DIFFERENTIOAL BOLD RESPONSE TO FOOD CUES UNDER STRESS IN WOMEN WITH BULIMIA NERVOSA: AN fMRI INVESTIGATION

by

BRITTANY LYNN COLLINS

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ABSTRACT

Bulimia Nervosa (BN) is characterized by chronic relapsing binge and purge behavior. Exposure to environmental food cues and subjective feelings of stress are proximal factors that trigger binge eating. Data suggests that both of these proximal factors increase subjective levels of craving, and subsequently consumption of foods high in fat and sugar. The limbic system is responsible for processing reward salience of food, and disruptions in this system can contribute to aberrant eating behavior such as binge eating. Behavioral studies and fMRI data support abnormal responses to food cues in women with BN. The interaction of the limbic system, prefrontal cortex, visual cortex, and hypothalamic-pituitary-adrenocortical (HPA) axis, which regulates stress, is not fully understood. Disruption within these neural systems may differentially affect behavioral and neurological responses to environmental food cues and exposure to stressors. Extensive evidence supports that women with BN experience more stress than healthy women, and that stress precedes binge eating for women with BN. There is currently a gap in fMRI and eating disorder literature explaining the neural systems implicated in food cue processing during acute stress. The purpose of this study was to test the hypothesis that women with BN (compared with healthy controls) have differential limbic, prefrontal, and visual...
system functioning while processing external food cues in a state of acute stress. Results partially support *a priori* hypotheses in that women with BN have differential BOLD signal response to food cues under stress relative to healthy controls; however, several regions activated in directions opposite of our original hypotheses, including precuneus, nucleus accumbens, and anterior insula. The current study highlights the need for further examination of neural systems involved in acute stress and appetitive (food) cue processing. Evidence from the current study suggests the default mode network and visual information processing systems may be particularly relevant in food cue processing during acute stress.

**INDEX WORDS:** Bulimia Nervosa, fMRI, Acute Stress, Food, Cue reactivity
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CHAPTER 1

INTRODUCTION

Bulimia Nervosa (BN) is a disorder classified by recurrent episodes of binge eating, inappropriate compensatory behavior via purging, excessive exercise, or extreme caloric restriction, and self-evaluation strongly influenced by shape and weight (American Psychiatric Association, 2013). The current estimated prevalence rate of BN is 2.3%, based on DSM-5 diagnostic criteria (American Psychiatric Association, 2013; Smink, van Hoeken, & Hoek, 2012). The binge-purge cycle observed in bulimia nervosa is characterized by chronic relapses in dysregulated eating behavior. Negative affect, specifically stress, and exposure to external cues are both proximal factors commonly noted to trigger binge eating (Levine, 2003; Neudeck, Florin, & Tuschen-Caffier 2001; Smyth et al., 2007; Staiger, Dawe, & McCarthy, 2000; Steiger et al., 2005; Schachter, Goldman, & Gordon, 1968). There is a large body of literature examining maintenance factors for binge eating using behavioral data, yet the use of functional magnetic resonance imaging (fMRI) to investigate neurobiological triggers for these behaviors in women with BN has only recently been explored. The use of fMRI to study functional differences in the processing of negative affect, specifically stress, and food cues in women with BN and non-eating disordered women contributes evidence of neurobiological correlates and potential risk factors associated with this disorder.

There is a paucity of literature examining the neurobiological changes associated with exposure to food cues during the acute experience of negative affect in women with BN. Thus, this study recruited women with BN to undergo fMRI evaluation of limbic, prefrontal, and visual
systems during exposure to two established acute triggers for binge eating: a negative affective state and the presence of external food cues. More specifically, the current study induced stress, one facet of negative affect, in an fMRI environment to examine simultaneous activation of negative affect and appetitive response to cues in the limbic, prefrontal, and visual systems. Regions of interest (ROIs) were identified within these systems and directly compared in a between groups design for women with BN and non-eating disordered women. *A priori* identified ROIs were hypothesized to be differentially activated in a BN sample (relative to normal-weight, healthy females) under stressful conditions.

**The Limbic System & Eating Behavior**

**Cortical Systems Associated with the Conditioned Reinforcement of Food Intake**

There are two systems through which the human body regulates food intake: homeostatic and hedonic (Lutter & Nestler, 2009). The homeostatic system regulates eating by signaling the body when energy has been depleted via the release of leptin and ghrelin (Lutter & Nestler, 2009; Zigman & Elmquist, 2003). The hedonic system described in animal models, analogous to the limbic system in humans, regulates the reward salience of food. The limbic system contains brain regions that are related to eating, reward, motivation to eat, learning (reinforcement) for eating, and other higher order functions for goal-directed behavior include the nucleus accumbens (NAcc), amygdala (Amg), anterior cingulate cortex (ACC), caudate nucleus, orbitofrontal cortex (OFC), and several regions in prefrontal cortex (PFC) (Morgane, Galler, Mokler, 2005). The insula also plays a critical role in eating behavior. While this brain region is not considered part of the limbic system, it has afferent and efferent connections with medial prefrontal cortex (mPFC), ACC, and prefrontal areas (Reep, Corwin, Hashimoto, & Watson, 1987).
Several sub-circuits within the limbic system have been implicated for their role in eating behavior such as dopaminergic or striatal-dopamine, GABAergic, striatal-opiod, fronto-striatal, and fronto-cingular circuits (Celone, Thompson-Brenner; Ross, Pratt, Stern, 2011; Joos et al., 2011; Kaye, Wagner, Fudge, & Paulus, 2011; Kelley, Baldo, Pratt, & Will, 2005). The dopaminergic and GABAergic pathways have been studied extensively in rats (Kelley et al., 2005). The striatal-dopamine or dopaminergic system is involved in conditioned reinforcement of food intake (Berridge & Robinson, 1998; Salamone & Correa, 2002; Wise, 2004); and the GABA output neurons (of the GABAergic system) within the NAcc shell have a direct influence on mechanisms for feeding motor patterns and food-seeking strategies (Kelley et al., 2005).

Other subsystems (e.g. fronto-striatal, fronto-cingular, and striatal-dopamine) have been studied in humans. There is evidence in both animal and human models supporting a relationship between dysfunctional activity in these subsystems and maladaptive eating behavior (Broft, Berner, Martinez, & Walsh, 2011; Bohon & Stice, 2011; Joos et al., 2011).

Dopaminergic, GABAergic, and opiate peptide systems may interact to influence overconsumption (Kelley et al., 2005). These systems are thought to interact with corticolimbic structures and structures that regulate energy balance and food intake. For example, the hedonic pathway (limbic system) may override the homeostatic pathway when there is a strong desire to eat (Kelley, Baldo, Pratt, & Will, 2005; Lutter & Nestler, 2009). Kelley and colleagues (2005) describe a complex neurobiological animal (rat) model through which the appetitive motivation for food may lead to overconsumption. In support of this model, GABA activity within the NAcc shell has been found to be related to increased intake of high-fat and sucrose food, but was not related to water or non-saccharin solutions (Maldonado-Irizarry & Kelley, 1995). Additionally, several studies support a functional link between the lateral hypothalamus (a region of the
homeostatic pathway) and NAcc. This link was established through observation that GABA blockades between the two structures did lead to food intake; and increased activity of GABA substrates in the lateral hypothalamus is necessary for rapid food intake mediated by the NAcc shell (Maldonado-Irizarry, Swanson, & Kelley, 1995; Stratford & Kelley, 1997; Stratford, Swanson, & Kelley, 1998; Stratford, Kelley, & Simansky, 1999). These results help to explain how GABA modulation can affect food preference and intake beyond that which is necessary for homeostatic needs (Stratford & Kelley, 1999); and more broadly how disruption in limbic related circuits is related to eating.

**Disrupted Cue Reactivity in BN**

*Behavioral Studies of Cue Reactivity in Healthy Adults*

Before investigators were able to study behaviors associated with eating at the neurobiological level in humans, they utilized cue-reactivity paradigms to study eating at a behavioral level. Healthy individuals have reacted to food exposure physiologically with changes in gastric activity, heart rate, blood pressure, and salivation (Jansen, 1998; Nederkoorn, Smulders, & Jansen, 2000; Wardle, 1990). These changes are hypothesized to occur in response to learned associations between cues that signal food and resulting consumption, and are thought to prepare the body for consumption and digestion (Jansen, 1998). There are positive associations between these physiological changes and craving, and between craving and food intake (Jansen, 1998; Nederkoorn et al., 2000). Over the last decade, there has been a large increase in studies examining the relationship of cue reactivity to food. Findings support that presentation of visual food cues vs. neutral cues elicits craving for food in laboratory paradigms (Sobik, Hutchison, & Craighead, 2005). Craving, specifically for highly palatable foods (foods high in fat or sugar), are associated with increased consumption of those food items compared to
other foods in a laboratory setting (Martin, O'Neil, Tollefson, Greenway, & White, 2008). In short, laboratory paradigms elicit craving in response to food cues, and several studies indicate that there is a positive association between craving ratings and subsequent consumption. Thus, results from behavioral studies have demonstrated that environmental, cue-elicited craving play a motivational role in the excessive consumption of food. These behavioral data are consistent with findings from studies utilizing fMRI that demonstrate that healthy adults have increased activation in the limbic and visual systems of the brain in response to food cues.

**Behavioral Studies of Cue Reactivity in BN**

Consistent with Schacter’s externality theory (1968) of eating and Jansen’s learning model of binge eating (1998), evidence suggest that women with BN may have differential reactivity to external food cues compared to women who do not have disordered eating behavior. The abnormal or heightened response to cues for women with BN is thought to occur through classical conditioning processes, and manifests as autonomic and/or biochemical responses in the presence of craving (Jansen, 1998). Women with BN (compared to healthy controls) report increased urges to binge (Neudeck, Florin, & Tuschen-Caffier, 2001; Staiger, Dawe, & McCarthy, 2000), low confidence in their ability to resist binging, and decreased sense of control over food intake when presented with their favorite binge foods (Staiger et al., 2000). One factor hypothesized to influence cue-reactivity in women with BN is mode of cue presentation. The type of cue and affected sensory systems may cause different physiological responses and desire to eat. Visual and olfactory cues may be non-threatening for women with BN because they are not forced with a choice of whether or not to eat; whereas presentation of physical food available for consumption may create a state of ambivalence. Results support differential physiological arousal in response to food cues under these two conditions for women with BN (LeGoff,
Leichner, & Spigelman, 1988; Bulik, Lawson, & Carter, 1996). Startle eye blink paradigms are used to assess physiological responses for motivational processing. In such paradigms, women with BN demonstrate startle inhibition when presented with food cues (Friederich et al., 2006). The response inhibition observed in women with BN suggests an exaggerated appetitive response to food that is not seen in women with anorexia nervosa (AN) or healthy controls. In addition to behavioral and physiological cue-reactivity studies examining craving and food consumption in women with BN, cue exposure has also been investigated in the context of biased attention. Cognitive theory suggests that food cues are more salient to individuals with eating disorders. Therefore, food cues distort information processing via preferential allocation of attentional resources to emotionally, salient food stimuli (Fairburn, 2008). Reviews of large bodies of literature on attentional bias processes in BN indicate that women with BN appear to have an exaggerated attentional bias to food cues relative to women with AN and healthy controls (Brooks, Prince, Stahl, Campbell, & Treasure, 2011a; Dobson & Dozois, 2004; Faunce, 2002; Formea & Burns, 1996; Lee & Shafran, 2004). For example, modified Stroop tests show that eating disordered patients perform objectively different from controls (based on interference scores) when reading food related stimuli (Bentovim & Walker, 1991; Bentovim, Walker, Fok, & Yap, 1989; Cooper, Anastasiades, & Fairburn, 1992; Johansson et al., 2004). In summary, behavioral studies of food cue reactivity and attentional biases in women with BN provide support for differential attention and motivation in response to food (Friederich et al., 2006).

