REWARD ABNORMALITIES AMONG WOMEN WITH BULIMIA NERVOSA: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY

by

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The current study measured BOLD brain response using functional magnetic resonance imaging (fMRI) to explore the hypothesis that women with bulimia nervosa have a hyper-responsivity of the mesolimbic reward system. Women with bulimia nervosa and healthy controls (N = 24) completed an fMRI paradigm involving anticipated and actual receipt of chocolate milkshake and a tasteless control solution. Women with bulimia nervosa showed less activation than healthy controls in the right anterior insula in response to anticipatory food reward and in the left medial orbitofrontal cortex, right posterior insula, right precentral gyrus, and right mid dorsal insula in response to consummatory food reward. Covariates related to bulimia diagnosis accounted for some of these effects, but not all. Results suggest that bulimia nervosa may be related to hypo-functioning of the brain reward system rather than hyper-functioning. Implications for intervention and future research are discussed.

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CHAPTER I

INTRODUCTION

Bulimia Nervosa: Diagnostic Features and Epidemiology

Bulimia nervosa is characterized by recurrent binge eating episodes and inappropriate compensatory behaviors. Binge episodes consist of two primary criteria. First, the individual must consume, in a discrete amount a time (e.g., two hours), an amount of food that most people would consider a large amount of food under similar circumstances. Additionally, the individual must exhibit a lack of control over their eating behavior. Inappropriate compensatory behaviors are an effort to compensate for the calories consumed during binge eating. These may include self-induced vomiting or excessive laxative or diuretic use (purge behaviors) or fasting or excessive exercise (nonpurge behaviors). In order to meet criteria for full threshold bulimia nervosa, the binge eating and compensatory behaviors must occur, on average, twice weekly for three months. Additionally, individuals must identify weight or shape as one of the primary determinants of self-evaluation (American Psychiatric Association, 2000).

Bulimia nervosa often shows a chronic course, a peak age of onset during adolescence, and a history of multiple treatment attempts (Herzog, Keller, & Lavori, 1988; Mitchell, Hatsukami, Pyle, & Eckert, 1985; Russell, 1979). Threshold and subthreshold bulimia nervosa are prevalent and associated with increased risk for future

obesity, depression, suicide attempts, substance abuse, and health problems (Wilson, Becker, & Heffernan, 2003; Stice & Bulik, 2008). Bulimia nervosa affects approximately 2% of individuals over the course of their lives (Bushnell et al., 1990; Garfinkel et al., 1995). Only 28% of individuals with bulimia nervosa seek treatment (Fairburn et al., 2000), and current treatments of choice result in lasting symptom remission for only 30-40% of individuals with this eating disorder (Stice & Bulik, 2008). Additionally, only 25% of prevention interventions significantly reduce eating disorder symptoms (Stice & Shaw, 2004).

Subthreshold Bulimia Nervosa

Many researchers have proposed changes to the current diagnostic criteria to reflect the significant levels of impairment among individuals engaging in less frequent, but recurrent bulimic behaviors (Mond, Hay, Rodgers, Owen, Crosby, & Mitchell, 2006; Sullivan, Bulik, & Kendler, 1998). Herzog and colleagues (1986) noted that, although the degree of social maladjustment was associated with frequency of bulimic behaviors, significant impairment was present in individuals engaging in bingeing or purging only once per week. LeGrange and colleagues (2006) found no significant differences between women with threshold and subthreshold levels of bulimia nervosa on measures of perfectionism, impulsivity, obsessive-compulsiveness, anxiety, depressive symptoms, or alcohol and substance problems. Studies of functional impairment and health care utilization suggest that current diagnostic thresholds may be too high, as many individuals engaging in subthreshold levels of bulimic pathology show impairment and present for treatment (Spoor, Stice, Burton, & Bohon, 2007). Thus, it is important to

include subthreshold cases when investigating correlates and risk factors of clinically meaningful bulimia nervosa.

Statement of the Problem

In light of the limitations of current treatment and prevention interventions, there is need for an improved understanding of etiologic factors that predict onset of bulimic pathology and of maintenance factors that predict persistence of bulimic pathology. These findings should inform the design of more effective prevention and treatment interventions. A number of biological factors may play a role in the development and maintenance of bulimia nervosa, particularly given the high heritability of the disorder found in some studies (between 28% and 83%; Bulik, Sullivan, Wade, & Kendler, 2000; Bulik, Sullivan, Tozzi et al., 2006; Klump et al., 2001; Wade et al., 2000). One possibility is that individuals who develop bulimia nervosa have heightened reward sensitivity in response to food intake and anticipated food intake (Davis, Strachan, & Berkson, 2004; Dawe & Loxton, 2004). Hyper-responsivity of the mesolimbic reward system may increase risk for binge eating and the development of bulimia nervosa. Accordingly, the present study tested whether individuals with bulimic pathology show abnormal brain activation in response to food intake or anticipated food intake relative to non-eating disordered controls.

CHAPTER II

BACKGROUND

Motivation for Normal Eating Behavior

In healthy adults, eating behavior is regulated in part by signals from the gastrointestinal tract (Woods, 2004). Woods posited that meal or eating initiation is based mostly on social or learned factors, like time of day, rather than energy needs in the body. Instead, regulatory control via chemical feedback functions over how much food is consumed rather than the initiation of an eating episode. Satiety signals, like CCK, are secreted from the GI tract during food intake proportionally to the number of calories consumed (Woods, 2005). These satiety signals are relayed to the hindbrain via nerves or the bloodstream (Woods, 2004). Other factors can influence how much food is consumed in an eating episode by influencing the sensitivity of the brain to the satiety signals (Woods, 2004). For example, adiposity signals, like leptin and insulin, are released based on weight and fat in the body and change the sensitivity of the brain to satiety signals, in turn, changing meal size. For example, after weight gain, greater levels of insulin and leptin would lead to an increased sensitivity to satiety signals in order to decrease meal size and maintain a homeostatic level of weight and fat in the body (Woods, 2005). Other factors may also influence the brain's sensitivity to satiety signals

and override this natural homeostatic process. These factors will be discussed as possible mechanisms that lead to binge eating.

Studies of healthy adults have shown that the amygdala and orbitofrontal cortex appear to process appetitive incentive stimuli and subsequent goal-directed behavior. The goal in this case, would be consuming palatable food (Hinton et al., 2004). The appetitive value of foods modulated response to the images in the bilateral insula, left operculum, and right putamen (Porubska et al., 2006). This could suggest that the reward value of food may override natural homeostatic processes regulating eating behavior in humans. Implications of this for bulimia nervosa will be discussed later in this chapter. However, in many healthy adults, satiety signals secreted in relation to nutritional needs of the body may also influence the appetitive response to foods. Food images elicited greater response in the amygdala, parahippocampal gyrus, and anterior fusiform gyrus when individuals were hungry compared to satiated, and this effect was specific to food images, relative to non-food images (LaBar et al, 2001). This differential response to food in hungry versus satiated states also was found in children and adolescents in the amygdala, medial frontal/orbitofrontal cortex, and insula (Holsen et al, 2005). Overfeeding diminished the response of the visual cortex, hypothalamus, and premotor cortex that had been heightened in response to images of pleasurable foods in a hungry state (Cornier et al, 2007). Small and colleagues (2001) found decreasing cerebral blood flow in a number of areas correlated with decreasing reward value of chocolate after overfeeding. These areas included the medial orbitofrontal cortex (OFC), dorsal insula/operculum, caudate nucleus, left thalamus, and right putamen. These studies

provide support for homeostatic processes influencing the appetitive value of foods as processed by regions of the brain associated with pleasure and goal-directed behavior. However, it is also evident that pleasure influences regulatory control centers, such as the hypothalamus, as Cornier and colleagues (2007) found greater activation in the hypothalamus in response to pleasurable food images compared to neutral food, even in an overfed condition, suggesting that this region is not specifically responding to nutritional need.

The brains of healthy adults can also differentiate between high-calorie and low-calorie foods, which could have implications for binge eating, as binge episodes often consist of high calorie food items. High-calorie food images uniquely activated the medial and dorsolateral prefrontal cortex, thalamus, hypothalamus, corpus collosum, and cerebellum (Killgore et al., 2003). Toepel and colleagues (2009) found, using visual event-related potential (ERP), that the brain can process energy values of foods quite quickly in the reward assessment and decision-making frontal regions. Thus, healthy adults are able to quickly make decisions about energy content that could lead to integration with homeostatic signal and stop eating high-calorie foods after meeting energy needs or continue eating due to reward-seeking behavior and knowledge of a food's pleasurable taste.

Although human systems have feedback mechanisms to tell us to stop eating when we have reached our nutritional needs, influenced in part by adiposity, food elicits strong response in reward areas in both hungry and satiated states (e.g., Cornier et al., 2007). The fact that food images elicit this brain response also suggests that food cues

have a great impact on eating behavior. Learned associations between food cues and reward response also impacts food intake. Food seeking occurs by habitual responses previously reinforced or by specific goal-directed behavior seeking reward (Balleine, 2005). If habitual responses, like eating a certain amount at a time of day, are overridden by goal-seeking or reward-seeking behaviors, problematic eating initiation may occur. It is possible that reward seeking may put individuals at risk for binge eating and at risk for decreased sensitivity to satiety signals. New learned eating habits could replace healthier habits. It is also possible that external cues more generally diminish responsiveness to internal regulatory cues in part due to parents' frequent use of regulatory control on their children's eating (Birch & Fisher, 1998). Studies showed that parents with high control over their children's food intake had children with low self-regulation of food intake. Additionally, this lack of self-regulation was related to adiposity among girls (Birch & Fisher, 1998). These studies were cross-sectional, however, so it could simply be that children who exhibit low self-regulation of food intake prompt parents to exert more control over their children's eating behavior..

Individuals who are able to maintain flexible representations of the reward value of food may be able to better adapt to their nutritional needs and seek rewarding food when needed, but not find it as rewarding when satiated (Gottfried, O'Doherty, & Dolan, 2003). Those without this flexibility also score higher on self-report scales of sensitivity to reward, which has been related to greater food cravings and high body mass index (BMI) among women (Franken & Muris, 2005). It is possible that individual differences

in reward sensitivity may lead to less sensitivity to the internal cues that typically regulate food intake.

