Division.

-Kandel, E. R., Schwartz, J. H., & Jessell, T. M. (Eds.). (2012). Principles of neural science (Vol. 5, pp. 1227-1246). New York: McGraw-Hill.

-Karhunen, L. J., Vanninen, E. J., Kuikka, J. T., Lappalainen, R. I., Tiihonen, J., & Uusitupa, M. I. (2000). Regional cerebral blood flow during exposure to food in obese binge eating women. Psychiatry Research: Neuroimaging, 99(1), 29-42.

-Karlsson, J., Persson, L. O., Sjostrom, L., & Sullivan, M. (2000). Psychometric properties and factor structure of the Three-Factor Eating Questionnaire (TFEQ) in obese men and women. Results from the Swedish Obese Subjects (SOS) study. Int J Obes Relat Metab Disord, 24(12), 1715-1725.

-Kelley, A. E. (2004). Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. Neurosci Biobehav Rev, 27(8), 765-776.

-Kelley, A. E., & Berridge, K. C. (2002). The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci, 22(9), 3306-3311.

-Kelley, A. E., Schiltz, C. A., & Landry, C. F. (2005). Neural systems recruited by drug- and food-related cues: studies of gene activation in corticolimbic regions. Physiol Behav, 86(1-2), 11-14.

-Kelley, A. E., Schiltz, C. A., & Landry, C. F. (2005). Neural systems recruited by drug- and food-related cues: studies of gene activation in corticolimbic regions. Physiol Behav, 86(1-2), 11-14.

-Kennis, M., Rademaker, A. R., & Geuze, E. (2013). Neural correlates of personality: an integrative review. Neurosci Biobehav Rev, 37(1), 73-95.

-Kerns, J. G., Cohen, J. D., MacDonald, A. W., Cho, R. Y., Stenger, V. A., & Carter, C. S. (2004). Anterior cingulate conflict monitoring and adjustments in control. Science, 303(5660), 1023-1026.

-Kip, K. E., Marroquin, O. C., Kelley, D. E., Johnson, B. D., Kelsey, S. F., Shaw, L. J., . . . Reis, S. E. (2004). Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. Circulation, 109(6), 706-713.

-Knutson, B., Adams, C. M., Fong, G. W., Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci, 21(16), RC159.

-Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport, 12(17), 3683–3687.
-Krause, E. G., & Sakai, R. R. (2007). Richter and sodium appetite: from adrenalectomy to molecular biology. Appetite, 49(2), 353-367.

-Krebs, R. M., Boehler, C. N., Egner, T., & Woldorff, M. G. (2011). The neural underpinnings of how reward associations can both guide and misguide attention. The Journal of Neuroscience, 31(26), 9752-9759.

-Kringelbach, M. L. (2004). Food for thought: hedonic experience beyond homeostasis in the human brain. Neuroscience, 126(4), 807-819.

-Kringelbach, M. L. (2005). The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci, 6(9), 691-702.

-Krmpotich, T. D., Tregellas, J. R., Thompson, L. L., Banich, M. T., Klenk, A. M., & Tanabe, J. L. (2013). Resting-state activity in the left executive control network is associated with behavioral approach and is increased in substance dependence. Drug Alcohol Depend, 129(1-2), 1-7.

-Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Haring, H. U., . . . Preissl, H. (2012). The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity. Hum Brain Mapp, 33(5), 1052-1061.

-Laessle, R. G, Tuschl, R. J., Kotthaus, B. C. and Pirke, K. M. (1989). A comparison of the validity of three scales for the assessment of dietary restraint. J Abnorm Psychol, 98, 504–507.

-Lahteenmaki, L., & Tuorila, H. (1995). Three-factor eating questionnaire and the use and liking of sweet and fat among dieters. Physiol Behav, 57(1), 81-88.

-de Lauzon, B., Romon, M., Deschamps, V., Lafay, L., Borys, J. M., Karlsson, J., . . . Fleurbaix Laventie Ville Sante Study, G. (2004). The Three-Factor Eating Questionnaire-R18 is able to distinguish among different eating patterns in a general population. J Nutr, 134(9), 2372-2380.

-Leech, R., Braga, R., & Sharp, D. J. (2012). Echoes of the brain within the posterior cingulate cortex. The Journal of Neuroscience, 32(1), 215-222.

-Leech, R., Kamourieh, S., Beckmann, C. F., & Sharp, D. J. (2011). Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. The Journal of Neuroscience, 31(9), 3217-3224.

-Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. Brain, 137(1), 12-32.

-Leidy, H., Lepping, R., Savage, C., Harris, C., 2011. Neural responses to visual food stimuli after a normal vs. higher protein breakfast in breakfast-skipping teens: a pilot fMRI study. Obesity 19, 2019–2025.

-Leyton, M., Boileau, I., Benkelfat, C., Diksic, M., Baker, G., & Dagher, A. (2002). Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. Neuropsychopharmacology, 27(6), 1027-1035.

-Leombruni, P., Rocca, G., Fassino, S., Gastaldi, F., Nicotra, B., Siccardi, S., & Lavagnino, L. (2014). An Exploratory Study to Subtype Obese Binge Eaters by Personality Traits. Psychother Psychosom, 83(2), 114-118.

-Loeb, K. L., Lock, J., Grange, D. L., & Greif, R. (2012). Transdiagnostic Theory and Application of Family-Based Treatment for Youth with Eating Disorders. Cogn Behav Pract, 19(1), 17-30.

-Lo Sauro, C., Ravaldi, C., Cabras, P. L., Faravelli, C., & Ricca, V. (2008). Stress, hypothalamic-pituitary-adrenal axis and eating disorders. Neuropsychobiology, 57(3), 95-115.

-Lowe, M. R., van Steenburgh, J., Ochner, C., & Coletta, M. (2009). Neural correlates of individual differences related to appetite. Physiology & behavior, 97(5), 561-571.