Food cue reactivity in women with BN may be an indicator for severity of psychopathology, specific disordered eating behavior, and unique physiology. For example, food cue reactivity correlated with increased eating disorder symptom severity at the end of treatment, 6-month, and 1-year follow up (Carter, Bulik, McIntosh, & Joyce, 2002); which suggests that
individuals with increased sensitivity to food cues may be more likely to engage in chronic cycles of binging and purging. In addition to binge eaters, restrained eaters (who share characteristic features of women with BN) have also been found to overeat when exposed to food cues, appetizers, or preload amounts of food (Fedoroff, Polivy, & Herman, 1997; Jansen & van den Hout, 1991; Jansen, 1994; Rogers & Hill, 1989). Even when levels of hunger are similar between restrained and unstrained eaters, exposure to food cues may differentially activate intrinsic, physiological responses to food cues. Some studies indicate that restrained eaters and women with BN produce more saliva in response to food cues than unstrained eaters indicating increased preparation for consumption (Brunstrom, Yates, & Witcomb, 2004; Legenbauer, Vodele, & Ruddel, 2004). However, several other studies fail to provide unique physiological responses in women with BN compared to healthy controls (Bulik, Lawson, & Carter, 1996; Neudeck, Florin, & Tuschen-Caffier 2001; Overduin, Jansen, & Eilkes, 1997; Tuschen-Caffier & Vogele, 1999). In summary, women with BN have variable physiological responses to food cues when compared to other populations, but they do display unique behavioral responses to food cues. The results of studies assessing response to food cues and food related stimuli in women with BN demonstrate unique responses at behavioral and cognitive levels. What is less clearly understood are the neurobiological underpinnings of food cue reactivity in women with BN.

**The Use of fMRI to Study Limbic System Function and Reinforcing Properties of Food**

Cue reactivity paradigms expose participants to external, salient cues and measure a response to the presentation (Schachter, Goldman, & Gordon, 1968). In accordance with advances in neuroimaging over the last few decades, investigators began to employ cue-reactivity studies in fMRI settings to measure the neurobiological activity underlying reward-
based behavior (e.g. eating, drug-use, gambling). fMRI data acquisition during cue-reactivity paradigms has demonstrated that visual cues of palatable foods compared to neutral cues increase activation in the OFC, inferior frontal gyrus (IFG), premotor cortex (PMC), ventral striatum (including the NAcc), insula, the ACC, precuneus, and occipital areas in healthy weight individuals (Beaver et al., 2006; Geliebter et al., 2006; Karhunen et al., 2000; Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Rolls & McCabe, 2007; Stice, Spoor, Bohon, Veldhuizen, & Small, 2008; Stoeckel et al., 2008; van der Laan et al., 2011). The pattern of fMRI results in humans is consistent with fast-scan cyclic voltammetry studies of rats that show dopamine levels in the NAcc are related to orienting responses to conditioned stimuli (Rotiman, Stuber, Phillips, Wightman, & Carelli, 2004). Acute increases in dopamine in the NAcc and striatum in response to cues increase motivation to consume, and reinforcement from consumption, while activation in the Amg may link memories of food to their rewarding properties (Rotiman, Stuber, Phillips, Wightman, & Carelli, 2004; Siep et al., 2008). Impaired inhibitory control due to decreased activation in the PFC and ACC may ultimately lead to the behavioral choice to engage in repeated consumption (Marsh et al., 2009; Joos et al., 2011).

Various types of food stimuli and/or subject conditions have been manipulated in order to understand neurobiological mechanisms for nuanced aspects of eating behavior. One such manipulation is the presentation of palatable food cues vs. low calorie food cues instead of neutral cues. Typically, palatable or high calorie food cues (compared to low calorie food cues) elicit increased activation across the limbic system (Rothemund et al., 2007; Stoeckel, et al., 2008). One study compared appetizing foods to bland foods and disgusting foods in individuals with varying levels of motivation for reward (Beaver et al., 2006). Results revealed a linear trend, such that individuals strongly motivated for reward had greater BOLD signal change in
response to appetizing food within the reward system (Beaver et al., 2006). An additional manipulation is hunger vs. satiety. Activation in the insula, Amg, and OFC appears to increase when healthy individuals are exposed to food cues under conditions of hunger compared to satiety (Killgore & Yurgelun-Todd, 2006; LaBar et al., 2001; Siep et al., 2009). Thus, several studies have indicated that limbic system activation increases in response to cues for palatable foods compared to other stimuli under varying conditions in healthy individuals. These studies have contributed to our understanding of the neurobiological pathways that may lead to overconsumption of food. Data from rat and human models indicating that increased dopamine and GABA activity in the nucleus accumbens results in increased consumption of palatable food cues are consistent with fMRI findings of nucleus accumbens responsivity to food cues. However, they were all conducted with healthy weight, non-eating disordered individuals.

**fMRI Studies of Cue Reactivity in Women with BN**

Limbic system processing for food cues is hypothesized to be disrupted in women with BN. Within the limbic system two subsystems, the ventral- and dorsal limbic circuits, may be specifically related to eating disorder pathology. The ventral limbic circuit (e.g. anterior insula, ACC, Amg, OFC) has afferent connections with the ventral striatum where the NAcc is located (Kaye, Wagner, Fudge & Paulus, 2011). This circuit is considered a “higher order” processing circuit for food and carries out functions of pleasure, motivation, and cognitive aspects of eating (Kaye et al., 2011). Within the ventral limbic circuit, the insula carries out several functions related to eating, including both homeostatic and hedonic regulating functions. The insula is theorized to be functionally organized along a caudal-rostral axis (Simmons et al., 2013). Posterior regions are related to taste and sensory specific properties of food, and anterior regions are specific for coding stimulus significance depending on homeostatic needs (Kaye et al., 2011).
ACC activation hypothesized to be a result of strong preference for food, and more globally is activated for emotional processing and response selection (Phan, Wager, Taylor, & Liberzon, 2002). The activation of both the insula and ACC may represent an attempt to regulate arousal and desire for food in BN women.

The dorsal limbic system is a circuit related to sensory aspects of eating (such as taste). The integration of signals from these two systems results in “eating” or “not eating” behavior. In eating disorders, the balance of these two subcircuits may be “tipped” in a way that overemphasizes motivation and rewarding properties of food (e.g. altered ventral limbic circuitry) for women with BN; or over-control in cognitive regions and disrupted sensory pathways (e.g. dorsal limbic circuitry) for women with anorexia nervosa. As with fMRI studies in healthy populations, several cue-reactivity paradigms have been designed to assess neural activation in women with BN and other various eating pathology. These paradigms include presentation of visual, olfactory, and gustatory stimuli. Cue-reactivity in various sensory modalities elicits unique responses when examining within-group (BN) reactivity to food cues as opposed to between-group (HC and BN) responses to food cues.

In general, contrasts for visual food cues vs. neutral or low-calorie foods in BN and HC samples reveal a greater response within limbic and visual regions. fMRI research thus far has documented within group (BN) increases in BOLD response for limbic regions when contrasting food vs. non-food or low-calorie food pictures. One study revealed that women with BN had greater insula, ACC, OFC activation in response to food cues vs. non-food cues (Schienle, Schafer, Hermann, & Vaitl, 2009). The observed increase of activation in the OFC was positively associated with their subjective reward responsiveness. Another study comparing BOLD response of BN women showed increased activity within the right occipital cortex, left
dorsolateral PFC (dIPFC), right insular cortex, and left precentral gyrus (Brooks et al., 2011). When stringent statistical criteria were applied to within group contrasts for women with BN, there were no differences in limbic system response to food cues vs. non-food cues (Joos et al., 2011). When these criteria were relaxed, the women with BN had increased activity in posterior cingulate cortex (PCC) and precuneus (Joos et al., 2011). Thus, results of contrasts for women with BN indicate patterns of increased activation in response to food cues compared to neutral cues, similar to contrasts in healthy controls.

Preliminary data from fMRI studies utilizing between groups designs demonstrates that women with BN have decreased or negative activation in limbic system regions in response to food cues relative to healthy controls. Negative BOLD signal response to food cues (relative to baseline tasks), has been demonstrated in BN women compared to controls in the bilateral superior temporal gyrus, insular cortex, left visual cortex, (Brooks et al., 2011), left frontal gyrus, right posterior insula, right precentral gyrus, and thalamus (Bohon & Stice, 2011), the ACC and the lateral prefrontal cortex (Joos et al., 2011). In some studies, BN women did not experience hypo- or negative activation in comparison to healthy controls in response to food cues. Instead, healthy control women had increased activation in limbic regions in comparison to BN women in response to food cues (Frank et al., 2006; Bohon & Stice, 2011). fMRI paradigms have also been utilized to determine if patterns of neural activity can classify eating disorder diagnosis or healthy status. Classifiers of BN (compared to healthy controls) in this study included differential activity within the left ACC, right insula, and left ventral striatum (Weygandt et al., 2012). Some studies of general response inhibition in women with BN and healthy controls indicate that there is a negative correlation between binge eating and engagement in the medial prefrontal cortex (mPFC), temporal cortex, and parietal cortex (Marsh et al., 2009) when performing tasks, which
require inhibition. These researchers hypothesized that the decreased activation seen in BN women reflects low levels of engagement in regions associated with inhibition of overlearned responses (Marsh et al., 2009). This indicates that women with BN may be less able to draw upon neural resources to stop themselves from binge eating in the presence of cues.

Although multiple recent studies have indicated that women with BN experience negative BOLD signal response to food cues in comparison to controls, other studies do indicate hyperactivation of limbic regions (Uher et al., 2004; Radeloff et al., 2012). Mixed findings are likely a product of the type of stimuli (e.g. chocolate milkshake, sucrose solution, tasteless solution) and study design (e.g. manipulating anticipation vs. receipt and level of satiety). Importantly though, women with BN demonstrate different limbic system responses to these cue-reactivity paradigms relative to healthy controls (Frank et al., 2006; Bohon & Stice, 2011; Radeloff et al., 2012). Together, these findings support differential awareness of food cues, arousal from exposure to food, and response to rewarding properties of food cues (Schienle et al., 2009).

**Stress**

Thus far literature pertaining to one proximal factor related to binge eating (external exposure to food cues) has been reviewed. Negative affect, more specifically stress, is another condition that is related to binge eating.

Animal models of feeding behavior under stress conditions indicate that chronic exposure to stress increases consumption of highly palatable, high fat foods (Dallman, Pecoraro, & la Fleur, 2005; Fachin et al., 2008). In animals, this is likely due to food choice as opposed to chronic excessive caloric consumption. It is important to note that while some forms of stress in animal models leads to weight loss, exposure to ongoing stress leads to the preference for high fat foods
(Dallman et al., 2003). For example, rats in an ongoing stress condition choose foods such as lard or sugar over other types of foods (Dallman et al., 2003, Dallman et al., 2005). Ingestion of foods high in fat or sugar are thought to ultimately reduce stress effects by stimulating the hypothalamic-pituitary-adrenocortical (HPA) axis, which releases corticotropin-releasing hormone (CRH) in response to stress. Ingestion of highly palatable foods also increases activation of opioid and cannabinoid systems (Adam & Epel, 2007).