Similarities Between Bulimia Nervosa and Drug Addiction

Halmi (2009) posited that the high comorbidity between bulimia nervosa and drug use suggested a possible biological link. She noted the similarity between the loss of control in limiting drug use and the loss of control in limiting food intake during a binge episode. Halmi suggested that dysregulation of reward circuits could lead to chronic bingeing. Indeed, Koob and LeMoal (1997) proposed a model of addiction of a spiraling dysregulation of the brain reward systems that progressively increases. Because of the similarities between loss of control in drug addiction and bulimia nervosa, it is possible that mechanisms that result in drug addiction could also lead to bulimia nervosa. Indeed, Berridge (2007b) suggested that repeated binge eating could result in similar neural processes as repeated drug use.

Berridge and Robinson (1998) proposed the incentive salience theory that suggests that reward related stimuli trigger a conditioned motivational response. The value of the incentive salience of a stimulus is dynamically generated by the mesolimbic system during each exposure and is dependent on the reward value of the stimulus. Repeated drug exposure results in neural sensitization of mesolimbic systems, which leads to addictive behavior (Berridge, 2007a). "Just one hit" of a drug could increase the incentive salience due to sensitization by repeated prior use, leading to increased motivation to use more of the drug, particularly since dopamine signaling relates to goal-directed behavior and motivation for action (Adinoff, 2007). There is evidence of this

sensitization in response to food, as well. When rats are given sucrose binges in between periods of deprivation, there is an increase in risk of overconsumption when allowed and greater neural response to presentation of food reward cues (Bello et al., 2003; Berridge, 2007b).

Studies have shown that increased availability of drugs and unhealthy foods increases risk for drug addiction and obesity (Volkow & Wise, 2005). Thus, high-fat, high-calorie foods and drugs both appear to be powerful reinforcers of behavior. Volkow & Wise (2005) related both drug addiction and obesity to the dopamine system, noting that a pharmacological blockade of forebrain dopamine systems attenuated free feeding and lever-pressing for food reward in rats, as well as the rewarding effects of cocaine, amphetamine, nicotine, and alcohol. Additionally, fMRI studies indicate that obese (relative to lean) individuals show greater activation in reward areas, including the insula, frontal operculum, orbitofrontal cortex, amygdala, and striatum in response to pictures of palatable foods (Rothemund et al., 2007; Stoeckel et al., 2008) and anticipated receipt of palatable food (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008b). Yet there is evidence that obese versus lean individuals show weaker responsivity to food receipt in the dorsal striatum and that this increases risk for future weight gain if coupled with genetic risk for reduced D2 receptor density in this brain region (Stice, Spoor, Bohon, & Small, 2008a). Although these findings were in relation to obesity, these findings could help inform our theory of bulimia nervosa, as similar processes could be involved in bulimia nervosa and binge eating behavior. Despite the strong reinforcing nature of food and food cues, not everyone engages in binge eating. Thus, despite daily exposure to food and the need to

eat, difference in brain response to this exposure could explain why some individuals are more susceptible to engage in binge eating. Greater reward sensitivity and dysfunction of the brain's reward circuitry could help explain why some individuals may be more likely to engage in drug addiction or unhealthy binge eating.

Heightened Reward Sensitivity in Bulimia Nervosa

In line with the reinforcement sensitivity model of drug addiction, it has been suggested that individuals who engage in binge eating may have greater reactivity of brain reward systems in response to food cues and food intake (Dawe & Loxton, 2004). This could reflect a hypersensitivity of the mesolimbic reward circuitry among those with bulimia nervosa. In support of this theory, several studies show heightened reward sensitivity in general among women with bulimia nervosa compared to healthy controls. Women with bulimia nervosa show greater sensitivity to financial reward than healthy controls when measured by behavioral performance in some (Farmer, Nash, & Field, 2001; Kane, Loxton, Staiger, & Dawe, 2004), but not all studies (Loxton & Dawe, 2007). Women with bulimic symptoms also report greater sensitivity to reward in general on questionnaires relative to healthy controls (Davis & Woodside, 2002; Kane et al., 2004; Loxton & Dawe, 2001, 2006, 2007; Nederkoorn, van Eijs, & Jansen, 2004). As noted previously, these findings are also congruent with studies showing that scores on a sensitivity to reward questionnaire positively correlated with BMI in normal and overweight individuals (Davis & Fox, 2008; Franken & Muris, 2005), suggesting that this reward sensitivity may be related to greater food intake.

Studies have also found that women with bulimia nervosa show heightened reward sensitivity to food specifically. Women with bulimia nervosa prefer sweeter and higher-fat foods than healthy controls (Drewnowski, Bellisle, Aimez, & Remy, 1987; Sunday & Halmi, 1990). Women with bulimia nervosa do not show the typical habituation to repeated tastes, as evidenced by a lack of reduction of salivary response after repeated tastes (Epstein, Saad et al., 2003; Wisniewski, Epstein, Marcs, & Kaye, 1997) and a lack of sensory-specific satiety when consuming one food type (LaChaussee, Kissileff, Walsh, & Hadigan, 1992). These findings collectively suggest that individuals with bulimia nervosa may have reduced sensitivity to the body's natural satiety signals, perhaps due to heightened sensitivity of the reward circuitry. It is important to note, however, that sensory-specific satiety (satiety to a single type of taste) may stem from different biological mechanisms than general satiety. To date, there is inconsistent evidence regarding the function of general satiety signals among individuals with bulimia nervosa, with some studies finding differences in some (e.g., release of CCK during meals), but not all (e.g., gastric compliance), gastric functions (Zimmerli, Walsh, Guss, Devlin, & Kissileff, 2006).

Brain imaging studies can provide more objective biological evidence of abnormalities in neural reward circuitry in response to food, as self-report measures are subject to social desirability bias and also require a degree of self-awareness by the participant. Among healthy adults, consumption of palatable foods relative to consumption of unpalatable foods or tasteless foods, results in greater activation of the orbitofrontal cortex (OFC) and frontal operculum/insula, as well as greater release of

dopamine in the dorsal striatum (O'Doherty, Deichmann, Critchley, & Dolan, 2002; Small, Jones-Gotman, & Dagher, 2003). PET studies have shown greater serotonin 1A receptor binding in the angular gyrus, medial prefrontal cortex, and the posterior cingulate cortex among women with bulimia nervosa compared to healthy controls (Delvenne et al., 1999; Tiihonen et al., 2004). Other studies using PET found that women who had recovered from bulimia nervosa showed less activation of the right anterior cingulate cortex and left cuneus in the occipital cortex in response to receipt of glucose versus artificial saliva and lower baseline medial OFC serotonin 2A receptor binding, even after a glucose preload (Frank et al., 2006; Kaye et al., 2001). Another PET study found less μ-opioid binding in the temporinsular cortex among women with bulimia nervosa compared to controls (Bencherif et al., 2005). These frontal and mesolimbic brain regions have been implicated in reward activation and motivation, thus these findings imply abnormal response in reward circuitry among women with bulimia nervosa. These findings of reduced activity in these regions diverges with self-report and behavioral studies showing greater reward sensitivity among individuals with bulimia nervosa. This abnormal reward circuitry could lead to decreased regulation of food intake.

Although abnormal activation of the mesolimbic reward circuitry in response to actual food intake may increase risk for binge eating, it could also be that elevated *anticipated* reward from food intake increases risk for binge eating (Roefs, Herman, MacLeod, Smulders, & Jansen, 2005). As discussed previously, incentive salience theory posits that over repeated presentations of a rewarding substance, individuals learn to

associate cues with the reward and that consummatory reward decreases while anticipatory reward increases (Berridge & Robinson, 1998). Cues such as sight and smell of food may eventually lead to physiological responses that trigger food craving and increase risk for binge eating (Jansen, 1998). Naïve monkeys initially showed firing of mesotelencephalic dopamine neurons only in response to food taste, but this firing began to precede food delivery after conditioning, with maximal firing eventually elicited by the conditioned stimuli that predicted or anticipated food delivery rather than the actual food receipt (Kiyatkin & Gratton, 1994; Schultz, Apicella, & Ljungberg, 1993). Another study found that dopaminergic firing was greater in the nucleus accumbens of rats after presentation of a conditioned stimulus that usually signaled food receipt than after delivery of an unexpected meal (Blackburn, Phillips, Jakubovic & Fibiger, 1989). Thus, reward activation in response to anticipation of food may be more important than response to consumption of food in predicting whether someone initiates an eating episode.

Some evidence suggests that different neural processes underlie consummatory and anticipatory food reward. Anticipated receipt of a palatable food, versus anticipated receipt of unpalatable food or a tasteless food, results in greater activation in the OFC, amygdala, cingulate gyrus, striatum (caudate nucleus and putamen), ventral tegmental area, midbrain, parahippocampal gyrus, and fusiform gyrus (O'Doherty et al., 2002; Pelchat et al., 2004). Many of these regions appear to respond to both consummatory and anticipatory food reward, which may be due to a learning effect, in which areas associated with consummatory reward begin to respond to anticipatory food reward as the

association between cues and food delivery is strengthened. These studies suggest that somewhat distinct brain regions are implicated in anticipatory and consummatory food reward, but that there is some overlap (OFC and striatum). To date only two studies have directly compared activation in response to anticipatory and consummatory food reward to isolate regions that show greater activation in response to one phase of food reward versus the other. Anticipation of a pleasant taste, versus actual taste, resulted in greater activation in the dopaminergic midbrain, nucleus accumbens, and the posterior right amygdala (O'Doherty et al., 2002). Another study found that anticipation of a pleasant drink resulted in greater activation in the amygdala and mediodorsal thalamus, whereas the receipt of the drink resulted in greater activation in the left insula/operculum (Small et al, 2008). These two studies suggest that the amygdala, midbrain, nucleus accumbens, and mediodorsal thalamus are more responsive to anticipated consumption versus actual consumption of food, whereas the frontal operculum/insula is more responsive to consumption versus anticipated consumption of food. Thus, available evidence seems to suggest that distinct brain regions have been implicated in encoding anticipatory and consummatory food reward, although more research will be necessary before firm conclusions are possible. Anticipation and receipt of money and psychoactive drugs also tend to activate the same distinct brain regions that are implicated in anticipatory and consummatory food reward (Delgado et al., 2000; Elliott, Friston, & Dolan, 2000; Hutchison et al., 2002; Knutson et al., 2001; Tricomi, Delgado, & Fiez, 2004).