-Loxton, N. J., Dawe, S., & Cahill, A. (2011). Does negative mood drive the urge to eat? The contribution of negative mood, exposure to food cues and eating style. Appetite, 56(2), 368-374.

-Lundy, R. F., Jr. (2008). Gustatory hedonic value: potential function for forebrain control of brainstem taste processing. Neurosci Biobehav Rev, 32(8), 1601-1606.

-Lynch, W. C., Everingham, A., Dubitzky, J., Hartman, M., & Kasser, T. (2000). Does binge eating play a role in the self-regulation of moods? Integr Physiol Behav Sci, 35(4), 298-313.

-MacDonald, A. W., Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science, 288(5472), 1835-1838.

-Macht, M. (2008). How emotions affect eating: a five-way model. Appetite, 50(1), 1-11.

-Maniam, J., & Morris, M. J. (2010). Palatable cafeteria diet ameliorates anxiety and depression-like symptoms following an adverse early environment. Psychoneuroendocrinology, 35(5), 717-728.

-Manwaring, J. L., Green, L., Myerson, J., Strube, M. J., & Wilfley, D. E. (2011). Discounting of Various types of rewards by women with and without binge eating Disorder: Evidence for general rather than specific Differences. Psychol Rec, 61(4), 561-582.

-Marchesini, G., Cuzzolaro, M., Mannucci, E., Dalle Grave, R., Gennaro, M., Tomasi, F., ... & Melchionda, N. (2004). Weight cycling in treatment-seeking obese persons: data from the QUOVADIS study. International journal of obesity, 28(11), 1456-1462.

-Marcus, M. D., & Kalarchian, M. A. (2003). Binge eating in children and adolescents. International Journal of Eating Disorders, 34(S1), S47-S57.

-Marek, R. J., Ben-Porath, Y. S., Ashton, K., & Heinberg, L. J. (2014). Impact of using DSM-5 criteria for diagnosing binge eating disorder in bariatric surgery candidates: Change in prevalence rate, demographic characteristics, and scores on the minnesota multiphasic personality inventory - 2 restructured form (MMPI-2-RF). Int J Eat Disord. Advance online publication. DOI: 10.1002/eat.22268

-Martin, J. (2012). Neuroanatomy Text and atlas. New York: McGraw-Hill Education.
Mahler, S. V., & Berridge, K. C. (2009). Which cue to "want?" Central amygdala opioid activation enhances and focuses incentive salience on a prepotent reward cue. J Neurosci, 29(20), 6500-6513.

-Mattes, R. D. (1997). Physiologic responses to sensory stimulation by food: nutritional implications. Journal of the American Dietetic Association, 97(4), 406-413.

-Mela, D. J. (2006). Eating for pleasure or just wanting to eat? Reconsidering sensory hedonic responses as a driver of obesity. Appetite, 47(1), 10-17.

-Mendelsohn, A., Pine, A., & Schiller, D. (2014). Between Thoughts and Actions: Motivationally Salient Cues Invigorate Mental Action in the Human Brain. Neuron, 81(1), 207-217.

-Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. Brain Structure and Function, 214(5-6), 655-667.

-Mesulam, M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Annals of neurology, 28(5), 597-613.

-Michaelides, M., Thanos, P. K., Volkow, N. D., & Wang, G. J. (2012). Dopamine-related frontostriatal abnormalities in obesity and binge-eating disorder: emerging evidence for developmental psychopathology. Int Rev Psychiatry, 24(3), 211-218.

-Mitchell, J. P., Heatherton, T. F., Kelley, W. M., Wyland, C. L., Wegner, D. M., & Macrae, C. N. (2007). Separating sustained from transient aspects of cognitive control during thought suppression. Psychological Science, 18(4), 292-297.

-Mobbs, O., Iglesias, K., Golay, A., & Van der Linden, M. (2011). Cognitive deficits in obese persons with and without binge eating disorder. Investigation using a mental flexibility task. Appetite, 57(1), 263-271.

-Morris, J. S., & Dolan, R. J. (2001). Involvement of human amygdala and orbitofrontal cortex in hunger-enhanced memory for food stimuli. J Neurosci, 21(14), 5304-5310.

-Munsch, S., Meyer, A. H., Quartier, V., & Wilhelm, F. H. (2012). Binge eating in binge eating disorder: a breakdown of emotion regulatory process? Psychiatry Res, 195(3), 118-124.

-Murray, E. A., & Izquierdo, A. (2007). Orbitofrontal cortex and amygdala contributions to affect and action in primates. Ann N Y Acad Sci, 1121, 273-296.

-Nasser, J. A., Gluck, M. E., & Geliebter, A. (2004). Impulsivity and test meal intake in obese binge eating women. Appetite, 43(3), 303-307.

-National Institutes of Health. (1998). Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. [Consensus Development Conference, NIH Guideline Practice Guideline Review]. Obes Res, 6 Suppl 2, 51S-209S.

-Ng, L., & Davis, C. (2013). Cravings and food consumption in Binge Eating Disorder. Eat Behav, 14(4), 472-5.

-Nicdao, E. G., Hong, S., & Takeuchi, D. T. (2007). Prevalence and correlates of eating disorders among Asian Americans: results from the National Latino and Asian American Study. Int J Eat Disord, 40 Suppl, S22-26.

-Nijs, I. M., Muris, P., Euser, A. S., & Franken, I. H. (2010). Differences in attention to food and food intake between overweight/obese and normal-weight females under conditions of hunger and satiety. Appetite, 54(2), 243-254.

-Noto, Y., Sato, T., Kudo, M., Kurata, K., & Hirota, K. (2005). The relationship between salivary biomarkers and state-trait anxiety inventory score under mental arithmetic stress: a pilot study. Anesth Analg, 101(6), 1873-1876.

-Ochner, C. N., Green, D., van Steenburgh, J. J., Kounios, J., & Lowe, M. R. (2009). Asymmetric prefrontal cortex activation in relation to markers of overeating in obese humans. Appetite, 53(1), 44-49.