These animal studies are analogous to human consumption of food during stress. While a subgroup of human individuals consume less and lose weight during exposure to stress, most report increased consumption (Adam & Epel, 2007; Epel et al., 2004). Some research suggests that stress has differential effects on gender, such that under stressful conditions women increase food consumption more than men (Greeno & Wing, 1994). Laboratory studies demonstrate that participants in stress manipulation conditions choose high fat foods as opposed to low calorie foods (Epel et al., 2001; Newman et al., 2007). Specific studies of food choice in humans, similar to animal studies, indicate that individuals choose high fat foods under stressful conditions (Grunberg & Straub, 1992; Oliver, Wardle, & Gibson, 2000). Thus, it is plausible that stress plays a role in dysregulated eating behavior and food craving.

Stress is specifically implicated for women with BN in dysregulated eating behavior. Women with BN are hypothesized to use binge eating in order to rid themselves of negative emotions, via the learned reinforcement properties described above. A large body of literature supports the hypothesis that acute stress and negative affect precedes binge eating (Abraham & Joseph, 1986; Barrios & Pennebaker, 1982; Johnson & Larson, 1982; Lingswiler, Crowther, & Stephens, 1989). Recently, more rigorous methodology has examined the temporal relationship of negative affect and binge eating with the use of ecological momentary assessment (EMA).
(Anestis et al. 2010; Crosby et al., 2009; Simonich et al., 2004; Steiger et al., 2005). Decreased positive affect, increased negative affect, and greater levels of stress preceded binge episodes in a BN sample (Smyth et al., 2007). EMA studies consistently yield results supporting the first component of the affect regulation hypothesis, where negative affect precedes binge eating episodes. In support of the second component of the affect regulation hypothesis, Smyth and colleagues (2007) found that negative affect rapidly recovered after binge eating episodes. The rapid recovery of negative affect in this sample reflects the fleeting relief women with BN experience after binge eating.

**The Additive Effects of Stress, Cue Exposure, and Attentional Biases on Eating Behavior**

Cue-induced craving and stress are frequently cited as reasons for return to maladaptive behavior patterns such as binge eating and substance abuse (Brown, Vik, Patterson, Grant, & Schuckit, 1995; Levine, 2003; Litt, Cooney, Morse, 2000; Ludwig, Wikler, & Stark, 1974; Marlatt & Gordon, 1985; Neudeck, Florin, & Tuschen-Caffier, 2001; Sinha, 2001; Smyth et al., 2007; Staiger, Dawe, & McCarthy, 2000; Steiger et al., 2005; Schachter, Goldman, & Gordon, 1968). Animal models show that both exposure to cues and stress are powerful precipitants to reinstatement of addictive behavior (Le, 2002; Stewart, 2000). Liu and Weiss (2002) found an additive effect of stress and cues, such that exposure to both evoked stronger reinstatement of addictive behavior in dependent animals than exposure to either in isolation. Because of the parallel addictive processes between substance use and binge eating (Jansen, 1998; Parylak, Koob, Zorrilla, 2011), it is important to consider the additive influence of stress and cues for women with BN, who engage in chronically relapsing binge eating.
Women with BN report higher levels of anxiety, distress, feelings of tension, and insecurity than controls when they are confronted with food cues (Friederich et al., 2006; Legenbauer, Vogele, & Ruddel, 2004). In a behavioral and physiological reactivity study, women with BN responded to an interpersonal stress task with increases in self-reported hunger and urges to binge. These responses differentiated women with BN from restrained eaters and healthy controls (Tuschen-Caffier & Vogele, 1999). Therefore higher levels of negative affect and stress are reported in the presence of food in samples of women with BN. Additionally, stress increases levels of hunger and urges to binge in this population. Increased levels of stress in women with BN appear to be specific to highly palatable food cues as opposed to low-calorie food cues. For example, Neudeck, Florin, and Tuschen-Caffier (2001) presented high- and low-calorie foods to women with BN on two separate days. Women with BN who were presented with high-calorie foods reported higher urges to binge, as well as increased levels of subjective and physiological stress compared to women with BN who viewed low-calorie foods. These results were replicated in the second day of food cue presentation, except that there were no longer differences in physiological stress responses in BN women between the two food cue groups. Physiological and psychological responses to food cues were not impacted by manipulation of blood sugar levels (Neudeck, Florin, & Tuschen-Caffier, 2001). Stress levels appear to be the highest for women with BN when they are exposed to food cues that involve visual, olfactory, and gustatory systems (Staiger, Dawe, & McCarthy, 2000). Stress is likely the highest in the presence of these cues because there is a perceived greater threat of loss of control or binge eating. Though causal relationships between stress, attentional bias, craving, and food consumption have not yet been tested, acute negative moods have been induced prior to the assessment of attentional bias to examine the causal role of mood in information processing. An
investigation of the causal relationship between negative mood states and attentional biases to
threatening stimuli showed that negative mood created attentional biases for threatening stimuli
(Green, Rogers, & Elliman, 1995; Green, Rogers, & Hedderley, 1996). These results are relevant
to women with BN as food cues are theorized to be threatening, or anxiety provoking, in this
population secondary to their influence on maladaptive behavior (e.g., binge eating; Cooper,
Anastasiades, & Fairburn, 1992; Friederich et al., 2006; Legenbauer, Vogele, & Ruddel, 2004).
In summary, behavioral results suggest that food cues and stress have a reciprocal and potentially
additive effect on behavior in women with BN, and stress may further potentiate attentional
biases towards food and subsequent maladaptive eating behavior.

Evidence to date supports that negative affect appears to trigger binge eating episodes in
women with BN. Furthermore, studies demonstrate positive associations between stress, craving,
selection of foods higher in fat and sugar, and excess consumption. Thus a chronically relapsing
pattern of behavior is established. While evidence from studies and laboratory tasks supports this
model of dysregulated eating, there is a lack of neurobiological data on the influence of stress on
reactivity to food cues in women with BN.

**Stress and neural circuitry: How does the limbic system respond to stress?**

A review by Sinha (2001) identified common pathways between stress and response to
rewards (e.g. palatable foods) in the mesolimbic dopamine system and the HPA axis. Under
conditions of stress, the HPA axis is activated which releases corticotropin-releasing hormone
from the hypothalamus, adrenocorticotropic hormone (ACTH) from the anterior pituitary, and
cortisol (in humans) from the adrenal cortex (Pruessner et al., 2008). Animal studies have
revealed the influence of cortisol within several components of the limbic system, including the
hippocampus, amygdala, and prefrontal cortex (Pruessner et al., 2008). These studies have
identified that the hippocampus has an inhibitory effect on the HPA axis (Herman et al., 2003), which may cause disruption in the feedback loop of cortisol (Bruder, Jacobson, & Raff, 2005; Herman, Ostrander, Mueller, & Figueiredo, 2005). The PFC and specifically the ACC (a neocortical regulatory structure) may have both inhibitory and excitatory effects on the HPA axis depending on which specific nuclei are activated, while the Amg is purely excitatory (Herman et al., 2005). During a phase of acute stress there is evidence from PET and fMRI studies of profound deactivation of limbic system regions, including Amg, insula, ventral striatum (NAcc), and medial OFC (Pruessner et al., 2008). The effect of the HPA axis on some limbic regions depends heavily on the release of cortisol. Individuals who fail to release cortisol have increased activity in the ACC during acute stress, where individuals who release cortisol have decreased activity in the same region (Pruessner et al., 2008). The complex relationship between neuroendocrine stress responses and the limbic system is not fully understood. However, preliminary data suggest that disruption in the HPA axis may have profound effects regarding stress and reward processing in the limbic system.

Only one study to date has utilized fMRI to investigate how negative affect relates to food cue reactivity (Bohon & Stice, 2011). Women with BN and healthy controls rated levels of negative affect prior to scanning. During the scan, individuals were cued to anticipate receipt of a chocolate milkshake. Results revealed that women with BN had positive associations between a composite score of negative affect and activity in caudate, putamen, and pallidum (Bohon & Stice, 2011). This study has somewhat contradictory results than fMRI studies of stress inductions, such that some regions in the limbic system may have higher BOLD signal response during negative affective states. The caudate, putamen, and pallidum are implicated in reward processing (Yin & Knowlton, 2006). Bohon and Stice (2011) theorize that increased activity in
these regions for women with BN who have temporary high levels of negative affect may be a function of greater reward encoding. Potentiated reward encoding was also found in a startle reflex study for women with BN (Mauler, Hamm, Weike, & Tuschen-Caffier, 2006). The observed potentiated reward was further enhanced by increased food consumption (Mauler et al., 2006). Regarding higher order functions of the limbic system, evidence supports fronto-striatal dysfunction in women with BN in the presence of conflict. Fronto-striatal dysfunction in BN populations results in under-recruitment of prefrontal regions such as ACC and deficits in self-regulatory behavior (Marsh et al., 2009). It is plausible that women with BN may have decreased activity in prefrontal regions during stress, but increased activity in regions that are specific for reward salience and learning.

The circuitry involved in stress and reward system responses, as well as other empirical evidence related to stress and relapse, allow for the generation of hypotheses regarding how stress may lead to increased levels of craving. Responses to cues may lead to greater levels of craving because of the reward salience attached to the cue. Individuals who have differential neural system activation, for processing involved in stress and reward, may exhibit different behavior and arousal in response cues compared to individuals with intact neural system functioning. Therefore, there is a need to understand the role of stress in response to food cues, excessive consumption, and risk for chronic relapsing behavior.

Evidence thus far leads to the following conclusions that underlie our specific hypotheses. There is increased activation for food cues compared to neutral cues in women with BN. Data suggests that women with BN have deactivation in response to food cues compared to healthy controls in group contrasts. Stress appears to cause deactivation in several prefrontal regions within the limbic system, but may cause hyperactivity within emotion- and reward based
regions for women with BN specifically (e.g. amygdala, insula). Theoretically, data suggests that women with BN may have fewer neural resources to cope with cues for food in a state of acute stress. Specifically, women with BN may under-recruit prefrontal regions and over-recruit reward regions. Research on activation of the limbic system in response to food cues under stressful conditions is an important step towards understanding the chronic relapsing nature of binge-purge episodes that characterize BN. Providing neurobiological data regarding stress and binge eating behavior can inform cognitive, behavioral, and possibly medical intervention for women with BN. No study to date has examined the differential response to appetitive food cues vs. neutral cues under conditions of stress using fMRI data acquisition in normal-weight or BN populations.