Studies have shown that individuals with bulimia nervosa or recurrent binge eating rate pictures of food as more interesting and arousing and report a greater desire to

eat than healthy controls (Karhunen, Lappalainen, Tammela, Turpeinen, & Uusitupa, 1997; Mauler et al., 2006). Food craving is cited by 70% of patients with bulimia nervosa as a reason for binge eating (Mitchell, Hatsukami, Pyle, & Eckert, 1985). It is thus likely that individuals with bulimia nervosa experience greater anticipatory reward from eating than healthy controls, which is congruent with findings that they report greater urges to binge and less confidence in their ability to control their food intake after exposure to the sight, smell, and taste of food (Bulik, Lawson, & Carter, 1996; Staiger, Dawe, & McCarthy, 2000). This increased desire to binge occurs in response to both palatable and unpalatable foods, suggesting greater sensitivity to reward from a variety of food types (Staiger et al., 2000).

Salivary response correlates positively with self-reported hunger and desire to binge eat and thus appears to serve as a proxy measure for food craving (Legenbauer et al., 2004). Studies measuring salivary response to food cues have produced mixed results. Some find that women with bulimia nervosa show more (Legenbauer, Vogele, & Ruddel, 2004; LeGoff, Leichner, & Spigelman, 1988), less (Bulik, Lawson, & Carter, 1996; Karhunen, Lappalainen, Tammela et al., 1997), or similar (Staiger et al., 2000) salivary response to food cues compared to healthy controls. Studies using other physiology measures have produced similarly mixed findings. Mauler and colleagues (2006) found that individuals with bulimia nervosa showed significantly reduced startle response to pictures of food and significantly increased corrugator facial muscle responses compared to healthy controls, but no significant differences in skin conductance and heart rate response. In contrast, Friederich and colleagues (2006) found

that individuals with bulimia nervosa did not show reduced startle response to pictures of food relative to healthy controls. These studies suggest that there are no reliable differences between individuals with and without bulimia nervosa in these physiological measures, although it could be that the measures themselves are unreliable or that these studies had small sample sizes that led to inconsistent results. It is also possible that individuals with bulimia nervosa have an approach-avoidance response to food cues, evidenced by a drive to consume food coupled with negative feelings toward food due to guilt and shame from prior binge eating or high levels of thin-ideal internalization. These positive and negative responses to food cues could lead to inconsistent physiological responses, as well. Indeed, individuals with bulimia nervosa often report more negative feelings while looking at, smelling, or touching food (Bulik et al., 1996; Legenbauer et al., 2004; Mauler et al., 2006; Staiger et al., 2000; Uher et al., 2004).

One brain imaging study found that individuals with bulimia nervosa showed greater activation in the medial OFC and anterior cingulate cortex in response to presentations of pictured food versus non-food images relative to healthy controls (Uher et al., 2004). Another study found that binge eaters showed greater activation of frontal and pre-frontal regions in response to pictures of food versus pictures of a landscape relative to healthy controls (Karhunen et al., 2000). Schienle and colleagues (2009) found that individuals with bulimia nervosa showed greater insula and anterior cingulate cortex activation than healthy controls and individuals with binge eating disorder in response to images of food versus images of household items. The authors speculate that

the combination of these regions may reflect the attempt to counter-regulate and compensate for increased arousal levels in response to food images.

Implications of Reward Sensitivity and Abnormal Reward Circuitry on Intervention Development

As stated earlier, only 28% of individuals with bulimia nervosa seek treatment (Fairburn et al., 2000), and current treatments result in maintained symptom remission for only 30-40% of individuals with this eating disorder (Stice & Bulik, 2008). Further, only 25% of prevention interventions significantly reduce eating disorder symptoms (Stice & Shaw, 2004). If individuals with bulimia nervosa indeed have greater sensitivity to food reward and abnormal neural response in the reward circuitry of the brain, interventions that decrease the reward value of high-fat, high-calorie foods may result in reduced frequency of binge eating. This could involve decoupling food cues from pleasant taste in order to decrease anticipatory reward and reduce the tendency to initiate eating outside of the presence of nutritional needs or healthy external cues, such as time of day, for meal initiation. Additionally, if women showing evidence of abnormal reward response are at risk for developing bulimia nervosa, it may be important to target prevention efforts toward this at-risk population.

Summary of Background and Aims of Present Study

In sum, there is evidence that individuals with bulimia nervosa show greater consummatory and anticipatory reward than healthy controls, although findings are not entirely consistent. To date, no fMRI brain imaging studies have examined activation in reward circuitry in response to actual food intake during brain scans among individuals

with bulimic pathology versus healthy controls. The use of an objective brain imaging paradigm is important because self-report measures of reward are vulnerable to self-presentation biases. Additionally, these measures may tap into anticipated food reward rather than actual reward experienced during food intake. We were only able to locate three brain imaging studies investigating brain differences between individuals with bulimia nervosa and healthy controls using food picture presentation paradigms that may be construed as measuring anticipatory food reward. These studies did not involve reactions to anticipated intake of actual food, but rather response to food images. Thus, it seems like a logical next step would be to investigate brain differences in anticipatory food reward between individuals with and without bulimia nervosa using a paradigm wherein individuals are anticipating actual food receipt. This study attempted to address these gaps in the current literature by measuring fMRI brain response among women with and without bulimia nervosa while anticipating and receiving a hedonically pleasurable and calorically dense taste. This study also was novel in controlling for the effects of acute food restriction. Although prior studies have implemented a standard fast before scans, this study added a standardized snack consumed 1-hour prior to the scan. Based on findings from prior brain imaging studies, we hypothesized that women with bulimia nervosa would show greater activation in the reward circuitry in response to both anticipated and actual food receipt relative to healthy controls. We also included a number of self-report measures that frequently correlate with bulimic pathology and reward circuitry abnormalities. These measures were used as covariates in the analyses for significant group differences between women with and without bulimia nervosa in

order to ensure that these variables do not better explain differences between these groups in reward circuitry activation.

CHAPTER III

METHOD

Participants

A total of 20 college females were recruited over one year from introductory psychology courses and through flyers posted around a university campus. Data from these women were combined with baseline data from a weight-loss study using the same fMRI paradigm, creating a final sample of 24 college females, aged 18-26 ($M = 20.2$, $SD = 1.79$). This sample included 12 healthy controls, 10 women with subthreshold bulimia nervosa, and 2 women with full threshold bulimia nervosa. The full sample comprised 4% Hispanic, 79% Caucasian, 13% Asian, and 4% African American. Participants had a mean body mass index (BMI) of 23.5 (Range = 19.5-28.2, $SD = 2.7$).

Procedure

Students in introductory psychology courses were screened with the Eating Disorder Diagnostic Scale (Stice, Telch, & Rizvi, 2000). Those reporting at least 4 binge episodes and compensatory behaviors in the prior month and those reporting no bulimic pathology were invited to participate. Additional participants were recruited via flyers posted on campus and surrounding areas. Participants were excluded if they had any contraindication for MRI scanning procedure (metal in body, braces, claustrophobia, etc.), if they had a food allergy to chocolate milkshake, or if they did not like chocolate

milkshake. Participants with any Axis I psychiatric disorder based on a screening measure (screening questions from the SCID-IV) or who were taking psychoactive medications other than selective serotonin-reuptake inhibitors were excluded to reduce sample heterogeneity and increase power. Participants excluded because of Axis I psychiatric disorder were provided with referrals to local counselors.

Study procedures were described to interested individuals over email or telephone and eligibility questions were administered. Those who remained eligible completed two appointments. On the first appointment, after providing informed consent, participants completed a diagnostic interview. If the diagnostic interview confirmed a threshold or subthreshold diagnosis of bulimia nervosa or no eating disorder symptoms, the participant scheduled a second appointment. Subthreshold bulimia nervosa was defined as engaging in binge eating and compensatory behaviors at least once per week, rather than the more stringent twice per week for a full threshold diagnosis. If the participants did not fall into the eating disordered or non-eating disordered group (e.g., reported partial symptoms or symptoms of anorexia nervosa), they were excluded. Exclusionary criteria resulted in 14 excluded participants (3 for metal contraindicators, 5 for psychotropic medications, 2 for Axis I disorders, and 4 due to the presence of partial symptoms (e.g., bingeing without compensatory behaviors)).

On the second appointment, participants completed a series of self-report measures that may be related to eating behaviors and the fMRI paradigm. They ate a standardized snack, consisting of a Nutri-Grain bar and a piece of fruit (e.g., apple, banana, or pear) to control for effects of acute food deprivation. They also rated the

tastes used in the study on pleasantness and craving. They reported their intake of chocolate milkshake over the prior month. During the paradigm, two pictures were presented: a glass of chocolate milkshake labeled "milkshake" and a glass of water labeled "water." We used a standard highly palatable and hedonically pleasurable milkshake for the milkshake condition. We used tasteless solution for the water condition to control for the effects of receiving and swallowing a liquid. Pictures were presented for 3 seconds followed by a jitter of 1-7 seconds during which time the screen was blank. Following 60% of the picture cues, a 3 second delivery of 0.5cc of the milkshake/tasteless solution was delivered following the jitter; for the remaining 40% of the pictures cues, no milkshake/tasteless solution was delivered (invalid presentations). A second jitter of 1-7 seconds followed milkshake/tasteless solution delivery. In total, there were 20 each of the valid and invalid pictures, in which the milkshake or tasteless solution was and was not delivered when cued: which are the key conditions involved in this paradigm. This was accomplished in 5 runs of 7.5 min duration (plus 13-secs of dummy scanning at the beginning of each scan to allow equilibrium to be reached). This design allowed us to identify the brain regions that were activated in response to expecting to get a taste of chocolate milkshake versus expecting tasteless solution and also in response to actual receipt of the chocolate milkshake versus tasteless solution.