-O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., Dolan, R.J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science,304(5669), 452–454.

-O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., & Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci, 4(1), 95-102.

-Ogden, C. L., Carroll, M. D., Curtin, L. R., McDowell, M. A., Tabak, C. J., & Flegal, K. M. (2006). Prevalence of overweight and obesity in the United States, 1999-2004. JAMA, 295(13), 1549-1555.

-Ohla, K., Toepel, U., le Coutre, J., & Hudry, J. (2012). Visual-gustatory interaction: orbitofrontal and insular cortices mediate the effect of high-calorie visual food cues on taste pleasantness. PLoS One, 7(3), e32434.

-Ongur, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex, 10(3), 206-219.

-Ouwehand, C., & Papies, E. K. (2010). Eat it or beat it. The differential effects of food temptations on overweight and normal-weight restrained eaters. Appetite, 55(1), 56-60.

-Pagoto, S., Bodenlos, J. S., Kantor, L., Gitkind, M., Curtin, C., & Ma, Y. (2007). Association of major depression and binge eating disorder with weight loss in a clinical setting. Obesity (Silver Spring), 15(11), 2557-2559.

-Palomero-Gallagher, N., Vogt, B.A., Schleicher, A., et al. (2009). Receptor architecture of human cingulate cortex: evaluation of the four region neurobiological model. Human brain mapping, 30(8), 2336–2355.

-Parker, J. G., Zalusky, E. J., & Kirbas, C. (2014). Functional MRI mapping of visual function and selective attention for performance assessment and presurgical planning using conjunctive visual search. Brain and behavior, 4(2), 227-237.

-Paus, T. S. (2001). Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nature Reviews Neuroscience, 2(6), 417-424.

-Pearson, J. M., Hayden, B. Y., Raghavachari, S., Platt, M. L. (2009). Neurons in posterior cingulate cortex signal exploratory decisions in a dynamic multi-option choice task. Current biology, 19(18), 1532-1537.

-Pecina, S., Schulkin, J., & Berridge, K. C. (2006). Nucleus accumbens corticotropin-releasing factor increases cue-triggered motivation for sucrose reward: paradoxical positive incentive effects in stress? BMC Biol, 4, 8.

-Pecina, S., Smith, K. S., & Berridge, K. C. (2006). Hedonic hot spots in the brain. Neuroscientist, 12(6), 500-511.

-Pelchat, M. L. (2002). Of human bondage: food craving, obsession, compulsion, and addiction. Physiology & Behavior, 76(3), 347-352.

-Pelchat, M. L., Johnson, A., Chan, R., Valdez, J., & Ragland, J. D. (2004). Images of desire: food-craving activation during fMRI. Neuroimage, 23(4), 1486-1493.

-Perneger, T. V. (1998). What's wrong with Bonferroni adjustments. Bmj, 316(7139), 1236-1238.

-Pettersen, G., Rosenvinge, J. H., & Ytterhus, B. (2008). The "double life" of bulimia: patients' experiences in daily life interactions. Eat Disord, 16(3), 204-211.

-Phelps, E. A. (2006). Emotion and cognition: insights from studies of the human amygdala. Annu Rev Psychol, 57, 27-53.

-Piech, R. M., Lewis, J., Parkinson, C. H., Owen, A. M., Roberts, A. C., Downing, P. E., & Parkinson, J. A. (2009). Neural correlates of appetite and hunger-related evaluative judgments. PLoS One, 4(8), e6581.

-Pérez-Cueto, F. J., Verbeke, W., de Barcellos, M. D., Kehagia, O., Chryssochoidis, G., Scholderer, J., & Grunert, K. G. (2010). Food-related lifestyles and their association to obesity in five European countries. Appetite,54(1), 156-162.

-Peterson, B. S., Skudlarski, P., Gatenby, J. C., Zhang, H., Anderson, A. W., & Gore, J. C. (1999). An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. Biological psychiatry, 45(10), 1237-1258.

-Petrovich, G. D., & Gallagher, M. (2007). Control of food consumption by learned cues: a forebrain-hypothalamic network. Physiol Behav, 91(4), 397-403.

-Piech, R. M., Lewis, J., Parkinson, C. H., Owen, A. M., Roberts, A. C., Downing, P. E., & Parkinson, J. A. (2009). Neural correlates of appetite and hunger-related evaluative judgments. PLoS One, 4(8), e6581.

-Pizzagalli, D. A., Sherwood, R. J., Henriques, J. B., & Davidson, R. J. (2005). Frontal brain asymmetry and reward responsiveness a source-localization study. Psychological Science, 16(10), 805-813.

-Pope, H. G., Jr., Lalonde, J. K., Pindyck, L. J., Walsh, T., Bulik, C. M., Crow, S. J., . . . Hudson, J. I. (2006). Binge eating disorder: a stable syndrome. Am J Psychiatry, 163(12), 2181-2183.

-Porubska, K., Veit, R., Preissl, H., Fritsche, A., & Birbaumer, N. (2006). Subjective feeling of appetite modulates brain activity: an fMRI study. Neuroimage, 32(3), 1273-1280.

-Potenza, M. N. (2014). A pilot study linking reduced fronto–Striatal recruitment during reward processing to persistent bingeing following treatment for binge-eating disorder. International Journal of Eating Disorders, 47(4), 376-384.

-Pritchard, T. C., Macaluso, D. A., & Eslinger, P. J. (1999). Taste perception in patients with insular cortex lesions. Behav Neurosci, 113(4), 663-671.

-Provencher, V., Begin, C., Piche, M. E., Bergeron, J., Corneau, L., Weisnagel, S. J., . . . Lemieux, S. (2007). Disinhibition, as assessed by the Three-Factor Eating Questionnaire, is inversely related to psychological well-being in postmenopausal women. Int J Obes (Lond), 31(2), 315-320.