**Current Study**

The purpose of the current study was to confirm that women with BN (compared with healthy controls) have dysregulated limbic system functioning under stress and during external food cue exposure. In order to confirm our hypothesis, we examined limbic system responses in a laboratory paradigm designed to model two conditions, which influence excessive consumption; environmental cues and stress exposure. The study will use a two-group mixed design, with the group independent variable being BN status vs. non-eating disordered, healthy status, and the within-subjects independent variable being pre-stress and post-stress. We will contrast BOLD activation in BN individuals (vs. healthy weight controls) regarding each group’s response to food cues prior to and following an acute stress induction. As a secondary aim, we intended to replicate studies that demonstrate dysregulated limbic system responses to food cues under a neutral mood state for women with BN (vs. healthy controls).
CHAPTER 2

METHODS

Participants

A total of 10 participants with BN and 10 healthy weight controls (HC) were recruited via advertisements in local newspapers retail stores within the northeast Georgia region. All participants were screened via the telephone for eligibility. Participants who were affected by any of the following were excluded from the study: ferrous-based tattoos, contraindicated surgical or metal implants, women who are pregnant or possibly pregnant, women who are nursing, individuals with Type I or Type II Diabetes, history of traumatic brain injury (TBI), Anorexia Nervosa (AN), Binge Eating Disorder (BED), individuals with substance dependence, history of psychotic symptoms, a diagnosis of Major Depression in the last 12 months, anyone under the age of 18 or over the age of 45. The current study was approved by the Institutional Review Board.

Materials

Assessments and Measures

Structured Clinical Interview of DSM Disorders-I (SCID-I; First, & Gibbon, 2004). The SCID-I is a semi-structured interview used for diagnosing DSM-IV Axis I disorders. A clinician or trained mental health professional conducts the interview. The SCID-I consists of separate modules for each axis I diagnosis. The modules that are utilized in the current study include assessment for substance dependence, major depression, and psychotic symptoms.
Eating Disorder Examination (EDE; Cooper & Fairburn, 2006) interview is a semi-structured interview designed to assess eating disorder symptoms and to assign eating disorder diagnoses. The EDE has four subscales including weight concern, shape concern, eating concern, and restraint. The composite score of these four subscales is a global score, which indicates levels of cognitive symptomatology and eating pathology. The EDE yields a frequency count of binge eating and purging behaviors within the past 28 days and throughout the past six months. The assessment of eating pathology, including frequency of binge eating and purging are utilized to diagnose BN.

Dutch Eating Behavior Questionnaire (DEB-Q; van Strein, 1986) is a 33-item self-report measure of eating behavior. Each item is scored on a 5-point Likert scale ranging from “1 - never” engaging in the behavior, to “5” engaging in the behavior “very often.” Scores on the DEB-Q are divided into seven categories: very high, high, above mean, mean, below the mean, low, and very low. The DEB-Q is normed on 1170 individuals including men and women. The DEB-Q contains emotional, external, and restrained eating subscales. Items on the external eating subscale assess individual differences in the tendency to eat in response to external cues.

Eating Expectancies Inventory (EEI; Hohlstein, Smith, & Atlas, 1998) is a 34 item self-report measure of what outcomes individuals expect from eating food. These are collectively referred to as eating expectancies, which are thought to have developed over the course of an individual’s life through various learning experiences. An example of an eating expectancy is “eating fills some emotional need” or “eating helps me deal with feelings about inadequacy about myself.” Five factor structures are identified in this measure and have been confirmed with independent samples (Hohlstein et al., 1998). These factors include expectations that eating will reduce negative affect, induce positive mood, result in loss of control, enhance cognition, and/or
relieve boredom. The five factors comprised within the EEI have discriminant and convergent validity in various clinical groups with eating disorders (Hohlstein et al., 1998).

Eating Motives Questionnaire (EMQ; Jackson, Cooper, Mintz, & Albino, 2003) is a 20 item self-report measure that has been adapted from the Drinking Motives Questionnaire. The EMQ has four subscales to assess different motivations for eating including, social motivation, coping with negative affect, compliance, and enhancement.

The Food-Craving inventory (FCI; White, Whisenhunt, Williamson, Greenway, & Netemeyer, 2002) is a self-report measure of general and specific food cravings. Twenty-eight food items representative of four food types are rated for frequency of craving using a 5-point Likert scale ranging from “Never” to “Almost every day.” Exploratory and confirmatory factor analyses reveal a four-factor structure representing four subscales: high fats, sweets, carbohydrates/starches, and fast-food fats. Each factor is also highly correlated, suggesting that each is a unitary dimension of a higher order factor of food-craving. Psychometric properties of the developmental sample reveal moderate to high internal consistency (range of $\alpha$ coefficients, 0.76 - 0.93) and test-retest reliability (range, 0.79 - 0.91) for all subscales and the total score. Self-reported craving, as measured by the FCI, is associated with subsequent specific food consumption within a laboratory setting, suggesting that specific cravings are related to corresponding food intake (Martin, O’Neil, Tollefson, Greenway, & White, 2008).

Other questionnaires include a demographics questionnaire, a questionnaire assessing conditions prohibiting scanning, a stressors questionnaire, and subjective ratings of stress and craving. The demographics questionnaire assesses demographic information from participants including: age, gender, social economic status, education level, and ethnicity. The assessment of conditions prohibiting scan and affecting cortisol reactivity, is a measure used to assess risk
factors for fMRI candidates. Conditions prohibiting scanning include (but are not limited to),
claustrophobia, metal implants or fragments in the body, pacemakers, internal stimulators,
shunts, surgical staples, screws, plates, respiratory conditions, and intrauterine devices. The
stressors questionnaire was created for the purpose of this study, which assesses the total number
of stressful life events that occurred within the last year. Examples of life stressors include, but
are not limited to, death in the family, separation or dissolution of family, and serious illness.
The stressors questionnaire is included to account for factors that may exacerbate participant’s
subjective stress levels during the study. Subjective ratings of stress and craving are self-report
measures that were utilized within and out of the MRI system. Participants were asked to rate
their levels of stress/craving on a seven point Likert scale ranging from “0 - no stress at all/no
craving to eat at all,” to “6 – the most stress I can handle/strong urge to eat food if it is
available.”

**Stimuli**

**Pilot study.**

Visual food cues and neutral cues were purchased from Shutter Stock Photos
(www.shutterstock.com) based on reference IAPS (International Affective Picture Set; Lang,
Bradley, & Cuthbert, 2005) images. Pilot data were collected to ensure that food and neutral cues
purchased from Shutter Stock Photos were comparable to IAPS cues. The criteria for comparison
of food cues and neutral cues between purchased photos and IAPS cues are discussed below. 15
participants (ages ranged from 22-30 years of age) were asked to rate 60 food cues on a Likert
scale of 1 to 5. A rating of “5” represented that each cue was clear, easy to interpret, and
appetizing. A rating of “1” represented that the cue had poor resolution, may be confused for
other food, or was not appetizing. Participants were encouraged to rate food cues based on their
preferences, not on the preferences of the general public (e.g. if a participant did not like apple pie, they were encouraged to rate it a “1”, even though another person may enjoy apple pie). A rating of “5” for food cues included that the cue had good resolution, was easily perceived, and was appetizing to the point of craving for the food item. Participants were additionally asked to rate 60 neutral cues on a Likert scale of “1” to “5”. A rating of “5” for neutral cues indicated the cue is clear and easily perceived. Additionally, the cue should not have elicited an emotional response, nor resembled food or drink in any way. Neutral cues that failed to meet these criteria (where cues that were difficult to interpret, were reminiscent of food/drink, or aroused any emotion) were rated a “1”. The mean of each cue was calculated. Only cues that had a mean of 3.00 or higher were used in the current paradigm.

*IAPS stimuli.*

Visual neutral cues (Figure 1a) and food cues (Figure 1b) are selected from the IAPS stimulus set (Lang, Bradley, & Cuthbert, 2005) and the pilot study described above. Highly palatable foods were used for several reasons. First, the theoretical model used to generate the hypotheses tested is based on a model of reward-motivated behavior. Consumption of food beyond what is required for energy balance/maintenance is one factor that contributes to overconsumption. Excessive consumption is hypothesized to be driven by several reward-based mechanisms. Foods that are viewed as highly rewarding/palatable are more likely to be those that are consumed in excess (Yeomans, Lee, Gray, & French, 2001). Additionally, previous research demonstrates that individuals exhibit differences in activation when viewing photographs of high calorie foods vs. low calorie foods (Arana et al., 2003; Killgore et al., 2003). The neutral cues that were utilized in the current study have similar levels of visual complexity as the palatable food images, and so are hypothesized to require similar levels of visual processing.
Stress Induction

Stress was induced using a paradigm based on the Trier Social Stressor Task (TSST; Kirschbaum, Pirke, & Hellhammer, 1993). The TSST requires participants to complete difficult math problems while being socially evaluated on their performance, in addition to being asked to prepare and deliver a public speech on an unfamiliar topic, also while being socially evaluated on their performance. The current study will utilize the arithmetic paradigm portion of the TSST. Several studies have documented that solving difficult arithmetic problems resulting in failure reliably induces stress (Kirschbaum et al., 1993; Pruessner, Hellhammer, & Kirschbaum, 1999; Dickerson & Kemeny, 2004). While mental arithmetic itself may produce stress, the social component is critical to the stress induction because it evokes social evaluative threat (Dickerson & Kemeny, 2004). The individual is expected to necessarily experience frustration during mental arithmetic, be informed of their failure as it occurs, and be aware that the failure is communicated to an audience. All of these components are conducive to the collection of fMRI data. The Montreal Imaging Stress Task (MIST) is another stress induction paradigm similar to the TSST and the paradigm used in the current study (Dedovic et al., 2005). The MIST has produced consistent data reflecting induced stress in fMRI data acquisition (Pruessner et al, 2008). The paradigm designed for the current study is a simpler version of the MIST and the TSST, but includes all elements necessary to induce stress.

Before inducing stress, participants will complete a series of subtraction problems that require minimal mental effort under timed constraints (e.g. 9999 – 0 = 9999). Both the TSST and the MIST have demonstrated that continually subtracting 17 from 4-digit numbers under time constraints results in enough failure to induce stress (Kirschbaum, Pirke, & Hellhammer, 1993; Dedovic et al., 2005). Therefore the paradigm in this study required all participants to perform
“17 subtractions” under timed conditions. In both the control and stress inducing problems, the participants chose their answer from four options using a 4-button serial response pad and were then informed of their accuracy. The participants were told that the accuracy of their performance is being relayed to an audience.

Procedure

Pre-Scanning Assessment Session

After meeting preliminary criteria via phone screen, participants were asked to come in for a pre-scanning assessment session. During the assessment, trained clinical interviewers obtained informed consent and administered the Structured Clinical Interview of DSM Disorders-I (SCID-I) for substance dependence, depression, and psychotic symptoms, the Eating Disorder Examination (EDE) Interview, the assessment of conditions prohibiting scan and affecting cortisol reactivity, Dutch Eating Behavior Questionnaire (DEB-Q), Eating Expectancies Inventory (EEI), Purging Motives Questionnaire (PMQ), Eating Motives Questionnaire (EMQ), Food Craving Inventory (FCI), and a demographics questionnaire. Participant’s height, weight, and shoulder width measurements were collected to ensure eligibility for scanning. Following the pre-scanning assessment, participants were compensated for their participation in the study.