In addition to the neural measure, subjects used a visual analogue scale to rate the perceived pleasantness of the milkshake and the intensity of the overall flavor. This provided us with hedonic and sensory measures of our stimulus. The scales chosen provided ratio-like data equivalent to magnitude estimation with the added ability to

compare individual differences in a more meaningful and sensitive way than traditional category scales (Bartoshuk et al., 2006; Green et al., 1996).

The milkshake was made fresh each day with 1 cup of vanilla Häagen Dazs ice cream, 1 cup of 2% milk, and 2 tablespoons of Hershey's chocolate syrup. The tasteless solution was made from USP grade KCL and $NaHCO_3$, to mimic the ionic components of saliva. The mixture was composed of 0.0125M KCl and 0.00125M $NaHCO_3$ M dissolved in water. Stimuli were stored in a refrigerator and brought to room temperature before use. New liquid tasteless solutions were made every 5 days.

fMRI Scanner and Data Acquisition

We used a Siemans Allegra 3T scanner at the Lewis Center for Neuroimaging at the University of Oregon to collect functional and anatomical imaging data. Participants practiced the paradigm prior to data collection, including swallowing without moving their heads. Foam padding and a vacuum pillow were used to limit involuntary head movement. Visual stimuli were presented with a digital projector/reverse screen display system. Taste stimuli were delivered with programmable syringe pumps (Braintree Scientific BS-8000). Participants completed scanning in one 60-minute session. Laterality for image processing was confirmed by taping a vitamin E capsule to the right temporal region in every subject. Echo planar imaging was used to measure the blood oxygen level dependent (BOLD) signal as an indication of cerebral brain activation. The OFC and amygdala were of particular interest in the proposed studies. These areas are subject to well-known signal distortions in fMRI (Parrish et al., 2000). To improve BOLD signal detection and minimize susceptibility-based distortion effects, we used a

protocol that utilized a high readout bandwidth, a shorter echo time, and localized shimming in the region of the OFC and amygdala to reduce the magnetic field distortion. Specifically, a susceptibility weighted single shot echo planar sequence was used to image the regional distribution of the BOLD signal with TR = 2100 ms, TE = 20ms, flip angle = 80°, with an in plane resolution of 3.0 x 3.0 mm^2 (64 x 64 matrix; 192 x 192 mm^2 field of view). To cover the whole brain, 32 4mm slices (interleaved acquisition, no skip) were acquired along the AC-PC transverse, oblique plane as determined by the midsagittal section. Slices were acquired in an interleaved mode to reduce the cross talk of the slice selection pulse. At the beginning of each functional run, the MR signal was allowed to equilibrate over 6 scans for a total of 12.6 sec, which was excluded from analysis. This procedure has consistently been able to measure signal in the amygdala and OFC in other labs (Small et al., 2003; Small et al., 2004; Veldhuizen et al., 2007). For each subject, a high resolution, T1 weighted 3D volume was acquired in 8 minutes (MP-RAGE with a TR/TE of 2100ms/2.4ms, flip angle of 15°, TI of 1100ms, matrix size of 256x256, FOV of 22cm, slice thickness of 1mm). The orientation of this 3D volume was identical to the functional slices and was used in conjunction with the activation maps to localize the function and determine the anatomic regions for investigation of the time course data. Distortion in EPI images was corrected based on the estimated parameters of the phase map (Jezzard & Balaban, 1995).

We monitored head movement in vivo during the scan and re-administered any block in which head movement exceeded 1 mm. Specifically, we used the Prospective Acquisition CorrEction (PACE) program to monitor head movement in real time. If head

movement exceeded 1 mm during a scan, the operator was notified so that he could stop the scan and re-administer that particular block. In addition, for smaller movements, PACE adjusts slice position, orientation and regrids the residual volume-to-volume motion during data acquisition. PACE combines techniques of prospective and retrospective motion correction by estimating motion parameters for subsequent volume acquisition based on detecting motion from reconstructed image data. There is a high level of consistency and accuracy for detected motion parameters in phantom experiments with PACE, (translation<40 μ m; rotation< 0.05°) and in vivo experiments demonstrate significant reduction of variance in pre- and post-motion volumes (Thesen, Heid, Mueller & Schad, 2000). In addition, we preprocessed the data within 1-week of the scan to ensure that all the data were usable.

Measures

Screening Measure for Bulimic Pathology: The Eating Disorder Diagnostic Scale (Stice, Telch, & Rizvi, 2000) was used to screen students for bulimic pathology. The EDDS assesses DSM-IV diagnostic criteria for anorexia nervosa, bulimia nervosa, and binge eating disorder. A frequency count of binge episodes and compensatory behaviors was used to select individuals to participate in the study. The EDDS has shown high agreement (κ = .78 - .83) with eating disorder diagnoses made with the Eating Disorder Examination (EDE; Fairburn & Cooper, 1993), internal consistency (α = .89), 1-week test-retest reliability (r = .87), sensitivity to detecting intervention effects, and predictive validity for future onset of eating pathology and depression (Stice, Telch, & Rizvi, 2000; Stice, Fisher, & Martinez, 2004).

Screening Measure for Axis I Disorders: The screening questions from the Structured Clinical Interview for DSM-IV Disorders was used to screen potential participants for psychiatric disorders. Specifically, the rule-out questions for the most common disorders (e.g., major depression, bipolar disorder, substance abuse, and anxiety disorders) were administered. Participants showing evidence of a psychiatric disorder on these questions were excluded from the study. The SCID shows good inter-rater reliability and test-retest reliability for major depression ($r = .80$ and .61 respectively), alcohol dependence/abuse ($r = 1.00$ and .77, respectively), and anxiety disorders ($r = .57$-.88 and .44-.78, respectively) (Zanarini & Frankenburg, 2001; Zanarini et al., 2000).

Handedness: Handedness was assessed with the Edinburgh Handedness Questionnaire (Oldfield, 1971), and both the laterality quotient and the laterality scale were calculated (Schachter, 1993). This measure asks participants which hand they use for a variety of activities such as writing, throwing, and using a knife and also asks whether they would only use the opposite hand when forced to. Scores above zero indicate more dominant use of the right hand, and below zero indicate more dominant use of the left hand. Someone scoring exactly zero would have no preference of one hand over the other. We did not exclude based on handedness, but used it as a covariate to ensure that it did not impact results.

Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ): This 48-item scale measures behavioral approach tendencies in the presence of cues for reward and avoidance tendencies in the presence of cues for punishment (Torrubia, Avila, Molto & Caseras, 2001). This scale has shown internal consistency ($\alpha = .75$-.78), 3-month test-

retest reliability (r = .87), and convergent validity with other self-report measures of general reward sensitivity (Caseras et al., 2003; Torrubia et al., 2001). Higher scores on the SPSRQ are associated with self-report of alcohol use disorders (Kambouropoulos & Staiger, 2006) and increased heart rate while intoxicated with alcohol and positive feelings afterward intoxication (Brunelle et al., 2004).

Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS): This 24-item measure consists of one inhibition scale (7 items; sample item "*Criticism or scolding hurts me quite a bit.*") and three activation subscales: Reward Responsiveness (5 items; sample item "*It would excite me to win a contest.*"), Drive (4 items; sample item "*I go out of my way to get things I want.*"), and Fun Seeking (4 items; sample item "*I often act on the spur of the moment.*") (Carver & White, 2004). Responses range from 1 = *very true for me* to 4 = *very false for me.* This measure is designed to assess avoidance and approach behaviors and has shown adequate internal consistencies (α = .66-.76) and 2-month test-retest reliability (r = .59-.69) (Carver & White, 1994).

Impulsivity: The Barratt Impulsiveness Scale (Patton, Stanford, & Barratt, 1995) assesses impulsivity with 30 items with a scale ranging from 1 = *rarely/never* to 4 = *almost always.* Internal consistency for the scale ranges from 0.79 to 0.83 for populations ranging from undergraduates to psychiatric patients to prison inmates. The mean score on this scale was used as a measure of overall impulsivity. This measure has been shown to be both reliable and valid (e.g., Stanford & Barratt, 1992).

Emotionality: Buss & Plomin's (1984) Emotionality Scale measures the individual's level of agreement on a 5-point scale (ranging from 1 = "*never true of me*" to

5 = "*always true of me*") regarding the tendency to become affectively distressed (sample item: "*I frequently get distressed.*"). The 12-item scale has shown internal consistency (α = .82), convergent validity with other measures of negative affect, and predictive validity (Buss & Plomin, 1984; Stice et al., 1998).

Self-esteem: An adapted version of the Rosenberg Self-Esteem scale (Rosenberg, 1979) assessed participants' general self worth. The adapted scale consists of six statements (e.g., *I feel that I have a number of good qualities*). Participants indicated their level of agreement with items using a 4-point response scale ranging from 1 = *strongly disagree* to 4 = *strongly agree*. Responses were averaged to form a scale score, wherein high scores reflect higher self-esteem. This scale has shown internal consistency (M = .82), test-retest reliability ($M r$ = .86), and convergent validity with self-esteem assessed by structured interviews, observer ratings, clinical ratings, and peer ratings ($M r$ = .51; Demo, 1985).

Positive and Negative Affect: The Positive and Negative Affect Schedule (PANAS: Watson, Clark, & Tellegen, 1988) assesses positive and negative affect. This scale consists of 10 adjectives loading on the positive affect factor and 10 adjectives loading on the negative affect factor. Participants rate how much each adjective describes their current mood from 0 to 5, where 0 is "*very slightly*" and 5 is "*extremely.*" This scale has shown internal consistency (α = .95), 3-week test-retest reliability (r = .78), convergent validity, and predictive validity (Stice, Trost, & Chase, 2003; Watson & Clark, 1992).

Depressive Symptoms: The Beck Depression Inventory (BDI: Beck, Steer, & Brown, 1996) measures the severity of 21 depressive symptoms. Each item is rated from 0-3, with each rating reflecting the intensity of the particular symptom. The BDI has acceptable internal consistency (α = .73 to .95), test-retest reliability (r = .60 to .90), and convergent validity with clinician ratings of depressive symptoms ($M r$ = .75; Beck et al., 1988).

Anxiety Symptoms: Anxiety symptoms were measured with the Beck Anxiety Inventory (BAI: Beck & Steer, 1990). The BAI consists of 21 items assessing the severity of anxiety symptoms. This scale shows high internal consistency (α = .92) and test-retest reliability over 1 week (r = .75). The scale discrimintated anxious diagnosotic groups from nonanxious diagnostic groups (Beck, Epstein, Brown, & Steer, 1988).