-Purves, D., Augustine, G. J., Fitzpatrick, D., et al. (2001). Neuroscience. Sunderland (MA): Sinauer Associates.
- Raczka, K. A., Becker, G., Seese, A., Frisch, S., Heiner, S., Marschhauser, A., ... & Schroeter, M. L. (2010). Executive and behavioral deficits share common neural substrates in frontotemporal lobar degeneration—a pilot FDG-PET study. Psychiatry Research: Neuroimaging, 182(3), 274-280.

-Raymond, N. C., Bartholome, L. T., Lee, S. S., Peterson, R. E., & Raatz, S. K. (2007). A comparison of energy intake and food selection during laboratory binge eating episodes in obese women with and without a binge eating disorder diagnosis. Int J Eat Disord, 40(1), 67-71.

-Robinson, T. E., & Berridge, K. C. (2003). Addiction. Annu Rev Psychol, 54, 25-53.

-Robinson, T. E., & Berridge, K. C. (2008). The incentive sensitization theory of addiction: some current issues. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1507), 3137-3146.

-Robinson, T. E., & Flagel, S. B. (2009). Dissociating the predictive and incentive motivational properties of reward-related cues through the study of individual differences. Biol Psychiatry, 65(10), 869-873.

-Rosenberg, N., Bloch, M., Ben Avi, I., Rouach, V., Schreiber, S., Stern, N., & Greenman, Y. (2013). Cortisol response and desire to binge following psychological stress: comparison between obese subjects with and without binge eating disorder. Psychiatry Res, 208(2), 156-161.

-Robinson, T. E., & Berridge, K. C. (2008). Review. The incentive sensitization theory of addiction: some current issues. Philos Trans R Soc Lond B Biol Sci, 363(1507), 3137-3146.

-Rothemund Y, Preuschhof C, Bohner G, Bauknecht HC, Klingebiel R, Flor H et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. Neuroimage 2007;37:410–421.

-Rutters, F., Nieuwenhuizen, A. G., Lemmens, S. G., Born, J. M., & Westerterp-Plantenga, M. S. (2009). Acute stress-related changes in eating in the absence of hunger. Obesity (Silver Spring), 17(1), 72-77.

-Schag, K., Teufel, M., Junne, F., Preissl, H., Hautzinger, M., Zipfel, S., & Giel, K. E. (2013). Impulsivity in binge eating disorder: food cues elicit increased reward responses and disinhibition. PLoS One, 8(10), e76542.

-Schienle, A., Schäfer, A., Hermann, A., & Vaitl, D. (2009). Binge-eating disorder: reward sensitivity and brain activation to images of food. Biological psychiatry, 65(8), 654-661.

-Schultz, W. (2002). Getting formal with dopamine and reward. Neuron, 36(2), 241-263.

-Schulz, S., & Laessle, R. G. (2010). Associations of negative affect and eating behaviour in obese women with and without binge eating disorder. Eat Weight Disord, 15(4), e287-293.

-Schur, E. A., Kleinhans, N. M., Goldberg, J., Buchwald, D., Schwartz, M. W., & Maravilla, K. (2009). Activation in brain energy regulation and reward centers by food cues varies with choice of visual stimulus. International Journal of Obesity, 33(6), 653-661.

-Sclafani, A. (2004). Oral and postoral determinants of food reward. Physiol Behav, 81(5), 773-779.

-Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., & Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. Nature Reviews Neuroscience, 12(3), 154-167.

-Shin, A. C., Zheng, H., & Berthoud, H. R. (2009). An expanded view of energy homeostasis: neural integration of metabolic, cognitive, and emotional drives to eat. Physiol Behav, 97(5), 572-580.

-Siep, N., Roefs, A., Roebroeck, A., Havermans, R., Bonte, M. L., & Jansen, A. (2009). Hunger is the best spice: an fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex. Behav Brain Res, 198(1), 149-158.

-Simmons, W. K., Martin, A., & Barsalou, L. W. (2005). Pictures of appetizing foods activate gustatory cortices for taste and reward. Cereb Cortex, 15(10), 1602-1608.

-Small, D. M., Gitelman, D., Simmons, K., Bloise, S. M., Parrish, T., & Mesulam, M. M. (2005). Monetary incentives enhance processing in brain regions mediating top-down control of attention. Cerebral cortex, 15(12), 1855-1865.

-Small, D. M., Jones-Gotman, M., & Dagher, A. (2003). Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. Neuroimage, 19(4), 1709-1715.

-Smith, J. B., & Alloway, K. D. (2010). Functional specificity of claustrum connections in the rat: interhemispheric communication between specific parts of motor cortex. The Journal of Neuroscience, 30(50), 16832-16844.

-Spielberger, C. D., Gorsuch, R.L., Edward, L.R. (1970). STAI manual for the state-trait anxiety inventory ("Self-evaluation questionnaire"). PA: Consulting Psychologists Press.

-Spinella, M., & Lyke, J. (2004). Executive personality traits and eating behavior. Int J Neurosci, 114(1), 83-93.

-Spitzer, R. L., Yanovski, S., Wadden, T., Wing, R., Marcus, M. D., Stunkard, A., . . . Horne, R. L. (1993). Binge eating disorder: its further validation in a multisite study. Int J Eat Disord, 13(2), 137-153.

-Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proceedings of the National Academy of Sciences, 105(34), 12569-12574.

-St-Onge, M. P., Sy, M., Heymsfield, S. B., & Hirsch, J. (2005). Human cortical specialization for food: a functional magnetic resonance imaging investigation. J Nutr, 135(5), 1014-1018.

-Steele, K. E., Prokopowicz, G. P., Schweitzer, M. A., Magunsuon, T. H., Lidor, A. O., Kuwabawa, H., . . . Wong, D. F. (2010). Alterations of central dopamine receptors before and after gastric bypass surgery. Obes Surg, 20(3), 369-374.