Scan Session

Following the assessment session, participants returned for a second session to acquire fMRI data. Each session began at approximately 1:30 pm. At the beginning of the scan session participants provided baseline ratings of subjective craving and stress. Each participant was provided a standardized meal consisting of approximately 20% fat, 20% protein, and 60% carbohydrates. Participants were asked to wait an hour to begin the next portion of the study to
allow sufficient time for digestion. During the hour waiting period, trained interviewers administered a timeline follow-back eating assessment for the 48 hours leading up to the scan session. Participants then completed the stressors questionnaire. Participants rated their subjective levels of craving and hunger for a second time after the one-hour waiting period. Participants were trained how to complete three different tasks in the scanner. Specifically, each participant was trained on how to use button response pads to answer subjective ratings for craving and stress, to choose picture stimulus orientation (horizontal vs. vertical), and lastly to choose correct answers to arithmetic problems. Participants were led to the scanning room where conditions prohibiting scanning were reviewed by an MRI technician. Scanning began at approximately 3:00 pm. After fMRI data acquisition, participants were debriefed and compensated for their participation in the scan session.

fMRI Data Acquisition

Structural scan.

MRI data acquisition was performed on a standard 3.0 T General Electric Scanner (Milwaukee, WI) using an 8-channel phased-array head coil. Participants were fitted with Resonance Technology Inc. stereo headphones and LCD goggles. An initial 2D gradient echo fast sequence scout (localizer) scan was acquired for setting landmarks. Participants then completed a high-resolution 3D spoiled gradient anatomical scan sequence covering the full brain (matrix = 256², flip angle = 20, TE=min full, FOV = 24 cm, TI = 450 ms, slice thickness = 1 mm, interscan spacing = 0, and an in plane resolution of 0.9375 x 0.9375 mm). Following the structural scan, participants were asked to rate their subjective stress level and their subjective level of food craving with a 4-button serial response pad which links to a set of visual analog
scales presented via the LCD goggles. The visual analog scales for subjective stress and craving ratings are analogous to those collected during the standardized meal.

**Functional scan.**

Functional images were acquired using a T2*-weighted gradient EPI pulse sequence in an oblique plane, with 22 cm FOV, a Flip angle of 90, a TE of 25 ms, a TR of 2000 ms, 1 echo with interleaved slices of 4 mm thickness, 0.0 slice gap, and an in plane resolution of 3.75 x 3.75 mm.

The study paradigm consisted of four functional runs. In the first run, participants viewed eight blocks of three neutral cues (18 second blocks, 6 seconds per cue), taken from or interpolated from the IAPS. The second run consisted of eight blocks of three highly palatable foods cues (pre-stress food cues; 18 second blocks, 6 seconds per cue) taken from or interpolated from the IAPS. In the third run, participants underwent the arithmetic portion of the TSST for stress induction while remaining in the scanner. In the final run, participants were exposed to eight blocks of highly palatable food cues (post-stress food cues; 18 second blocks, 6 seconds per cue). Interspersed between all blocks of visual stimuli are baseline blocks of a centered crosshair for initial contrasts. Likewise, a centered crosshair is interspersed between each block of arithmetic problems. Photographs of all visual stimuli were presented either in “landscape” or “portrait” orientation in a fixed random manner by stimulus type. In the first, second, and fourth run, participants were instructed to respond to each visual cue by indicating stimulus orientation with the button response pad. Response to stimulus orientation is included in the design to ensure that participants are alert and attending to stimuli. No images were presented more than once in order to minimize habituation. Subjective ratings of stress and craving were assessed immediately following each run.
fMRI Analyses

Image preprocessing

MRI data was pre-processed and analyzed using Analysis of Functional NeuroImages software (AFNI; Cox, 1996) with follow-up analyses conducted in SPSS version 22 (SPSS Inc., USA). Quality assurance steps were implemented for all functional data. EPI data was transformed into cardinal space, or the same grid space as the anatomical data for registration purposes. In order to account for the temporal offset of slice acquisition, voxel time series data were aligned into the same temporal origin using a Fourier transformation. This step ensures that the data are temporally aligned as if each slice was collected at the same time and in the same grid space for statistical analysis purposes. Outliers in the EPI data were identified on a voxel-by-voxel basis by estimating the difference between a smooth curve placed over the functional time series and the corresponding voxel’s residual value. Extreme values (spikes) in the EPI data were replaced with new values derived from the upper range of the allowed deviation from the fitted curve. Functional data were smoothed with a 4-mm full-width at half-maximum (FWHM) Gaussian filter, then resampled into a 4-mm³ grid resulting in voxel dimensions representative of the in-plane resolution. Functional data were registered to a within-subject base volume that was determined using the FINDBASE algorithm. The BOLD signal was characterized at the individual level with a general linear model (Ward, 2006) for each run (neutral cue, pre-stress food cue, and post-stress food cue). Motion parameters (roll, pitch, yaw, dS, dP, dL) calculated during registration and were included in the general linear model analysis of EPI data to account for movement artifacts. Subjects’ functional maps and SPGR structural images were transformed into Talairach space using a nonlinear warping method. Specifically, the warping method utilized was a 12 parameter weighted local Pearson coefficient (LPC) cost function, which carries out
multiple transformations in order to minimize the amount of interpolation applied to the data (Saad et al., 2009). These registration methods were employed to find the warp parameters that optimize the amount of interpolation necessary for data transformation.

**ROI analysis**

Based on our *a priori* hypotheses, we used a region of interest (ROI) analysis to determine region specific activation for each participant within each condition. ROI analyses followed methods presented by Dykman, Camchong, Clementz, and McDowell (2007). *A priori* ROIs were determined by regions consistently reported in previous fMRI studies of food cue reactivity in HC and women with BN. ROIs were defined by previously reported center masses for each region. Spheres with 8mm radii were centered on each mass for each region (see Figure 2). Mean beta coefficients were calculated for each region within each participant and condition. Mean beta coefficients for each region were then utilized for within-subjects and between-groups t-tests. The relationship between craving following cue exposure, stress following cue exposure, and ROI activation was assessed with post-hoc Pearson correlation analyses.

**Whole brain analysis**

Whole brain analyses were conducted to examine diffuse areas of activation in each group for each condition. A fixed effects model was implemented to perform two, 2x2 ANOVAs (consistent with 2x2 ROI ANOVA designs) on whole brain BOLD activation for examination of effects with AFNI’s 3dANOVA3. In order to correct for multiple comparisons, Monte Carlo simulations were performed on F-maps using 3dClustSim in AFNI software (http://afni.nimh.nih.gov/afni) with the following parameters: individual voxel p-value=0.025, 10,000 simulations, FWHM = 7, with a whole brain mask including 29911 resampled voxels. According to results of the simulations, a corrected significance level of p<0.05 could be
obtained with cluster size > 52 voxels (sharing sides or edges) and individual voxel height threshold of p < 0.025. In the occurrence of significant main effects and interactions, t-tests were performed on surviving clusters to determine directionality of between- and within-group effects.

**Specific Hypotheses**

**fMRI data (see Table 1)**

The first 2x2 ANOVA consisted of cue-type (neutral cue/pre-stress food cue) x group (BN/HC) comparisons; and the second consisted of condition (pre-stress food cue/post-stress food cue) x group (BN/HC). For the first ANOVA (cue-type x group), a main effect of condition was hypothesized such that food cues (vs. neutral cues) would evoke a greater degree of response for both BN and HC groups. Additionally, we hypothesized a main effect of group where women with BN (vs. HC) would have general hypo-activation within subcortical limbic system and prefrontal regions in response to cues, and greater activation than HC in visual regions. In the second ANOVA (condition x group), a main effect of condition was hypothesized where women would have relatively less activation within the prefrontal limbic system regions (dlPFC, mPFC, IPFC, ACC, OFC, IFG) for post-stress food cues vs. pre-stress food cues; but would show increased BOLD signal for post-stress vs. pre-stress food cues in subcortical limbic and related regions (Amg, NAcc, caudate, putamen, insula, occipital cortex, PMC/precentral gyrus, precuneus, lingual gyrus, angular gyrus, inferior occipital gyrus). Lastly, a main effect of group was hypothesized for the second ANOVA where women with BN would have less activation relative to HC in prefrontal regions (dlPFC, mPFC, IPFC, ACC, OFC, IFG), and more activation in subcortical limbic and visual regions (Amg, NAcc, caudate, putamen, insula, occipital cortex, PMC/precentral gyrus, precuneus, lingual gyrus, angular gyrus, inferior occipital gyrus).
Behavioral data

Statistical analysis for behavioral data was conducted with SPSS version 22 (SPSS Inc., USA). Independent samples $t$-tests were conducted between groups on demographic and descriptive variables to determine group differences. We hypothesized that women with BN would differ significantly from the HC group on measures of eating pathology, eating behavior, eating expectancies, and food craving. Because women with BN and HC were expected to differ in their self-report of eating behavior and pathology, correlations between self-report data and subjective craving/stress ratings were carried out for each group independently.
CHAPTER 3

RESULTS

Participants

81 participants were screened for the study. 30 qualified for the study following the phone screen, 27 completed an in-person assessment, and 21 completed the fMRI portion of the study. Due to technological difficulties, 1 participant’s fMRI data was not included for analyses. See Table 2 for demographic information. The final sample consisted of ten females with bulimia nervosa (mean age = 21 years, sd = 2.45) and ten healthy-weight, control females (mean age = 24 years, sd = 5.53). The total sample was 90% Caucasian, 10% African American/Black. Women in the bulimia sample were predominantly Caucasian (20% African-American). The healthy weight group consisted only of Caucasian females. As expected, women with BN reported more eating pathology and maladaptive eating behaviors than HC (see Table 3).

fMRI results

Previous fMRI data were examined by investigators to determine regions implicated in food cue reactivity and acute stress. Regions that were consistently cited in the literature were included as a priori ROIs. These regions were defined by 8mm spheres placed over previously reported centers of mass. Refer to Table 4 for a summary of findings in each a priori ROI.

A priori ROI results.

Group (BN, HC) x cue-type (neutral cue, pre-stress food cue) (see Table 5).

A 2x2 ANOVA for group (BN, HC) by cue-type (neutral cues, pre-stress food cues) revealed a main effect of group in the inferior occipital cortex ($F = 11.10$, $p < .01$), such that
women with BN had less BOLD signal response (mean $\beta = .35$) than HC (mean $\beta = .70$) regardless of cue-type (see Figure 3). A main effect of cue-type was found in the anterior insula ($F = 10.18, p < .01$) where than pre-stress food cues (mean $\beta = .05$) evoked less activation than neutral cues (mean $\beta = .13$) across groups (see Figure 4).

**Group (BN, HC) x condition (pre-stress food cue, post-stress food cue) (see Table 6).**

A main effect of group was found in the nucleus accumbens ($F = 5.35, p < .05$) for the condition x group ANOVA (see Figure 5). Within the nucleus accumbens, women with BN had less activation (mean $\beta = -.10$) across pre- and post-stress food cue conditions than HC (mean $\beta = .11$).

**Whole brain results.**

**Group (BN, HC) x cue-type (neutral cue, pre-stress food cue) (see Table 7).**

In addition to examination of *a priori* ROIs, whole brain analyses were conducted to examine areas of activation that are unique to food cue processing and acute stress, as there is currently very limited data regarding the interaction of these conditions. The same two 2 x 2 ANOVA designs implemented in *a priori* ROI analyses were utilized to probe main effects and interactions of the BOLD signal across the whole brain. All reported main effects and interactions were significant at a threshold of corrected $p < .05$ ($F = 4.41$); with the exception of the main effects of cue-type in the cue-type x group ANOVA, which were significant at a threshold of corrected $p = .03$ ($F = 5.55$).