Dutch Eating Behavior Questionnaire: The Dutch Eating Behavior Questionnaire (van Strien, Fritjers, Bergers, & Defares, 1986) assessed emotional eating, restrained eating, and external eating. These three subscales have shown internal consistency (α = .86 to .97; van Strien et al., 1986) and shows convergent (preliminary study) and predictive validity (Stice et al., 2002). The restraint scale shows good test-retest reliability (2-week r = .92, van Strien et al., 1986). Furthermore, emotional eaters identified by this scale showed different neural response to food cues and food intake relative to non-emotional eaters in a past study (Bohon, Stice, & Spoor, 2008). Although the restraint scale correlates inversely with self-reported caloric intake (van Strien, Breteler, & Ouwens, 2002), it shows much weaker relations to unobtrusively measured caloric intake (Ouwens, van Strien, & van der Staak, 2003; Stice et al., 2004).

Three Factor Eating Questionnaire: The Three Factor Eating Questionnaire (TFEQ; Stunkard & Messick, 1985) assessed hunger, disinhibited eating, and restrained eating. The scale consists of true/false statements and questions asking about frequency of various eating behaviors. A sample item from the hunger subscale is "I am usually so hungry that I eat more than three times a day." This scale has shown adequate internal consistency and test-retest reliability (Bond, McDowell, & Wilkinson, 2001). Scores on these subscales have been associated with obesity in adult women (Boschi et al., 2001).

Self-reported Consummatory and Anticipatory Food Reward: The Food Craving Inventory (FCI, White, Whisenhunt, Williamson, Greenway, & Netemeyer, 2002) assesses the degree of craving for a variety of listed food items. We adapted this scale by also asking subjects to rate how much the like each of the listed foods. The original FCI has shown internal consistency ($\alpha = .93$), 2-week test-retest reliability ($r = .86$), and sensitivity to detecting intervention effects (Martin, O'Neil, & Pawlow, 2006; White et al., 2002). In a pilot study ($N = 27$) the craving scale and the liking scale showed internal consistency ($\alpha = .91$ and .89 respectively). We included this scale with the hope that it would correlate with our fMRI and behavioral measures of anticipatory and consummatory food reward, as it has in previous studies (Stice et al., 2008b). It would also be desirable to generate a self-report measure of these constructs.

Eating Expectancies: The Eating Expectancies Inventory (Hohlstein, Smith, & Atlas, 1998) was used to measure eating expectancies. This 34-item measure assesses five types of expectancies: eating helps manage negative affect, alleviates boredom, is pleasurable and useful as a reward, leads to feeling out of control, and enhances cognitive

competence. The scale has shown internal consistency ($\alpha = .90$) and association with eating disorder symptoms among adolescents (MacBrayer et al., 2001; Simmons et al., 2002). Additionally, it has shown predictive validity for future increases in bulimic symptoms (Smith et al., 2007).

Thin-ideal Internalization: The Beliefs About Appearance Scale, which measures the belief that achieving the thin-ideal improves relationships, achievement, self-view, and mood, assessed thin-ideal internalization: this 20-item scale has shown internal consistency ($\alpha = .95$), 3-week temporal reliability ($r = .83$), and convergent validity (Spangler & Stice, 2001).

Body Dissatisfaction: Body dissatisfaction was assessed with 9 items from the Satisfaction and Dissatisfaction with Body Parts Scale that assessed body parts that are often of concern to females (e.g. stomach, thighs and hips) (Berscheid, Walsther & Bohrnstedt, 1973). Participants indicate their level of dissatisfaction with body parts on a scale ranging from 1 = *extremely satisfied* to 5 = *extremely dissatisfied.* This scale has shown internal consistency ($\alpha = .91$), 2-week test-retest reliability ($r = .80$) and predictive validity for bulimic symptom onset (Stice, Shaw, Burton & Wade, 2006).

Bulimic Symptoms: The diagnostic items from the Eating Disorder Examination, a structured psychiatric interview, were used to assess DSM-IV criteria for bulimia nervosa over the past year (EDE 12th Edition; Fairburn & Cooper, 1993). Past research has documented that the EDE has a strong inter-rater reliability, internal consistency, discriminant validity, and concurrent validity (Fairburn & Cooper, 1993; Williamson, Anderson, Jackman, & Jackson, 1995) and the measure has been shown to distinguish

between eating disordered individuals and controls (Cooper, Cooper, & Fairburn, 1989; Fairburn & Cooper, 1993). The shortened version of this interview (Eating Disorder Diagnostic Interview) has been used extensively in studies conducted by Dr. Eric Stice's lab. The continuous eating disorder symptom composite has shown internal consistency (α = .92), 1-week test-retest reliability (r = .90), sensitivity to detecting intervention effects, and predictive validity for future onset of depression in past studies of adolescent and young adult females (Presnell & Stice, 2003; Stice, Burton et al, 2004). Moreover, the eating disorder diagnoses from this adapted interview show high inter-rater agreement between independent and blinded assessors (α = .86) and high 1-week test-retest reliability (alpha = .96; Stice et al., 2006). Clinical interviewers for this study were trained to produce high inter-rater reliabilities (kappas = .90 or higher) before they began conducting the interviews for this study.

Body Mass Index (BMI; Kg/M^2): Height was measured to the nearest millimeter using a portable direct reading stadiometer. Participants were measured without shoes and with the body positioned such that the heels and buttocks were against the vertical support of the stadiometer and the head aligned so that the auditory canal and lower rim of the orbit were in a horizontal plane. Weight was assessed to the nearest 0.1 kg using digital scales with participants wearing light clothing without shoes or coats. At each assessment, two measures of height and weight were obtained and averaged. BMI correlates with direct measures of total body fat such as dual energy x-ray absorptiometry (r = .80 to .90) and with health measures including blood pressure, adverse lipoprotein profiles, atherosclerotic lesions, serum insulin levels, and diabetes mellitus in adolescent

samples (Dietz & Robinson, 1998; Pietrobelli et al., 1998). BMI also shows high test-retest reliability over a 1-month period (r = .99; Stice et al., 2005).

Social Functioning: Items adapted from the Social Adjustment Scale (SAS; Weissman & Bothwell, 1976) were used to assess impaired psychosocial functioning. Specifically, 17 items assessing role functioning in the family, peer group, school, and work were used. The SAS has been shown to possess internal consistency (M = .74), to discriminate between controls and psychiatric patients (depressives, alcoholics, and schizophrenics), and to be sensitive to treatment effects (Edwards, Yarvis, Mueller, Zingale, & Wagman, 1978; Weissman & Bothwell, 1976; Weissman, Prusoff, Thompson, Harding, & Myers, 1978).

Healthcare Utilization: Health care utilization was assessed with four items adapted from the Health Survey Utilization Scale (HSUS; Ryan, Millstein, Greene & Irwin, 1996), which assess frequency of utilization of health and mental health services (sample item: "In the past year, did you get health care for a medical problem or an illness when you were feeling sick?"). If participants endorsed health care service utilization, they were asked to indicate the primary reason for treatment. This scale possessed acceptable internal consistency (α= .77) and test-retest reliability (r = .62) in a bulimia nervosa treatment study (Burton & Stice, 2006).

Data Analysis

Data were analyzed on a Windows workstation with Matlab software (MathWorks, Inc., Sherborn, MA) using SPM5 (Wellcome Department of Cognitive Neurology, London, UK). The functional images were time-acquisition corrected to the

slice obtained at 50% of the TR. All functional images were then realigned to the scan immediately preceding the anatomical T1 image. The images (anatomical and functional) were then normalized to the Montreal Neurological Institute template (MNI-305), which approximates the anatomical space delineated by Talairach and Tournoux (1988). Functional images were smoothed with a 7 mm FWHM isotropic Gaussian kernel. For time series analysis on all participants, a high-pass filter was included in the filtering matrix (according to convention in SPM5) in order to remove low frequency noise and slow drifts in the signal, which could bias the estimates of the error.

Condition specific effects at each voxel were estimated using the general linear model. The response to events (i.e. indicated by stimulus onsets) were modeled by a canonical hemodynamic response function (HRF), consisting of a mixture of 2 gamma functions that emulate the early peak at 5 seconds and the subsequent undershoot. Our paradigm had 4 events of interest. In the anticipatory aspect of the paradigm this included the picture of milkshake and the picture of water as the baseline for milkshake picture (invalid presentations). For the consummatory aspect of the paradigm the 2 events included receipt of milkshake and tasteless solution at baseline. The temporal derivative of the hemodynamic function was also included as part of the basis set to enable examination of differences in timing between events (Henson et al., 2002). Condition-specific estimates of neural activity (betas, corresponding to the height of the HRF) were computed independently at each voxel for each subject, using the general linear model.

Within and between-group comparisons were performed using a random effects model in order to account for inter-subject variability. SPM assigns significance t-fields from all analyses using the theory of Gaussian Random Fields (Friston et al., 1995; Worsley & Friston, 1995). Activations were considered significant at $p < 0.05$ after correction for multiple comparisons either across all voxels in the volume or within regions of interest, specified using the small volume correction option a priori. Inclusive logical masking, an option in SPM5, was used to ensure that brain regions show significant activation in the relevant reference experimental task or comparison. For example, milkshake – tasteless was inclusively masked by milkshake to ensure that activity isolated in the contrast reflects activation in milkshake. The SPM software also enables single and multiple regression analyses for examining the influence of various covariates, such as intensity or pleasantness ratings on activations.

Additionally, we conducted analyses testing the relation between the functional data and the survey measures to determine if brain response to consummatory or anticipatory food reward was related to other self-report measures. T-tests were conducted to determine differences between groups on the survey measures. Variables with large differences were included as covariates in fMRI analyses. These analyses were also conducted with SPM5, with these measures used as covariates in the standard GLM analyses described previously.