-Stein, M. B., Simmons, A. N., Feinstein, J. S., & Paulus, M. P. (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am J Psychiatry, 164(2), 318-327.

-Stevens, F. L., Hurley, R. A., Hayman, L. A., & Taber, K. H. (2011). Anterior cingulate cortex: unique role in cognition and emotion. The Journal of neuropsychiatry and clinical neurosciences, 23(2), 121-125.

-Stice, E., Burger, K., & Yokum, S. (2013). Caloric deprivation increases responsivity of attention and reward brain regions to intake, anticipated intake, and images of palatable foods. Neuroimage, 67, 322-330.

-Stice, E., Spoor, S., Bohon, C., & Small, D. M. (2008). Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele.Science, 322(5900), 449-452.

-Stice, E., Spoor, S., Bohon, C., Veldhuizen, M. G., & Small, D. M. (2008). Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. J Abnorm Psychol, 117(4), 924-935.

-Stone, A. A., Shiffman, S. (1994). Ecological momentary assessment (EMA) in behavorial medicine. Annals of Behavioral Medicine, 16, 199-202.

-Striegel-Moore, R. H., Dohm, F. A., Kraemer, H. C., Taylor, C. B., Daniels, S., Crawford, P. B., & Schreiber, G. B. (2003). Eating disorders in white and black women. Am J Psychiatry, 160(7), 1326-1331.

-Striegel-Moore, R. H., Dohm, F. A., Solomon, E. E., Fairburn, C. G., Pike, K. M., & Wilfley, D. E. (2000). Subthreshold binge eating disorder. Int J Eat Disord, 27(3), 270-278.

-Striegel-Moore, R. H., Wilfley, D. E., Pike, K. M., Dohm, F. A., & Fairburn, C. G. (2000). Recurrent binge eating in black American women. Arch Fam Med, 9(1), 83-87.

-Stroebe, W., van Koningsbruggen, G. M., Papies, E. K., & Aarts, H. (2013). Why most dieters fail but some succeed: a goal conflict model of eating behavior. Psychological review, 120(1), 110.

-Stunkard, A. J., & Messick, S. (1985). The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res, 29(1), 71-83.

-Stunkard, A.J., & Messick, S. (1988). The Eating Inventory. San Antonio, TX: Psychological Corporation.

-Svaldi, J., Brand, M., & Tuschen-Caffier, B. (2010). Decision-making impairments in women with binge eating disorder. Appetite, 54(1), 84-92.

-Svaldi, J., Naumann, E., Trentowska, M., & Schmitz, F. (2014). General and food-specific inhibitory deficits in binge eating disorder. International Journal of Eating Disorders.

-Svaldi, J., Schmitz, F., Trentowska, M., Tuschen-Caffier, B., Berking, M., & Naumann, E. (2014). Cognitive interference and a food-related memory bias in binge eating disorder. Appetite, 72, 28-36.

-Sysko, R., Devlin, M. J., Walsh, B. T., Zimmerli, E., & Kissileff, H. R. (2007). Satiety and test meal intake among women with binge eating disorder. Int J Eat Disord, 40(6), 554-561.

-Tammela, L. I., Paakkonen, A., Karhunen, L. J., Karhu, J., Uusitupa, M. I., & Kuikka, J. T. (2010). Brain electrical activity during food presentation in obese binge-eating women. Clin Physiol Funct Imaging, 30(2), 135-140.

-Tataranni, P. A., Gautier, J. F., Chen, K., Uecker, A., Bandy, D., Salbe, A. D., . . . Ravussin, E. (1999). Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. Proc Natl Acad Sci U S A, 96(8), 4569-4574.

-Taylor, C. B., Bryson, S., Celio Doyle, A. A., Luce, K. H., Cunning, D., Abascal, L. B., . . . Wilfley, D. E. (2006). The adverse effect of negative comments about weight and shape from family and siblings on women at high risk for eating disorders. Pediatrics, 118(2), 731-738.

-Taylor, K. S., Seminowicz, D. A., & Davis, K. D. (2009). Two systems of resting state connectivity between the insula and cingulate cortex. Hum Brain Mapp, 30(9), 2731-2745.

-Teegarden, S. L., & Bale, T. L. (2008). Effects of stress on dietary preference and intake are dependent on access and stress sensitivity. Physiol Behav, 93(4-5), 713-723.

-Telch, C. F., & Agras, W. S. (1994). Obesity, binge eating and psychopathology: are they related? Int J Eat Disord, 15(1), 53-61.

-Telch, C. F., & Agras, W. S. (1996). Do emotional states influence binge eating in the obese? Int J Eat Disord, 20(3), 271-279.

-Tindell, A. J., Smith, K. S., Pecina, S., Berridge, K. C., & Aldridge, J. W. (2006). Ventral pallidum firing codes hedonic reward: when a bad taste turns good. J Neurophysiol, 96(5), 2399-2409.

-Tomie, A. (1996). Locating reward cue at response manipulandum (CAM) induces symptoms of drug abuse. Neurosci Biobehav Rev, 20(3), 505-535.

-Torralva, T., Roca, M., Gleichgerrcht, E., Bekinschtein, T., & Manes, F. (2009). A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. Brain, 132(5), 1299-1309.

-Uher, R., & Rutter, M. (2012). Classification of feeding and eating disorders: review of evidence and proposals for ICD-11. World Psychiatry, 11(2), 80-92.

-van der Laan, L. N., de Ridder, D. T., Viergever, M. A., & Smeets, P. A. (2011). The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues. Neuroimage, 55(1), 296-303.

-Verhagen, J. V. (2007). The neurocognitive bases of human multimodal food perception: consciousness. Brain research reviews, 53(2), 271-286.

-Vincent, J. L., Snyder, A. Z., Fox, M. D., Shannon, B. J., Andrews, J. R., Raichle, M. E., & Buckner, R. L. (2006). Coherent spontaneous activity identifies a hippocampal-parietal memory network. Journal of neurophysiology,96(6), 3517-3531.