The group (HC, BN) x cue-type (neutral cues, pre-stress food cues) ANOVA revealed several main effects and an interaction. A main effect of cue-type was found across seven voxel clusters (see Figure 7). Follow-up $t$-tests showed that pre-stress food cues evoked less activation relative to neutral cues in the middle frontal gyrus, superior temporal gyrus, precentral gyrus, and
supramarginal gyrus. Pre-stress food cues evoked greater activation than neutral cues in bilateral lingual gyrus. Additionally, there was a main effect of group bilaterally in declive where women with BN had less activation than HC (see Figure 6).

A two-way interaction was found in the cuneus with activation extending through fusiform gyrus, lingual gyrus, middle occipital gyrus, and Brodmann area 19. Follow up t-tests show that women with BN had increased activation from the neutral cue to pre-stress food cue condition, while HC had decreased activation from the neutral cue to pre-stress food cue condition (see Figure 8 & 9).

**Group (BN, HC) x condition (pre-stress food cue, post-stress food cue) (see Table 8).**

A second whole brain ANOVA for group (HC, BN) and condition (pre-stress food cues, post-stress food cues) was conducted. Results include several main effects and two significant interactions discussed below.

A main effect of group was found in five regions including medial frontal gyrus, culmen, cingulate gyrus, and lingual gyrus (see Figure 10). Follow-up t-tests show that HC had greater activation than women with BN in the medial frontal gyrus, culmen, cingulate gyrus, and postcingulate gyrus; but the opposite pattern was found in the lingual gyrus (BN > HC). There were main effects of condition in bilateral inferior parietal lobule and bilateral middle occipital gyrus. Pre-stress food cues evoked greater activation relative to post-stress food cues in bilateral inferior parietal lobules, and the reverse (post-stress food cues > pre-stress food cues) was found in bilateral middle occipital gyrus (see Figure 11).

Significant two-way interactions were found in the culmen and precuneus (see Figures 12-14). Planned follow-up t-tests show that activation increased in the culmen and precuneus for
HC women from pre-stress to post-stress food cue exposure. Women with BN had decreased activation within culmen and precuneus from pre-stress to post-stress food cue exposure.

**Post-hoc follow-up analyses**

The pattern of activation observed in the main effect of condition (see Table 8) proved interesting because it appeared that the decreased activation in bilateral inferior parietal lobules may be negatively associated and increased activation in bilateral middle occipital gyri. Therefore, the relationship between these two regions was investigated with post-hoc analyses. Exploratory Pearson correlations were calculated in each group and condition to assess the relationship between BOLD signal response to food cues in the inferior parietal lobule and middle occipital gyrus. No significant correlations were found. Mean beta weights of bilateral inferior parietal lobule and middle occipital gyrus are displayed in scatter plots with linear trend lines for each group and condition (see Figure 15a & 15b).

**Subjective ratings of craving and stress during fMRI paradigm.**

In order to examine between group differences for craving and stress on the day of the fMRI procedure a series of repeated measures ANOVAs were carried out with time as the within subject factor and group as the between subject factor. Of note, women with BN reported higher levels of craving relative to HC across all time points \( F(1,19) = 12.72, p<.01 \). Craving decreased following consumption of the standardized meal \( F(1,19) = 40.92, p<.001 \). Craving did not increase following post-meal ratings and the baseline assessment of craving in the fMRI environment; Craving increased following exposure to neutral cues in both groups \( F(1,19) = 5.40, p<.05 \), and further increased significantly following exposure to pre-stress food cues \( F(1,19) = 36.51, p<.001 \). A significant group x time interaction indicated that craving increased significantly more for women with BN than HC following pre-stress food cue exposure. Craving
decreased for both groups following the stress induction ($F(1,19) = 12.24$, $p<.01$). Both groups reported increased craving following exposure to post-stress food cues ($F(1,19) = 14.58$, $p<.01$). Craving trajectories for both groups are presented in Figure 16.

The same design was utilized to examine changes in stress over the course of the scan session. Similar to the pattern observed regarding craving, women with BN reported significantly higher levels of stress relative to HC across the scan session ($F(1,19) = 24.01$, $p<.001$). Stress decreased following consumption of the standardized meal ($F(1,19) = 7.63$, $p<.05$). A significant group x time interaction showed that HC stress levels decreased significantly more than women with BN after the meal was finished ($F(1,19) = 4.88$, $p<.05$). There were no changes in stress upon entering the fMRI environment, following the neutral cue, or pre-stress food cue conditions. Stress increased significantly following the stress induction ($F(1,19) = 32.91$, $p<.001$), and decreased following exposure to post-stress food cues ($F(1,19) = 88.20$, $p<.001$). See Figure 17 for stress trajectories during the scan session in both groups.

**Self-Report & Behavioral Results**

Women with bulimia differed significantly from control women on eating and craving related measures (see Table 3). Tables 9 and 10 display bivariate correlations for HC and women with BN (respectively) on self-report, subjective craving, and subjective stress measures, which are discussed below.

HC’s report of shape concern and restraint over eating was positively associated with craving throughout all of the scan session. A positive relationship was found between eating concern and stress following initial exposure to food cues. Number of life stressors experienced by HC was not associated with self-reported stress levels during the scan session. Finally, eating
expectancies for affect regulation were positively associated with craving following each cue exposure in HC.

In women with BN (see Table 10), no relationship was found between subjective craving during the fMRI scan and eating pathology assessed by the EDE. However, eating pathology was positively associated with stress throughout the scan session. Similar to HC, no relationship was found between number stressful life events in the last year and self-reported stress levels during the fMRI scan for women with BN.
CHAPTER 4

DISCUSSION

The purpose of this study was to examine differences between women with BN and HC regarding BOLD activation in response to food cues prior to and following an acute stress induction. Minimal data exists regarding the role of negative affect in food cue reactivity. This construct is especially critical in women with BN, since negative mood (specifically stress) precedes frequently occurring maladaptive behavior. The novel inclusion of a stress induction in this paradigm provides investigators the opportunity to expand our currently limited knowledge of neurobiological mechanisms associated with chronically relapsing eating disordered behavior. In addition, this study sought to replicate previous findings of the BOLD signal response in prefrontal, limbic, and visual regions for palatable food cues compared to neutral cues in both groups. Self-report measures of eating pathology, eating behavior, eating expectancies, experiences of stress, and behavioral data regarding changes in craving and stress throughout the fMRI paradigm were also collected.

Summary of fMRI data regarding pre-stress food cue reactivity

Differential neural activation for BN vs. HC during satiated and neutral mood state

We hypothesized that women with BN (vs. HC) would globally have less activation within subcortical limbic system and prefrontal regions in response to pre-stress and neutral cues, but increased activation in visual regions for pre-stress and neutral cues. ROI analysis showed a main effect of group such that women with BN had less activation in the inferior occipital gyrus relative to HC when looking at pre-stress and neutral cues in the inferior occipital gyrus.
Secondary whole brain analysis showed that women with BN also had less activation (than HC) in the declive (cerebellar vermis) for neutral and pre-stress food cues. A significant interaction in the cuneus (extending into fusiform gyrus) revealed that the BOLD signal response in women with BN increased from neutral cues to pre-stress food cues, but decreased for HC.

The inferior occipital cortex, declive, and cuneus all have a role in visual information processing. Of these visual regions, *a priori* hypotheses were only made regarding the inferior occipital cortex, such that increased activation (for BN vs. HC) was expected to demonstrate attentional biases towards food cues, because primary and secondary visual areas have been correlated with visual cue salience (Bradley et al., 2003; Lang et al., 1998; Moratti et al., 2004). The salience of food stimuli in the occipital cortex was initially established by healthy participants’ greater BOLD response in occipital (inferior) gyrus for food vs. neutral cues (Simmons, Martin, & Barsalou, 2005). Additionally, healthy controls had greater activation in the inferior occipital gyrus when looking at food-related utensils vs. neutral cues (Killgore et al., 2003), and lean non-binge eaters showed the same pattern when viewing pictures of highly palatable food cues (Geliebter et al., 2006). Consistent with previous studies (Killgore et al., 2003; LaBar et al., 2001), women in both groups of the current study showed an increased response in the inferior occipital cortex for pre-stress food compared to neutral cues, but women with BN did not activate to the same degree as HC, or more, as expected.

Certain aspects of sensory cortex activation, such as reduced or exaggerated BOLD signal responsiveness, have been explained by bottom-up processing. “Bottom-up” refers to a phenomena of sensory (e.g., visual) processing where stimuli is first identified by simple, lower-order components and that identification facilitates subsequent synthesis at a higher, more abstract level (Kinchla & Wolfe, 1979). Bottom-up visual attention alerts us to salient items in
our environment (Connor, Egeth, & Yantis, 2004). Bottom-up sensory processing can go awry when attention is biased. Behavioral studies demonstrate that women with BN have attentional biases toward food stimuli and may perceive food cues as threatening (Brooks, Prince, Stahl, Campbell, & Treasure, 2011a; Dobson & Dozois, 2004; Faunce, 2002; Formea & Burns, 1996; Lee & Shafran, 2004), but these studies cannot fully resolve whether attentional biases indicate hypervigilance or avoidance of food (Brooks et al., 2011a). Attentional biases have been noted to interfere with visual system processing of salient cues (Field & Cox, 2008). Inferior occipital cortex may not be hyperactivated for women with BN relative to HC if attention towards food cues is biased and women with BN are attempting to engage in cognitive avoidance. Hunger is one factor that could explain avoidant vs. hypervigilant attentional biases. Women with BN in a satiated stated may avoid attending to food cues, as opposed to responding with hypervigilance during a state of hunger (Santel et al., 2006).

The declive is one of 9 lobules within the cerebellar vermis, and has been functionally identified in oculomotor tasks (Hayakawa, Nakajima, Takagi, Fukuhara, & Abe, 2003). Results in the current study are consistent with previous food cue functional imaging studies, which have shown that BN and AN patients have less activation in the declive than HC (Uher et al., 2004). The specific role of the declive, and more broadly the cerebellar vermis in food cue reactivity is not well understood; however, several drug and alcohol cue related studies have documented the involvement of the cerebellum, which is comprised of the cerebellar vermis among other structures. Specifically, activation in the cerebellar cortex was correlated with cue-elicited craving in studies of participants who abuse alcohol and cocaine (Grant et al., 1996, Olbrich et al., 2006). Several authors have suggested that the cerebellar cortex activation is related to
emotional processing and memory during gustatory and olfactory cue-elicited craving (Olbrich et al., 2006; Schneider et al., 2001).