CHAPTER IV

RESULTS

Descriptive Statistics and Self-report Data

Means and standard deviations for all self-report measures are reported in Table 1. We conducted independent samples t-tests to determine whether women with bulimia nervosa differed from control women on the measures. As expected, there were a number of significant differences on measures of eating behaviors and mood. All statistical values for these analyses are reported in Table 1. Women with bulimia nervosa had significantly lower self-esteem and body satisfaction. They reported higher levels of depressive symptoms, negative affect, emotional eating, dietary restraint, external eating, craving, disinhibited eating, hunger, expectation that eating helps manage negative affect and leads to a loss of control, thin-ideal internalization, positive expectations about thinness, and social functioning. In this sample, the women with bulimia nervosa tended to be more left-handed, suggesting that laterality effects in brain response should be interpreted cautiously.

There were no significant differences between the groups on the number of hours they had eaten prior to their fMRI scan, the amount of time since they last drank a chocolate milkshake, and the frequency with which they had chocolate milkshakes. There were also no significant differences between the pleasantness ratings of the

chocolate milkshake and tasteless solution for the two groups. This is important, as it suggests that any differences in brain response to the milkshake are not related to acute food restriction, frequency of milkshake consumption, or pleasantness ratings.

Anticipatory Food Reward Group Differences

ANOVAs were conducted using SPM5 to determine whether group differences existed between brain activation in regions of interest to anticipating receipt of chocolate milkshake versus anticipating receipt of the tasteless control solution (the anticipatory food reward contrast). This contrast utilized the incongruent trials (e.g., when the cue signaled subsequent delivery of chocolate milkshake, but no taste was delivered). This allowed us to separate the effect of anticipation from the effect of taste delivery. There was no main effect of bulimia nervosa diagnosis for this contrast significant at the $p < .05$ corrected level. There was one significant effect at the $p = .005$ uncorrected level. Women with bulimia nervosa showed less activation in the right anterior insula (see Table 2 for a summary of brain areas and contrasts). Figure 1 shows the activation location and a graph of parameter estimates for each group and each type of cue. While the control women showed an expected heightened activation of the anterior insula in response to the cue signaling chocolate milkshake delivery, and decreased activation in response to the cue signaling tasteless solution delivery, women with bulimia nervosa did not show much change in this brain region between the two cue types.

Consummatory Food Reward Group Differences

We conducted a similar ANOVA investigating group differences in response to milkshake receipt versus tasteless solution receipt (the consummatory food reward

contrast). There was no main effect of bulimia nervosa diagnosis for this contrast significant at the $p < .05$ corrected level. There were four significant effects at the $p < .005$ level. Participants with versus without bulimic pathology showed less activation in the left medial orbitofrontal cortex (OFC), right posterior insula, right precentral gyrus, and right mid dorsal insula. Patterns of activation were similar to the anterior insula effect for the anticipatory reward contrast. For each effect, women in the control group showed expected greater activation in these regions in response to milkshake receipt and less activation in response to tasteless solution receipt. Women with bulimia nervosa, however, did not show significant change in activation for these conditions. Figure 2 shows activation locations and a graph of parameter effects for one of the brain regions. Each brain region significant at the $p < .005$ uncorrected level showed the same pattern of activation for each group and condition.

Post-hoc Analyses

We ran analyses with self-report measures that may have influenced brain response to food reward and were also related to bulimia diagnosis. The largest difference found between women with bulimia nervosa and healthy controls were in the eating expectancies (expectation that eating alleviates negative affect and the expectation that eating leads to loss of control), external eating, disinhibited eating, emotional eating, hunger, depressive symptoms, and social functioning. We included these as covariates to determine whether they better explained the variance in brain response to food reward. For anticipatory food reward, the anterior insula no longer showed significantly different activation between groups when controlling for each of these covariates. However, when

error variance was accounted for by a number of these covariates, other reward regions became significant for the effect of bulimia diagnosis on anticipatory food reward. These brain regions included the right precuneus, bilateral precentral gyrus, left thalamus, left anterior cingulate, bilateral posterior cingulate, and bilateral mid frontal gyrus. For consummatory food reward, the right precentral gyrus no longer showed significantly different activation between groups when controlling for the covariates. The right posterior insula remained significant when the expectation that eating would lead to loss of control, disinhibited eating, and depression were included, but not with the other covariates. The left medial OFC remained significant when external eating, emotional eating, and disinhibited eating were included, but not with the other covariates. The right mid dorsal insula remained significant when social functioning, external eating, both eating expectancies, and depression were included, but not with hunger, emotional eating, or disinhibited eating. Similar to the results from anticipatory reward analyses, when error variance was accounted for by a number of these covariates, other reward regions became significant for the effect of bulimia diagnosis on consummatory food reward. These regions included the right medial frontal gyrus, left insula, bilateral precentral gyrus, and left thalamus. The effects of bulimia on brain activation when covariates are included are reported in Tables 3 and 4.

Thus, it appears that some differences in brain response to anticipatory and consummatory brain response may be accounted for by other factors, although unique effects of bulimia diagnosis remained for consummatory reward even after controlling for these factors. Additionally, unique effects of bulimia were better detected when error

variance was accounted for by the covariates, suggesting that there are additive effects of bulimia and related factors on brain response to food reward.

CHAPTER V

DISCUSSION

General Summary

The primary aim of the current study was to use fMRI to detect differences between women with and without bulimia nervosa in brain response to anticipating and receiving a chocolate milkshake. Contrary to hypotheses, women with bulimia nervosa tended to show less response in brain reward areas in both anticipatory and consummatory conditions relative to healthy controls, though none of these effects were significant using the most conservative corrected .05 alpha level.

The addition of covariates to analyses resulted in subtle changes to findings. Eight variables were included as covariates (individually) because they were most strongly related to bulimia diagnosis. These covariates appeared to account for the differential anterior insula response to anticipatory reward, suggesting that abnormal response in this region to anticipating a pleasant taste is not unique to bulimia, but rather, to factors that appear to be related to bulimia. However, the addition of these covariates resulted in additional variance explained by the model and thus allowed for the detection of additional effects in anticipatory reward differences between bulimics and controls. Specifically, new effects were detected in the right precuneus, bilateral precentral gyrus, left thalamus, left anterior cingulate, bilateral posterior cingulate, and bilateral mid frontal

gyrus. Findings were less consistent for consummatory reward, as effects of bulimia on brain response to receipt of chocolate milkshake remained with the addition of some covariates, but not others. Additionally, effects of bulimia on activation in the right medial frontal gyrus, left insula, bilateral precentral gyrus, and left thalamus were revealed with the addition of these covariates. For each of these effects, patterns of activation remained consistent (i.e., less activation in reward regions among women with bulimia nervosa compared to health controls).

It is surprising that women with bulimia nervosa would show weaker activation in reward regions given prior research revealing heightened reward sensitivity based on both self-report measures and behavioral reward paradigms. Additionally, these findings are inconsistent with prior brain imaging studies finding greater brain reward response to food images (Karhunen et al., 2000; Schienle et al., 2009; Uher et al., 2004). These findings are consistent, however, with studies of recovered bulimics showing blunted reward activation in response to tastes of a glucose solution (Frank et al., 2006; Kaye et al., 2001). Studies among women with obesity have suggested that patterns of overeating may result in decreased activation of reward areas, which may put them at risk for future weight gain (Stice et al, 2008). It could be that women with bulimia nervosa may respond similarly to repeated binge eating, resulting in decreased reward activation and a need for continued binge eating to achieve the same level of satisfaction.

This study was the first imaging study of women with bulimia nervosa to include a standardized snack prior to the imaging session. Although this was added to the study in attempt to control for possible differences between women with and without bulimia in

acute food restriction, it may have reduced overall brain activation in response to the tastes, decreasing our ability to detect differences between groups. We did not scan any participants without consuming the snack, so we were unable to directly examine the effects of the snack on brain activation during the fMRI paradigm. Theoretically, hunger may result in heightened reward activation in response to pleasurable taste in all populations, so differences between women with and without bulimia nervosa may be more evident after a snack. This was not true in the current study, suggesting that it may be important for future studies to pay close attention to the time of last food intake prior to scan. Schienle and colleagues (2009) instructed participants to fast overnight and found no difference in self-reported time of intake, but reported lower levels of blood glucose in women with bulimia nervosa, suggesting a longer fast than controls. Uher and colleagues (2004) instructed participants to eat 3 hours prior to the scan, although patients with bulimia nervosa reported a longer duration of fast (M = 4.5 hours compared to M = 3.3 hours for the control group). Because it appears that women with bulimia nervosa may go longer between eating episodes, feeding them 1-hour prior to the brain scan may have abolished differences in reward activity naturally present during a more deprived state in which binge eating may occur.

The prior fMRI studies of bulimia nervosa and this study also differed on the time of day during which the scans took place. Uher and colleagues (2004) conducted scans in the evening, whereas Schienle and colleagues (2009) and Karhunen and colleagues (2000) conducted scans in the morning. Scans for this study were conducted in the afternoon (between 13:00 and 15:30). Response to food rewards may differ based on

time of day. Studies have shown differences in cocaine sensitization and reward based on circadian rhythm (Abarca, Albrecht, & Spanagel, 2002).

Another possible explanation for the incongruent findings between this study and prior fMRI studies of bulimia nervosa is the inclusion of subthreshold bulimia nervosa. Although the criteria used in this study were more conservative than those used in other studies of subthreshold bulimia nervosa (binge eating and compensatory behaviors occurring at least once per week for prior 3 months, as opposed to twice per month; e.g., Spoor et al., 2007), the inclusion of less frequent and severe cases may have attenuated effects. It is uncertain, however, whether Uher and colleagues (2004) included subthreshold cases, as they did not conduct diagnostic interviews. Instead, they recruited from inpatient and outpatient treatment programs, which may have included subthreshold cases, as many women with less frequent bulimic pathology present for treatment (Spoor et al., 2007).

It is also noteworthy that women with bulimia nervosa did not appear to differentiate between the milkshake and tasteless stimuli as much as the healthy controls. Rather than showing much more or less activation in response to the milkshake, it appeared that their reward circuitry showed overall blunted activity. This is important, as it suggests that the pleasurable aspects of a particular taste are not driving the reward circuitry activation in individuals with bulimia nervosa, as it may be for healthy controls. Instead, it may be that individuals with bulimia nervosa have down-regulation of dopamine receptors and change in opioid receptors after recurrent binge eating. This

could, in turn, lead to continued binge eating in order to compensate for this reward deficit, as has been proposed by obesity research (e.g., Wang et al., 2001).