-Vogt, B. A. (2005). Pain and emotion interactions in subregions of the cingulate gyrus. Nature Reviews Neuroscience, 6(7), 533-544.

-Volkow, N. D., Fowler, J. S., & Wang, G. J. (2004). The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. Neuropharmacology, 47 Suppl 1, 3-13.

-Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Jayne, M., Franceschi, D., . . . Pappas, N. (2002). "Nonhedonic" food motivation in humans involves dopamine in the dorsal striatum and methylphenidate amplifies this effect. Synapse, 44(3), 175-180.

-Volkow, N. D., Wang, G. J., Telang, F., Fowler, J. S., Logan, J., Childress, A. R., . . . Wong, C. (2006). Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. J Neurosci, 26(24), 6583-6588.

-Wagner, D. D., Boswell, R. G., Kelley, W. M., & Heatherton, T. F. (2012). Inducing negative affect increases the reward value of appetizing foods in dieters. J Cogn Neurosci, 24(7), 1625-1633.

-Wallner-Liebmann, S., Koschutnig, K., Reishofer, G., Sorantin, E., Blaschitz, B., Kruschitz, R., . . . Mangge, H. (2010). Insulin and hippocampus activation in response to images of high-calorie food in normal weight and obese adolescents. Obesity, 18(8), 1552-1557.

-Wang, G. J., Volkow, N. D., Logan, J., Pappas, N. R., Wong, C. T., Zhu, W., ... & Fowler, J. S. (2001). Brain dopamine and obesity. The Lancet, 357(9253), 354-357.

-Wang, G. J., Volkow, N. D., Telang, F., Jayne, M., Ma, Y., Pradhan, K., ... & Fowler, J. S. (2009). Evidence of gender differences in the ability to inhibit brain activation elicited by food stimulation. Proceedings of the National Academy of Sciences, 106(4), 1249-1254.

-Wang, G. J., Volkow, N. D., Telang, F., Jayne, M., Ma, J., Rao, M., . . . Fowler, J. S. (2004). Exposure to appetitive food stimuli markedly activates the human brain. Neuroimage, 21(4), 1790-1797.

-Wedig, M. M., & Nock, M. K. (2010). The functional assessment of maladaptive behaviors: a preliminary evaluation of binge eating and purging among women. Psychiatry Res, 178(3), 518-524.

-Westenhoefer, J. (1991). Dietary restraint and disinhibition: is restraint a homogeneous construct? Appetite, 16(1), 45-55.

-Westenhoefer, J., Stunkard, A. J., & Pudel, V. (1999). Validation of the flexible and rigid control dimensions of dietary restraint. Int J Eat Disord, 26(1), 53-64.

-Weygandt, M., Schaefer, A., Schienle, A., & Haynes, J. D. (2012). Diagnosing different binge-eating disorders based on reward-related brain activation patterns. Hum Brain Mapp, 33(9), 2135-2146.

-Wilfley, D. E., & Cohen, L. R. (1997). Psychological treatment of bulimia nervosa and binge eating disorder. Psychopharmacol Bull, 33(3), 437-454.

-Wilfley, D. E., Wilson, G. T., & Agras, W. S. (2003). The clinical significance of binge eating disorder. Int J Eat Disord, 34 Suppl, S96-106.

-Williamson, D. A., Lawson, O. J., Brooks, E. R., Wozniak, P. J., Ryan, D. H., Bray, G. A., & Duchmann, E. G. (1995). Association of body mass with dietary restraint and disinhibition. Appetite, 25(1), 31-41.

-Wise, R. A. (2004). Dopamine, learning and motivation. Nature reviews neuroscience, 5(6), 483-494.

-Wonderlich, S. A., Gordon, K. H., Mitchell, J. E., Crosby, R. D., & Engel, S. G. (2009). The validity and clinical utility of binge eating disorder. Int J Eat Disord, 42(8), 687-705.

-Woolley, J. D., Gorno-Tempini, M. L., Seeley, W. W., Rankin, K., Lee, S. S., Matthews, B. R., & Miller, B. L. (2007). Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. Neurology,69(14), 1424-1433.

-Yanovski, S. Z. (1993). Binge eating disorder: current knowledge and future directions. Obes Res, 1(4), 306-324.

- Yanovski, S. Z., Nelson, J. E., Dubbert, B. K., & Spitzer, R. L. (1993). Association of binge eating disorder and psychiatric comorbidity in obese subjects. The American journal of psychiatry.

-Yanovski, S. Z., Leet, M., Yanovski, J. A., Flood, M., Gold, P. W., Kissileff, H. R., & Walsh, B. T. (1992). Food selection and intake of obese women with binge-eating disorder. Am J Clin Nutr, 56(6), 975-980.

-Yanovski, S. Z., Nelson, J. E., Dubbert, B. K., & Spitzer, R. L. (1993). Association of binge eating disorder and psychiatric comorbidity in obese subjects. Am J Psychiatry, 150(10), 1472-1479.

-Zhang, J., Berridge, K. C., Tindell, A. J., Smith, K. S., & Aldridge, J. W. (2009). A neural computational model of incentive salience. PLoS Comput Biol, 5(7), e1000437.