Evidence suggests that the cerebellum is associated with limbic system functioning and even emotionally-driven behavior, though a distinct anatomical substrate has yet to be defined (Berman, 1997; Berntson, Potolicchio, & Miller, 1973; Strick, Dum, & Fiez, 2009). The cerebellum has traditionally been related to aspects of motor control, but a review of cerebellum anatomy and function cited that “the range of tasks associated with activation in the cerebellum is dauntingly large,” (Glickstein, 2007; Strick, Dum, & Fiez, 2009). Such task domains include, but are not limited to, addiction, emotion, executive control, language, working memory, learning, and pain (Glickstein, 2007; Timmann & Daum 2007). Strick and colleagues (2009) raised several important cautions when interpreting task-related cerebellar activation. First, cerebellar activation may be associated with aspects of cognition that are not task-specific (Glickstein, 2007), and this hypothesis is likely supported by evidence of cerebellar activation in a wide-array of research domains. Also, many neuroimaging studies state that cerebellar activation is not related to motor functioning, but their paradigms involve some motor component, such as pushing a button. Importantly, the current study included that very motor component during each cue exposures. Lastly, the hemodynamic response in the cerebellum does not necessarily behave the same it does in cerebral cortex. The cerebellar cortex has expansive anatomical connections throughout the cerebral cortex and functional activation is not well understood. Despite difficulty theorizing the specific role of the cerebellum in the current study, it is important to document that women with BN displayed differential activation in the cerebellum than HC.
Significant interaction of eating disorder diagnosis and type of cue

Regarding the significant interaction of the BOLD signal within the cuneus (extending into fusiform gyrus), our results revealed that activation in women with BN increased from neutral to pre-stress food cues, but decreased for HC (see Figure 9). Increased activation in the cuneus for salient vs. neutral cues in women with BN is consistent with findings in a meta-analysis of food cue reactivity (van der Laan, De Ridder, Viergever, & Smeets, 2011); and a meta-analysis of smoking cue reactivity (Engleman et al., 2012). Though women with BN’s larger BOLD response in visual areas (such as the cuneus) for food cues vs. neutral cues parallels previous hypotheses referencing increased allocation of attention towards food (Engleman et al., 2012); this hypothesis does not support current results of activation in all visual regions (e.g., main effect of cue-type in inferior occipital gyrus). Interestingly, the cuneus and inferior occipital cortex did not show similar BOLD signal patterns in response to pre-stress and neutral cues, but appetitive cue-elicited craving has not always activated both of these regions. For example, cue-elicited craving in response to smoking cues activated the cuneus, but not inferior occipital cortex (Brody et al., 2007); food cues (vs. neutral cues) activated inferior occipital gyrus, but not the cuneus (Killgore et al., 2003); and high calorie (but not low-calorie) food cues elicited activation in the middle occipital gyrus, but not other visual regions (Killgore et al., 2003). The differential role of visual processing for appetitive cues in several regions (precuneus, cuneus, fusiform, angular, and inferior and middle occipital gyri) is in need of further investigation.

Food and neutral cues evoke differential activation in several neural systems

For main effects of cue-type, we hypothesized that pre-stress food cues (vs. neutral cues) would evoke a greater BOLD signal response in both BN and HC groups in all a priori ROIs.
(IFG, lPFC, dIPFC, mPFC, ACC, OFC, Amg, NAcc, caudate, putamen, insula, PMC, precentral gyrus, precuneus, angular gyrus, fusiform gyrus, inferior occipital gyrus). BOLD signal response for pre-stress food cues relative to neutral cues was decreased in the anterior insula. The anterior insula comprises the primary taste cortex (Kim, Ku, Lee, Lee, & Jung, 2012), and has been implicated in the experience of emotion (Phan et al., 2002). For example, the anterior insula was activated in women with BN during a state of disgust (Schienle et al., 2004). Additionally, the anterior insula is responsible for processing physical properties of food and their reward salience (Small et al., 2001). Regarding the insular cortex’s role in desire for food (Pelchat et al., 2004), the BOLD signal in the anterior portion has been shown to be greater during states of hunger and food cue exposure (Gordon et al., 2000; Small et al., 2001; Wang et al., 2004); and increased for obese (vs. controls) when viewing highly palatable food (vs. neutral) visual stimuli. Women with BN may have decreased anterior insula activation in the current study due to an interaction of negative emotion and food cue processing. Even though stress had not yet been induced, women with BN reported higher levels of stress throughout the scan day relative to HC. Because the insular cortex is involved in emotional experience, interoceptive awareness, and gustatory processing, insular activation may become disrupted in women with BN when appetitive responses to food images and memories are affected by negative mood, or even desires to be thin (Brooks et al., 2012).

Secondary whole brain results yielded support for our hypotheses that the visual regions, specifically the lingual gyrus, would elicit greater activation in for pre-stress food cues vs. neutral cues. Food and drug cue meta-analyses have documented responsiveness of the lingual gyrus for appetitive cues relative to neutral cues (van der Laan, De Ridder, Viergever, & Smeets, 2011; Tang, Fellows, Small, & Dagher, 2012), and have cited that lingual gyrus activation is
likely influenced by attention towards salience. Thus it appears that hunger may not modulate activation in the lingual gyrus since participants in the current study had greater activation for rewarding food cues relative to neutral cues.

Whole brain results showed that neutral cues aroused greater activation than pre-stress food cues in bilateral precentral gyrus. Healthy participants have shown greater precentral activation for food cues vs. objects (Dimitropoulos, Tkach, Ho, & Kennedy, 2012). However, women with BN have less activation in precentral gyrus than healthy women when provided with gustatory food cues (Bohon & Stice, 2011). Some studies have shown that the precentral gyrus is responsive to food vs. neutral cues when hunger is induced via intravenous ghrelin administration and 3 hours after a meal (Malik, McGlone, Bedrossian, & Dagher, 2008). Therefore, precentral gyrus activation for food may be heightened during states of hunger, which is not consistent with the parameters of this study. Lastly, animal models have shown that precentral gyrus activation in response to food cues may be modulated by the orientation of food in a visual cue and whether gross motor movements can be made to retrieve the food item (Godschalk, Lemon, Kuypers, & Van Der Steen, 1985). This study did not account for gross motor accessibility of food in visual cue presentation.

Secondary whole brain results also included a main effect of cue-type in the middle frontal gyrus and supramarginal gyrus for neutral cues > pre-stress food cues. No specific hypotheses were made regarding the directions of activation in these regions. The middle frontal gyrus covers one third of the frontal lobe and specific locations within middle frontal gyrus are hypothesized to process sensory properties of cues (Kringelbach, de Araujo, & Rolls, 2004). In previous fMRI studies of food cue reactivity, participants with BN have shown less activation in the middle frontal gyrus (Bohon & Stice, 2011), but middle frontal gyrus was more responsive to
high vs. low calorie foods in a meta-analysis of healthy participants (van der Laan et al., 2011). The supramarginal gyrus is located within the inferior parietal lobe (IPL) and is traditionally known for its role in visual word processing (Stoeckel, Gough, Watkins, & Devlin, 2009), though the IPL broadly is thought to have many functions, due it’s complex distribution of connectivity with prefrontal, limbic, and visual systems (Andersen, 1987). Limited literature is available regarding the specific role of supramarginal gyrus in food cue reactivity, however its role in appetitive cue processing has frequently been cited (Brody et al., 2007; Liu et al., 2009; Wilcox, Teshiba, Merideth, Ling, & Mayer, 2011). Hypotheses have postulated that the role of the supramarginal gyrus in cue-reactivity involves visuomotor integration (Yalachkov, Kaiser, & Naumer, 2010). Most studies reference hyperactivation of the supramarginal gyrus for appetitive vs. neutral cues (e.g., Brody et al., 2007; van der Laan et al., 2011), but neutral cues aroused greater activation that appetitive cues in our study. We suggest that hunger levels influenced the amount of supramarginal activation for food vs. neutral cues in the current study; which is consistent with Tataranni and colleagues’ (1999) finding of a relationship between satiety and IPL activation. Additionally, studies with “fed” conditions have not reported significant supramarginal hyperactivation for food cues in various populations (Castellanos et al., 2009; Ochner et al., 2012), and have reported reductions in inferior parietal lobule activation in satiated eating disorder populations (Santel, Baving, Krauel, Münte, & Rotte, 2006).

**Summary of fMRI data regarding the role of acute stress in food cue reactivity**

Currently, there is limited research regarding the effect of acute stress on food cue processing with fMRI methodology. Therefore, our original hypotheses regarding food cue processing under stressful conditions were primarily theory driven. Several findings in the current study were not consistent with theoretically driven *a priori* hypotheses regarding limbic
and visual functioning, but may be better explained by default mode network functioning that is discussed below.

Our original hypotheses regarding food cue processing under stress were founded on results from behavioral and functional imaging studies of stress. Behavioral studies have demonstrated that after experiencing psychosocial stress, participants chose foods with higher energy density (Born et al., 2009). Furthermore, stress has also been shown associated with increases craving, urges to binge, and consumption of calorically dense food in women with BN (Neudeck, Florin, & Tuschen-Caffier, 2001; Staiger, Dawe, & McCarthy, 2000). Functional imaging studies have shown that acute stress is associated with decreased limbic system activation (Born et al., 2009; Pruessner et al., 2008). Decreased activation in the hypothalamus, medial-orbitofrontal cortex, anterior cingulate cortex, putamen, amygdala, hippocampus, and cingulate gyrus has been documented in healthy participants during stress inductions (relative to baseline tasks) similar to that of the one used in the current study (Born et al., 2009; Pruessner et al., 2008). Regarding stress and food cue reactivity, there is evidence of decreased limbic system response following an acute stress induction when participants were asked to choose visually presented food items for their next meal (Born et al., 2009). In addition to reports of decreased, negative functional activation in the limbic system, the default mode network has been shown be negatively activated during task demands following acute stress (Soares et al., 2013). The default mode network is hypothesized to perform internal cognitive functions, and to link internal and external attention regarding experiences in our external world (Mason et al., 2007). It consists of the posterior cingulate cortex, precuneus, the medial prefrontal cortex, inferior parietal lobule, and temporal lobules (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001). Broadly speaking, the default mode network has been documented to function aberrantly in
psychiatric populations (Whitfield-Gabrieli & Ford, 2012). Negatively activation during task demands following acute stress was observed in the precuneus, middle occipital cortex, angular gyrus, middle temporal gyrus, and parahippocampal cortex. Decreased task-related activation in regions of the default mode network is thought to be associated with cognitive control and goal-directed behaviors (Harrison et al., 2007; Soares et al. 2013). More precisely, decreased activity in the default mode network during stress suggests that individuals could be functionally limited in their ability to shift from internal, self-focus towards external environmental processing (Soares et al., 2013; Sridharan, Levitin, & Menon 2008). With the limited literature available regarding the additive effects of acute stress and food cue reactivity, negative and decreased activation of regions within the default mode network has not been addressed.

**Differential responses to food cues prior to and following stress in BN (vs. HC)**

Given that stress may contribute to overconsumption of highly palatable foods and the roles of the limbic system, prefrontal, and visual regions in the processing of food images, we hypothesized that women with BN would have less activation relative to HC in prefrontal regions (dlPFC, mPFC, lPFC, ACC, OFC, IFG); but more activation in subcortical limbic and visual regions (Amg, NAcc, caudate, putamen, insula, occipital cortex, PMC/precentral gyrus, precuneus, lingual gyrus, angular gyrus, inferior occipital gyrus) for both food cue conditions. ROI analysis results revealed that women with BN had negative activation within the nucleus accumbens for pre and post-stress food cues relative to a fixation baseline, while HC had positive activation. The nucleus accumbens, within the ventral striatum, has been associated with motivational properties of food (Volkow et al., 2002). However, increases in dopamine levels may occur exclusively in the dorsal striatum when hungry controls are exposed to food cues, and nucleus accumbens activation may be blunted in a satiated state (Small, Jones-Gotman,
Dagher, 2003), such as that induced in the current study. Altered striatal (nucleus accumbens) activation has been documented in women with BN in reward salience tasks (Wager et al., 2010). Therefore, nucleus accumbens may be disrupted, but not necessarily positively activated, during craving and food cue processing in women with BN who are satiated.