Implications

If women with bulimia nervosa indeed have less reward activation to tastes of food, this suggests that their binge eating is occurring despite the decreased neural reward drive. It is possible that the urge to binge is based in a more complex drive-to-eat manner, rather than simply hypersensitivity to food cues and tastes. If women with bulimia nervosa had shown greater activation in reward circuitry, it could suggest that the binge results from this heightened response to the sight, smell, or taste of foods. Instead, binge eating may be due to other situational factors, like habit (e.g., binges that occur at a certain time of day) or emotional factors (e.g., bingeing in response to negative affect). The guilt and shame associated with the binge, which reportedly leads to compensatory behaviors, could also result in blunted reward response over time in response to binge foods. Indeed, most women with bulimia nervosa in this sample reported high levels of emotional eating and negative affect. A sample with lower levels of these emotion-related variables may show more "pure" reward-driven binge eating and perhaps a different pattern of brain activation in response to chocolate milkshake anticipation and consumption. Exploring the effect of affect on reward response may result in better development of treatments targeting different presentations of symptoms.

If women with bulimia nervosa had shown greater activation of reward circuitry in response to food cues and food intake, interventions could focus on decoupling food cues from pleasant taste in order to decrease anticipatory reward and reduce the tendency

to binge eat. Given the current findings, however, it may be beneficial to enhance the reward value of foods. Perhaps if pleasurable foods resulted in reward activation equal to that of healthy controls, individuals would not be as likely to binge eat on the food. More research will be necessary before clinical implications can be determined more confidently.

If these results are supported in future prospective research, it could suggest targeting prevention interventions for populations with weakened reward circuitry activity. Perhaps providing these individuals with skills to eat healthfully will reduce their susceptibility to develop bulimia nervosa.

Limitations

Although this study provides novel findings about the functioning of reward circuitry among women with a current diagnosis of bulimia nervosa in response to actual food intake rather than just food images, it is not without limitations. First, the small sample may have limited our ability to detect effects in a number of brain regions. Although we discussed the marginally significant effects with $p < .005$ uncorrected, no activations met our more stringent $p < .05$ corrected requirements. A larger sample could result in significant effects.

A second limitation is the cross-sectional design of the study. Although it is possible that abnormalities in food reward increase vulnerability to bulimic pathology, it is also possible that this eating disorder contributes to these abnormalities. Animal studies have found down-regulation of post-synaptic D2 receptors, increased D1 receptor binding, and decreased D2 sensitivity and μ-opioid binding after repeated intake of sweet

and fatty foods (Bello, Lucas, & Hajnal, 2002; Colantuoni et al., 2001; Kelley et al., 2003). Thus, binge eating among women with bulimia nervosa could impact the brain function, as it does in animals, and serve to maintain the disorder. Cross-sectional studies, like the current one, cannot differentiate between risk factors, causes, or consequences of a disorder. Although it seems logical to first investigate reward differences among women currently suffering from bulimia nervosa to know how to focus future work, prospective studies are necessary to establish temporal precedence to provide information about the timing of these symptoms and features.

Third, the brain response to a taste of chocolate milkshake or the anticipation of a taste is fundamentally different than the anticipation or experience of a full binge episode. Although women with bulimia nervosa showed blunted reward activation in response to these tastes in the current study, it is possible that they would show greater response to anticipation of an actual binge or to the binge experience. Perhaps eating a large amount of food would trigger greater brain activation compared to a small taste. If individuals with bulimia nervosa engage in binge eating to compensate for diminished reward response to tastes of food, it could be that they are able to achieve satisfaction after consuming a greater amount.

Fourth, the paradigm used to measure consummatory food reward may not have optimally separated anticipation from consumption, as participants always anticipated receipt of the milkshake taste (there was no un-cued delivery of taste). Animal studies showed different neural responses to cued and uncued delivery of food (Blackburn,

Phillips, Jakubovic & Fibiger, 1989), suggesting that unanticipated food receipt is necessary to truly separate anticipatory and consummatory food reward.

Conclusion

In sum, these findings did not support the hypothesis that women with bulimia nervosa exhibit hyper-responsive reward circuitry in response to anticipatory and consummatory food reward. In contrast, marginally significant findings revealed less activation in reward regions, like the insula and OFC, during anticipation and receipt of a chocolate milkshake taste. This could suggest that women with bulimia nervosa are more similar to women with obesity in response to food reward, which may explain the tendency to engage in binge eating. As posited in the obesity literature, the blunted reward response could lead to greater amounts of food consumed in order to achieve the same level of satisfaction as healthy controls (Wang et al., 2001).

Alternatively, this finding of decreased activation could reflect particular characteristics of the sample, including high levels of depressive symptoms, negative affect, and emotional eating. If these individuals engage in binge eating that is driven more strongly by emotion rather than reward incentive of the food, the decreased reward response may reflect a learned response to food that involves guilt or shame rather than reward. Future research should measure reward response in women with bulimia nervosa and a wider range of depressive symptoms and emotional eating scores in order to determine the effect these factors may have on reward circuitry activation.

Future research should evaluate these findings prospectively in order to determine temporal precedence for decreased reward activation and onset of bulimia nervosa.

Because this cross-sectional study and studies of recovered bulimics found this blunted response, it may be that bulimic behavior leads to abnormal brain functioning rather than the brain function serving as a risk factor for bulimia. Prospective studies are necessary to tease apart these two possibilities. Finally, if these marginally significant findings are supported in larger samples and replications, addressing these abnormalities in treatment and prevention interventions may be important for alleviating this chronic and pernicious disorder.

APPENDIX

TABLES AND FIGURES

Table 1: Means, standard deviations, and independent sample t-tests on self-report measures

	Bulimia Nervosa ($N = 12$) M (SD)	Control ($N = 12$) M (SD)	$t(22)$	η^2
Sensitivity to Reward	45.75 (18.37)	34.75 (13.01)	-1.69	.12
Sensitivity to Punishment	38.25 (15.73)	34.25 (14.72)	-.64	.02
Behavioral Inhibition	3.11 (.44)	3.13 (.30)	.12	.001
Behavioral Activation - Drive	2.61 (.66)	2.81 (.37)	.91	.04
Behavioral Activation – Fun Seeking	3.36 (.44)	3.23 (.63)	-.61	.02
Behavioral Activation – Reward Responsiveness	3.54 (.40)	3.48 (.34)	-.38	.01
Impulsivity	2.42 (.08)	2.48 (.11)	1.42	.08
Emotionality	2.92 (.48)	2.62 (.36)	-1.75	.12
Self-esteem	3.22 (.66)	4.00 (.38)	3.54	.36*
Depressive symptoms	20.04 (10.76)	6.08 (6.46)	-3.85	.40*
Anxiety symptoms	1.55 (.46)	1.36 (.40)	-1.08	.05
Negative Affect	2.65 (.80)	1.87 (.46)	-2.95	.28*
Positive Affect	3.00 (.90)	3.32 (.43)	1.12	.05
Emotional Eating	3.93 (.64)	2.33 (.67)	-5.96	.62**
Dietary Restraint (DEBQ)	3.62 (.59)	2.64 (.78)	-3.47	.35*
External Eating	3.96 (.42)	3.11 (.43)	-4.90	.52**
Craving	2.77 (.43)	2.26 (.36)	-3.08	.30*
Liking	2.72 (.39)	2.48 (.38)	-1.56	.10
Disinhibited Eating	8.92 (.99)	5.08 (3.11)	-4.07	.43*
Hunger	9.00 (2.51)	4.46 (1.70)	-5.19	.55**
Dietary Restraint (TFEQ)	7.15 (1.58)	4.75 (2.03)	-3.23	.32*
Expectation that eating helps manage negative affect	3.44 (.34)	2.47 (.80)	-3.76	.39*
Expectation that eating is rewarding	3.02 (.36)	3.07 (.23)	.40	.01
Expectation that eating leads to a loss of control	3.33 (.47)	2.31 (.61)	-4.60	.49**
Expectation that eating enhances cognitive competence	3.23 (.94)	3.42 (1.02)	.47	.01
Expectation that eating alleviates boredom	3.06 (.32)	2.88 (.24)	-1.62	.11
Thin-ideal internalization	4.06 (.30)	3.70 (.29)	-3.02	.29*
Body Satisfaction	2.31 (.86)	3.51 (.72)	3.68	.38*
BMI	23.83 (2.92)	23.19 (2.52)	-.574	.02
Social Functioning	2.58 (.38)	1.93 (.28)	-4.78	.51**
Healthcare utilization	3.04 (2.97)	1.63 (1.12)	-1.55	.10

Note: *$p<.01$, **$p<.001$

Table 2. Significant brain regions (MNI coordinates of cluster centers), cluster Z-score, p-value, and effect size for each contrast

Contrast	x	y	z	Max Z	p	η^2	Brain Region
Anticipatory Reward							
	27	27	15	-2.99	.001	.43	Right Anterior Insula
Consummatory Reward							
	-24	42	-3	-3.09	.001	.31	Left Medial OFC
	45	-9	-6	-3.02	.001	.48	Right Posterior Insula
	60	-12	39	-3.01	.001	.32	Right Precentral Gyrus
	39	6	12	-2.73	.003	.40	Right Mid Dorsal Insula

Table 3. Significant brain regions (MNI coordinates of cluster centers), cluster Z-score, and p-value for effect of bulimia nervosa group on anticipatory reward when covariates included