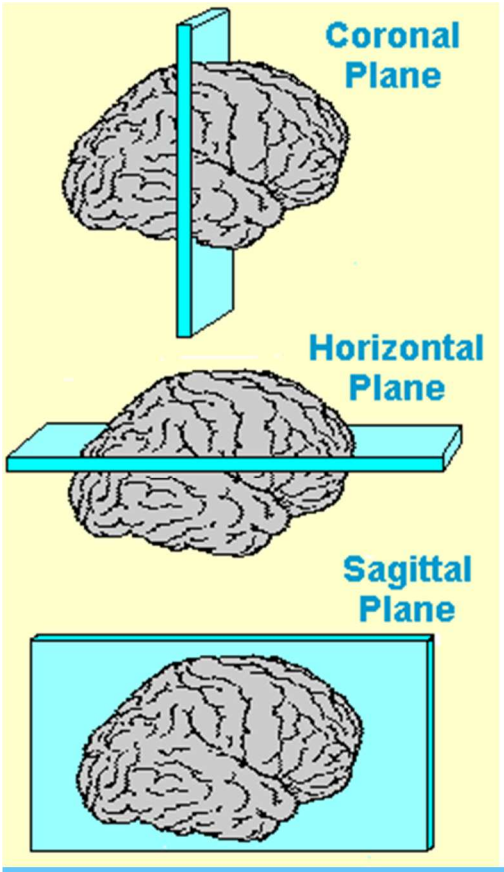
-Zink, C. F., Pagnoni, G., Martin-Skurski, M. E., Chappelow, J. C., Berns, G. S. (2004). Human striatal responses to monetary reward depend on saliency. Neuron,42(3), 509 –517.

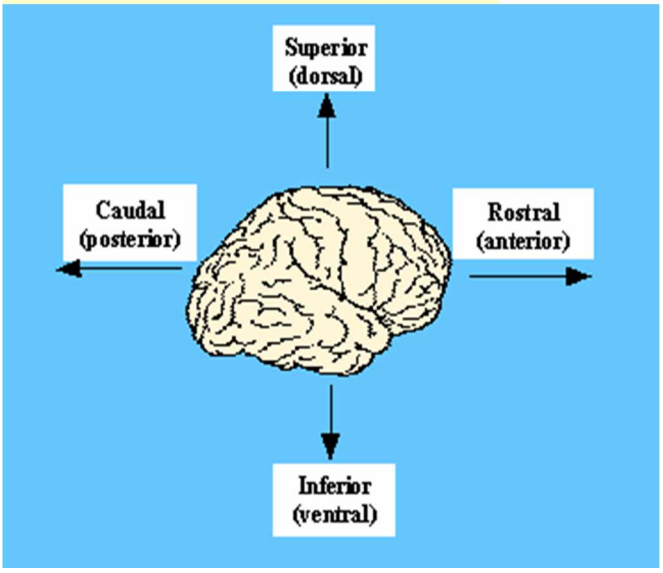
-Zocca, J.M., Shomaker, L.B., Tanofsky-Kraff, M., Columbo, K.M., Raciti, G.R., Brady, S.M., et al.(2011). Links between mothers' and children's disinhibited eating and children's adiposity. *Appetite*, *56*(2), 324–331.

-Zung, W. W. (1965). A Self-Rating Depression Scale. *Arch Gen Psychiatry*, 12, 63-70.
Ziauddeen, H., Farooqi, I. S., & Fletcher, P. C. (2012). Obesity and the brain: how convincing is the addiction model? *Nat Rev Neurosci, 13*(4), 279-286.

APPENDICES

Appendix A: Directions and planes of brain section (Chudler, 2012)





Appendix B: Questionnaires

Self-Evaluation Questionnaire (STAI)

(State Trait Anxiety Inventory)

Instructions: A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel right now, that is, at this moment. There are no wrong or right answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

1 = Not at all 2 = Somewhat 3 = Moderately so 4 = Very much so

1. I feel calm.....	1 2 3 4
2. I feel secure.....	1 2 3 4
3. I am tense.....	1 2 3 4
4. I am strained.....	1 2 3 4
5. I feel at ease.....	1 2 3 4
6. I feel upset.....	1 2 3 4
7. I am presently worrying over possible misfortunes....	1 2 3 4
8. I feel satisfied.....	1 2 3 4
9. I feel frightened.....	1 2 3 4
10. I feel comfortable.....	1 2 3 4
11. I feel self-confident.....	1 2 3 4
12. I feel nervous.....	1 2 3 4
13. I feel jittery.....	1 2 3 4
14. I feel indecisive.....	1 2 3 4
15. I am relaxed….....	1 2 3 4
16. I feel content.....	1 2 3 4

17. I am worried.....……... 1 2 3 4

18. I feel confused.....…… 1 2 3 4

19. I feel steady.....……. 1 2 3 4

20. I feel pleasant.....……. 1 2 3 4

BAS (Behavioral Activation System)

Name: _____

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses. Choose from the following four response options:

1 = very true for me
2 = somewhat true for me
3 = somewhat false for me
4 = very false for me

1. A person's family is the most important thing in life.
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness.
3. I go out of my way to get things I want.
4. When I'm doing well at something I love to keep at it.
5. I'm always willing to try something new if I think it will be fun.
6. How I dress is important to me.
7. When I get something I want, I feel excited and energized.
8. Criticism or scolding hurts me quite a bit.
9. When I want something I usually go all-out to get it.
10. I will often do things for no other reason than that they might be fun.
11. It's hard for me to find the time to do things such as get a haircut.
12. If I see a chance to get something I want I move on it right away.
13. I feel pretty worried or upset when I think or know somebody is angry at me.
14. When I see an opportunity for something I like I get excited right away.
15. I often act on the spur of the moment.
16. If I think something unpleasant is going to happen I usually get pretty "worked up."
17. I often wonder why people act the way they do.
18. When good things happen to me, it affects me strongly.

19. I feel worried when I think I have done poorly at something important.
20. I crave excitement and new sensations.
21. When I go after something I use a "no holds barred" approach.
22. I have very few fears compared to my friends.
23. It would excite me to win a contest.
24. I worry about making mistakes.

TFEQ (Three Factor Eating Questionnaire)

Eating Inventory (part I)

Read each of the following statements carefully. If you agree with the statement, or feel that it is true as applied to you, fill in the bubble on the scantron that is marked with a T (true). If you disagree with the statement, or feel that it is false as applied to you, fill in the bubble on the scantron that is marked with an F (false). Be certain to answer every question.

T for true

F for False

1. When I smell a sizzling steak or see a juicy piece of meat, I find it very difficult to keep from eating, even if I have just finished a meal.

2. I usually eat too much at social occasions, like parties and picnics.

3. I am usually so hungry that I eat more than three times a day.

4. When I have eaten my quota of calories, I am usually good about not eating anymore.

5. I deliberately take small helpings as a means of controlling my weight.

6. Dieting is so hard for me because I just get too hungry

7. Sometimes things just taste so good that I keep on eating even when I am no longer hungry.

8. Since I am often hungry, I sometimes wish that while I am eating, an expert would tell me that I have had enough or that I can have something more to eat.

9. When I feel anxious, I find myself eating.

10. Life is too short to worry about dieting.

11. Since my weight goes up and down, I have gone on reducing diets more than once.

12. I often feel so hungry that I just have to eat something.

13. When I am with someone who is overeating, I usually overeat too.

14. I have a pretty good idea of the number of calories in common foods.

15. Sometimes when I start eating, I just can't seem to stop.

16. It is not difficult for me to leave something on my plate.

17. At certain times of the day, I get hungry because I have gotten used to eating then.

18. While on a diet, if I eat a food that is not allowed, I consciously eat less for a period of time to make up for it.

19. Being with someone who is eating often makes me hungry enough to eat also.

20. When I feel blue, I often overeat.

21. I enjoy eating too much to spoil it by counting calories or watching my weight.

22. When I see a real delicacy, I often get so hungry that I have to eat right away.

23. I often stop eating when I am not really full as a conscious means of limiting the amount that I eat. 24. I get so hungry that my stomach often seems like a bottomless pit.

25. My weight has hardly changed at all in the last ten years.

26. I am always hungry so it is hard for me to stop eating before I finish the food on my plate.

27. When I feel lonely, I console myself by eating.

28. I consciously hold back at meals in order not to gain weight.

29. I sometimes get very hungry late in the evening or at night.

30. I eat anything I want, any time I want.

31. Without even thinking about it, I take a long time to eat.

32. I count calories as a conscious means of controlling my weight.

33. I do not eat some foods because they make me fat.

34. I am always hungry enough to eat at any time.

35. I pay a great deal of attention to changes in my figure.

36. While on a diet, if I eat a food that is not allowed, I often then splurge and eat other high calorie foods.

37. If I eat a little bit more on one day, I make up for it the next day.

38. I pay attention to my figure, but I still enjoy a variety of foods.

39. I prefer light foods that are not fattening.

40. If I eat a little bit more during one meal, I make up for it at the next meal.

41. I eat diet foods, even if they do not taste very good.

42. A diet would be too boring a way for me to lose weight.

43. I would rather skip a meal than stop in the middle of one.

44. I alternate between times when I diet strictly and times when I don't pay much attention to what and how much I eat.

45. Sometimes I skip meals to avoid gaining weight.

46. I avoid some foods on principle even though I like them.

47. I try to stick to a plan when I lose weight.

48. Without a diet plan I wouldn't know how to control my weight.

49. Quick success is most important for me during a diet.

Eating Inventory (PART II)

Each question in this section is followed by a number of answer options. After reading each question carefully, fill in the letter on the scantron form (general purpose answer sheet) that corresponds to the option which most applies to you.

50. How often are you dieting in a conscious effort to control your weight?

a/rarely

b/sometimes

c/usually

d/always

51. Would a weight fluctuation of 5 lbs. affect the way you live your life?

a/ rarely

b/ sometimes

c/ usually

d/ always

52. How often do you feel hungry?

a/ rarely

b/ sometimes

c/ usually

d/ always

53. Do your feelings of guilt about overeating help you to control your food intake?

a/ never

b/ rarely

c/ often

d/ always

54. How difficult would it be for you to stop eating halfway through dinner and not eat for the next few hours?

a/ easy

b/ slightly difficult

c/ moderately difficult

d/ very difficult

55. How conscious are you of what you are eating?

a/ not at all

b/ slightly

c/ moderately

d/ extremely

56. How frequently do you *avoid* “stocking up” on tempting foods?

a/ almost never

b/ seldom

c/ usually

d/ almost always

57. How likely are you to shop for low calorie foods?

a/ unlikely

b/ slightly likely

c/ moderately likely

d/ very likely

58. Do you eat sensibly in front of others and splurge alone?

a/ never

b/ rarely

c/ often

d/ always

59. How likely are you to consciously eat slowly in order to cut down on how much you eat?

a / unlikely

b/ slightly likely

c/ moderately likely

d/ very likely

60. How frequently do you skip dessert because you are no longer hungry?

a/ almost never

b/ seldom

c/ at least once a day

d/ Almost every day

61. How likely are you to consciously eat less than you want?

a/ unlikely

b/ slightly likely

c/ moderately likely

d/ very likely

62. Do you go on eating binges even though you are not hungry?

a/ never

b/ rarely

c/ sometimes

d/ at least once a week

63. Do you deliberately restrict your intake during meals even though you would like to eat more?

a/ never

b/ rarely

c/ often

d/ always

64. To what extent does this statement describe your eating behavior?

"I start dieting in the morning, but because of any number of things that happen during the day, by evening I have given up and eat what I want, promising myself to start dieting again tomorrow."

a/ not like me

b/ little like me

c/ pretty good description of me

d/ describes me perfectly

65. On a scale of 1 to 5, where 1 means no restraint in eating (eat whatever you want, whenever you want it) and 5 means total restraint (usually or constantly limiting food intake and rarely or never "giving in"), what number would you give yourself?

a/ eat whatever you want, whenever you want it

b/ usually eat whatever you want, whenever you want it

c/often eat whatever you want, whenever you want it

d/ often limit food intake, but often "give in"

e / usually or constantly limit food intake, rarely or never "give in"