Covariate	x	y	z	Max Z	p	Brain Region
Disinhibited Eating						
	0	-9	72	-3.67	<.001	Left Medial Frontal Gyrus
	-21	39	6	-3.51	<.001	Left Anterior Cingulate
	-12	-27	0	-3.15	.001	Left Thalamus
	51	-6	9	-2.89	.002	Right Precentral Gyrus
Emotional Eating						
	15	-57	27	-3.10	.001	Right Precuneus
	-42	-15	42	-2.76	.003	Left Precentral Gyrus
Expectation that Eating Leads to Loss of Control						
	51	-6	9	-3.35	<.001	Right Precentral Gyrus
	-60	-9	27	-3.30	<.001	Left Precentral Gyrus
	-12	-27	0	-3.19	.001	Left Thalamus
	6	-45	27	-3.13	.001	Right Cingulate Gyrus
	39	51	-3	-3.10	.001	Right Middle Frontal Gyrus
	-42	-18	45	-3.03	.001	Left Postcentral Gyrus
Expectation that Eating Alleviates Negative Affect						
	-15	-24	-6	-3.75	<.001	Left Thalamus
	51	-6	9	-3.54	<.001	Right Precentral Gyrus
	39	51	-3	-3.25	.001	Right Middle Frontal Gyrus
	-60	-9	27	-3.20	.001	Left Precentral Gyrus
	6	-45	24	-3.09	.001	Right Cingulate Gyrus
	-21	36	6	-2.89	.002	Left Anterior Cingulate
	-3	-42	21	-2.75	.003	Left Posterior Cingulate
	-15	-45	27	-2.61	.004	Left Cingulate Gyrus

Covariate	x	y	z	Max Z	p	Brain Region
Expectation that Eating Alleviates Negative Affect (continued)						
	39	6	12	-2.60	.005	Right Insula
External Eating						
	-21	48	9	-3.28	.001	Left Anterior Cingulate
	-42	36	0	-3.25	.001	Left Middle Frontal Gyrus
	0	-72	15	-2.77	.003	Left Cuneus
	3	33	51	-2.65	.004	Right Superior Frontal Gyrus
Social Functioning						
	-33	-30	27	-3.06	.001	Left Postcentral Gyrus

Table 4. Significant brain regions (MNI coordinates of cluster centers), cluster Z-score, and p-value for effect of bulimia nervosa group on consummatory reward when covariates included

Covariate	x	y	z	Max Z	p	Brain Region
Depressive Symptoms						
	3	-45	24	-3.40	<.001	Right Posterior Cingulate
	-12	-27	0	-3.29	.001	Left Thalamus
	42	-9	-6	-3.02	.001	Right Insula
Disinhibited Eating						
	-3	-45	21	-3.50	<.001	Left Posterior Cingulate
	-12	-27	0	-3.45	<.001	Left Thalamus
	-39	-15	45	-3.41	<.001	Left Precentral Gyrus
	-24	45	9	-3.32	<.001	Left Medial Frontal Gyrus
	6	0	60	-3.21	.001	Right Medial Frontal Gyrus
	-33	6	15	-3.15	.001	Left Insula
	51	-6	9	-3.04	.001	Right Precentral Gyrus
	45	-9	-6	-2.91	.002	Right Insula
	-24	39	-3	-2.90	.002	Left Middle Frontal Gyrus
	12	-57	24	-2.89	.002	Right Precuneus
Emotional Eating						
	15	-57	27	-3.59	<.001	Right Precuneus
	-42	-15	45	-3.28	.001	Left Precentral Gyrus
	6	-42	27	-2.81	.002	Right Cingulate Gyrus
	51	-6	9	-2.80	.003	Right Precentral Gyrus
	-24	48	9	-2.74	.003	Left Middle Frontal Gyrus
Expectation that Eating Leads to Loss of Control						
	6	-45	27	-3.66	<.001	Right Cingulate Gyrus
	51	-6	9	-3.49	<.001	Right Precentral Gyrus

Covariate	x	y	z	Max Z	p	Brain Region
Expectation that Eating Leads to Loss of Control (continued)						
	-12	-27	0	-3.47	<.001	Left Thalamus
	-39	-18	45	-3.47	<.001	Left Postcentral Gyrus
	6	0	60	-3.29	.001	Right Medial Frontal Gyrus
	45	-18	42	-3.03	.001	Right Postcentral Gyrus
	-48	0	6	-2.79	.003	Left Precentral Gyrus
	-3	-15	72	-2.77	.003	Left Medial Frontal Gyrus
	39	6	15	-2.73	.003	Right Insula
Expectation that Eating Alleviates Negative Affect						
	-15	-24	-6	-4.12	<.001	Left Thalamus
	6	-45	24	-3.81	<.001	Right Posterior Cingulate
	12	-57	24	-3.72	<.001	Right Precuneus
	51	-6	9	-3.70	<.001	Right Precentral Gyrus
	39	6	12	-3.43	<.001	Right Insula
	-60	-9	27	-3.24	.001	Left Precentral Gyrus
	-39	-18	45	-3.02	.001	Left Postcentral Gyrus
External Eating						
	-24	51	9	-3.23	.001	Left Superior Frontal Gyrus
	0	-72	15	-3.00	.001	Left Cuneus
	-33	6	12	-2.93	.002	Left Insula
	33	12	12	-2.91	.002	Right Insula
Hunger						
	6	0	60	-2.96	.002	Right Medial Frontal Gyrus
	-42	-15	45	-2.86	.002	Left Precentral Gyrus
	-3	-42	24	-2.69	.004	Left Posterior Cingulate

Covariate	x	y	z	Max Z	p	Brain Region
Social Functioning						
	6	-42	27	-3.10	.001	Right Cingulate Gyrus
	-33	-30	27	-2.82	.002	Left Postcentral Gyrus
	36	3	12	-2.73	.003	Right Insula

Figure 1. Results from the ANOVA model of anticipatory food reward. The color bar represents the *t* values representative for the figure. Axial sections of differential activation in the right anterior insula in response to anticipated receipt of chocolate versus tasteless control solution between the two groups. The bar graph represents relative activation in this region [27 27 15] in response to anticipatory reward.

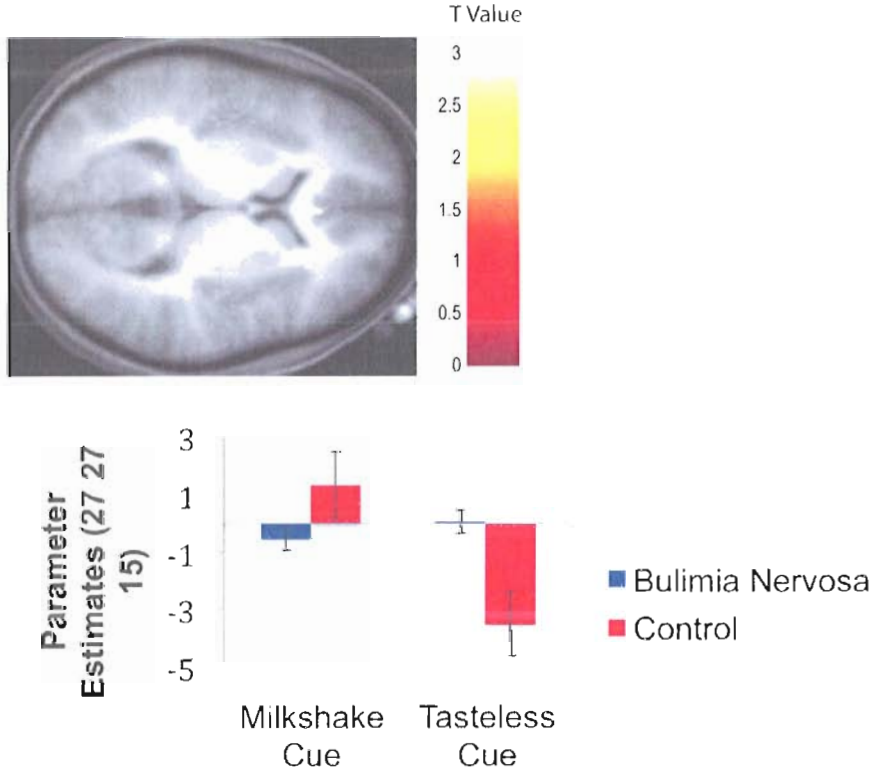
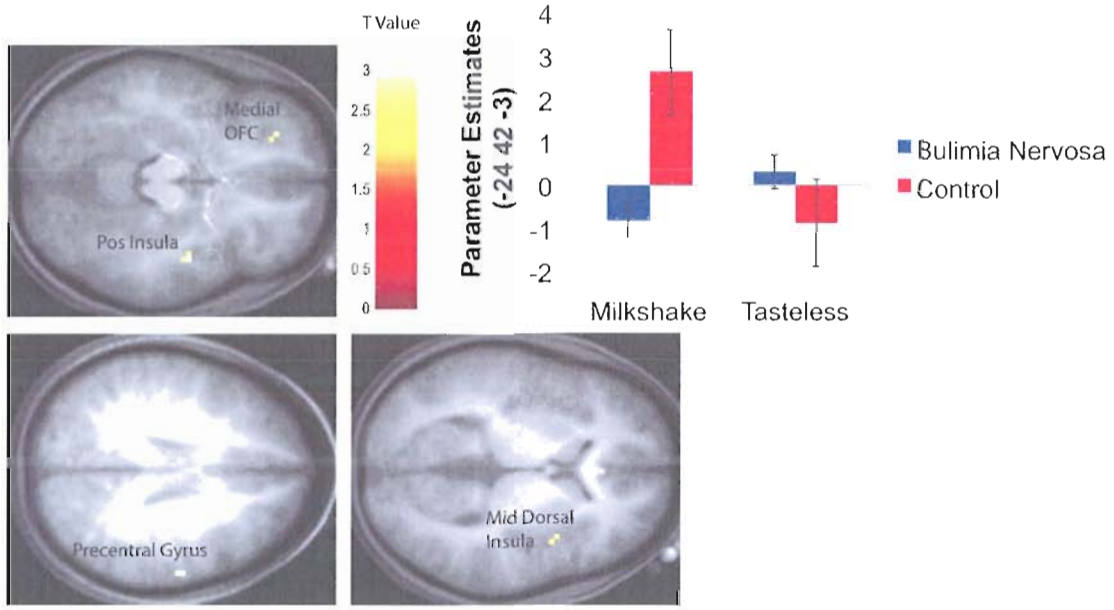


Figure 2. Results from the ANOVA model of consummatory food reward. The color bar represents the *t* values representative for all figures. Axial sections of differential activation between groups in the left medial OFC, right posterior insula, right precentral gyrus, and right mid dorsal insula in response to receipt of chocolate versus tasteless control solution. The bar graph represents relative activation in the left medial OFC [-24 42 -3] in response to consummatory reward. Results from other regions followed the same overall pattern of activation.



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