Our hypothesis that women with BN would have greater activation in visual regions than HC was supported by a main effect of group found in whole brain analyses within the lingual gyrus. This finding is consistent other studies which reported that women with BN had more lingual activation relative to a comparison group when viewing food stimuli (Uher et al., 2004). Additionally, stress has been found to amplify lingual gyrus activation relative to neutral mood conditions (Henckens, Hermans, Pu, Joëls, & Fernández, 2009). Since women with BN reported greater subjective reports of stress in across food cue conditions relative to HC, it follows that lingual gyrus activation may be particularly heightened in the BN group.

Other regions that survived whole brain cluster analysis include medial frontal gyrus, posterior cingulate gyrus/cingulate gyrus, and culmen; however the main effect in the culmen is better explained by a significant two-way interaction, which is discussed below. Main effects of group were found in these regions such that HC had greater activation than women with BN. Moreover, women with BN had negative activation in medial frontal gyrus and posterior cingulate gyrus when viewing pre- and post-stress food cues, while HC had hyperactivation. Medial frontal gyrus includes supplementary motor area and is involved in response inhibition tasks (Talati & Hirsch, 2005). As previously described with middle frontal gyrus activation, women with BN also display less BOLD signal response (relative to healthy participants) within the medial frontal gyrus during gustatory food cue presentation (Bohon & Stice, 2011). Women with BN may have regional grey matter abnormalities in medial frontal areas (Schäfer, Vaitl, &...
Schienle, 2010). Therefore, inhibition and motor planning functions in medial frontal gyrus may be compromised in women with BN, particularly when presented with appetitive cues and under conditions of stress. The posterior cingulate cortex contains Brodmann areas 29, 30, 23, and 31, and is involved in monitoring eye movements, responding to sensory stimuli, and evaluative functions such as monitoring one’s own behavior regarding spatial orientation and memory (Vogt, Finch, & Olson, 1992). Additionally, the posterior cingulate cortex is also recognized as part of a “default mode network” and has been noted to have decreased, negative activation during an array of tasks (Raichle & Snyder, 2007). There is little evidence of decreased posterior cingulate cortex activation for food cues in any diagnostic group. However, drug cue reactivity studies have documented decreased posterior cingulate activation with increases in craving (Wilcox, Teshiba, Merideth, Ling, & Mayer, 2011), and during acute stress (Li, Kosten, & Sinha, 2005). It’s possible that the experience of craving and acute stress decreased posterior cingulate activation in women with BN relative to HC.

Stress alters BOLD response to palatable food cues in BN and HC women

Regarding main effects of food-cue condition, we hypothesized that women in both groups would have relatively less activation within the prefrontal limbic system regions (dIPFC, mPFC, lPFC, ACC, OFC, IFG) for post-stress food cues vs. pre-stress food cues; but would show increased BOLD signal for post-stress vs. pre-stress food cues in subcortical limbic and visual regions (Amg, NAcc, caudate, putamen, insula, occipital cortex, PMC/precentral gyrus, precuneus, lingual gyrus, angular gyrus, inferior occipital gyrus). Although no main effects of condition were found a priori ROIs, there was increased activation for post-stress vs. pre-stress food cues for both groups in the middle occipital gyrus, a visual area that is modulated by visual attention and has been positively associated with increases in craving (Rubinstein et al., 2011).
Middle occipital gyrus has been activated in many groups and conditions of food cue presentation (Killgore et al., 2003; Malik, McGlone, Bedrossian, & Dagher, 2008; Santel et al., 2006; van der Laan et al., 2011). Results of the current study suggest that both HC and women with BN have increased visual processing of visual food stimuli following acute stress. A second main effect of condition was found in the inferior parietal lobule where the BOLD response was decreased for post-stress food cues and positively activated for pre-stress food cues. In addition to functions described above, the inferior parietal lobule has been implicated in top-down attentional control and inhibition of intended action (Hopfinger, Buonocore, & Mangum, 2000; Garavan et al., 1999). Selective activation within the inferior parietal lobule is cited as a form of voluntary visual attentional control, which modulates sensory processing in areas such as fusiform and lingual gyrus (Hopfinger, Buonocore, & Mangum, 2000). Because food cues are especially salient to women with BN, hyperactivation in the inferior parietal lobule would be expected and was observed for both groups of women in this study during pre-stress food cue exposure. The experience of stress likely negatively affected activation within the inferior parietal lobule for women with BN, as has been observed in functional studies of the default mode network and stress (Soares et al., 2013). HC did not have the same response to post-stress food cues, which implies that inferior parietal lobule, and potentially the default mode network, is differentially activated during appetitive processing in satiated women under stress.

BN diagnosis interacts with acute stress during food cue processing

Significant two-way interactions were found within the precuneus and culmen. Women with BN showed negative BOLD signal response in the precuneus for post-stress (vs. pre-stress) food cues; and HC had hyperactivation. Figure 14 depicts that the opposite directions of activation in the precuneus for each group. Data suggest the precuneus may have a role in a wide
range of higher-order cognitive functions, though the exact functions have been difficult to determine. fMRI studies of healthy subjects suggest that the precuneus has functional roles in the default mode network (Soares et al., 2013), and for visuo-spatial imagery, episodic memory retrieval, self-processing operations (Cavanna & Trimble, 2006). Of note, ICA analyses of the default mode network show that the precuneus tonically and consistently activates with posterior cingulate cortex and inferior parietal lobule (Fransson & Marrelec, 2008; Raichle et al, 2001); both of which were negatively activated following stress induction in the current study. Acute stress, induced by solving difficulty math problems, is related to “deactivation” in the precuneus, posterior cingulate, and parietal lobule (among other regions) for stress vs. non-stress conditions (Dagher, Tannenbaum, Hayashi, Pruessner, & McBride, 2009). The BN group’s negative activation in the precuneus for post-stress food cues is consistent with reports of decreased BOLD signal response in the default mode network during stress (Soares et al., 2013), which may indicate utilization of attentional resources during other cognitive experience, such as craving and appetitive processing (Raichle et al, 2001).

A significant interaction was also observed in the culmen, another lobule within the cerebellar vermis (Bispo et al., 2010). Both groups’ BOLD signal responses for food cues were increased relative to baseline fixation task, but women with BN had less activation in the culmen for post-stress vs. pre-stress food cues and HC displayed the opposite pattern (see Figure 13). Like the declive, the role of the culmen in food cue reactivity is currently not well understood. Often, findings of activation in the culmen are referred to under a broader umbrella term of cerebellum (Bapi, Miyapuram, Graydon, & Doya, 2010) or (anterior) cerebellar vermis. Results reported in this broad manner are difficult to interpret, as there are 9 lobules within the cerebellar vermis and several functionally distinct regions of the cerebellum. Activation in the anterior...
cerebellar vermis/cerebellum has been reported for a wide spectrum of mental health disorders and medical syndromes (Berquin et al., 1998; Courchesne et al., 1988; DelBello et al., 1999; Ferland et al., 2004; Linden & Connor, 1993; Rae et al., 1998). The cerebellar vermis/cerebellum has been functionally implicated in discriminating positive and negative emotions (Schraa-Tam et al., 2012). Heeding cautions from Strick and colleague (2009) and based on the vast array of findings it is difficult to offer an interpretation for culmen activation during food cue reactivity and acute stress in the current study. Again, it is remarkable that the culmen is another region in the cerebellum differentially activated by women with BN. Further investigation is needed to understand the functional role of the culmen in salient cue processing during various mood states.

**Summary of Behavioral Data**

Assessment of subjective levels of craving and stress were utilized to conduct manipulation checks across the scan day procedure. Administration of a standardized meal was useful in decreasing craving for both groups prior to fMRI scanning. All participants reported increases in craving following food cue exposure prior to and following the stress induction, similar to previously reported relationships between food cues and craving (Sobik, Hutchison, & Craighead, 2005). Women with BN reported higher levels of subjective craving throughout the day of scanning. Our participants’ self-report of stress during scanning, and qualitative reports after scanning, demonstrated that our stress induction was successful in both groups. Women with BN reported higher levels of subjective stress during the scan session, which was expected given evidence of higher levels of negative affect in women with BN in general (Wegner et al., 2002, Engelberg, Steiger, Gauvin, & Wonderlich, 2007; Smyth et al., 2007), and during food cue confrontation (van den Eynde et al., 2013).
Conclusions

Conceptual analysis of results in the current study may inform nomological networks of eating behavior and functional neural activation. Importantly, results from the current study suggest that in a satiated state, the default mode network and visual systems are differentially activated for women with BN (vs. HC), especially during acute stress and food cue processing. The role of the default mode network has not been sufficiently investigated regarding food cue reactivity in negative mood states. Effects of differential default mode and visual processing may relate to poor cognitive functioning (e.g. executive control, emotion regulation, attentional biases) instead of maladaptive eating behavior in women with BN under stressful and satiated conditions. We found partial support for our hypotheses \textit{a priori} ROIs. Broadly, we expected to confirm hypotheses that women with BN show divergent neural activation from HC, and this was supported regardless of direction of the BOLD signal in a satiated state. Results may have been surprising, in part, because participants in the current study had eaten a meal prior to scanning, which is different than methods employed by other investigators. Regarding the unexpected direction of some findings in visual and limbic regions, previous studies have yielded altered findings when participants were in fed vs. fasted state (Santel et al., 2006). In fact, a meta-analysis of food cue reactivity noted that the state of hunger in various studies might be the source of inconsistent findings (van der Laan et al., 2011). Acute satiation is noted to affect neuronal responses to food cue; and thus state of hunger influences functional activation regarding processing of external food stimuli (Führer, Zysset, & Stumvoll, 2008; LaBar et al., 2001; O’Doherty et al., 2006; Smeets et al., 2006). Furthermore, investigators found the state of hunger modulates neural response to food cues in several limbic regions (van der Laan et al., 2011). The limbic system was identified to be particularly relevant in the current study because
of its role in emotional, motivational, and salience processing (Morgane, Galler, & Mokler, 2005). The limbic system was minimally activated in the current study, which may be interpreted to mean that women with BN activate regions outside of the limbic system when presented with food stimuli in a fed state, regardless of mood. Thus in a satiated state, reward processing specifically may not diverge from HC, which is consistent with attenuated limbic activation in healthy participants after overfeeding (Cornier, Von Kaenel, Bessesen, & Tregellas, 2007). Additionally, risk for binge eating may be reduced for women with BN in satiated states, even in the midst of acute stress. Cognitive restraint theories posit that risk for overconsumption is greatest when individuals restrict their diet and caloric intake (Heatherton & Baumeister, 1991; Polivy & Herman, 1985; Spencer & Fremouw, 1979). Reduced risk for binge eating in satiated state is also consistent with behavioral treatment approaches for binge eating, which encourage eating regularly throughout the day as a means of reducing risk for overconsumption (Fairburn, 2008). In addition to states of hunger, expectancies to eat have also been shown to modulate limbic and visual system activation (Malik, McGlone, & Dagher, 2011) Though limbic system and reward functioning may be regulated by satiety, the current study demonstrated unique responses to food cues for women with BN compared to HC.

There have been several methods for investigating abnormal neural processing in for food cues including, but not limited to: fasted/fed conditions, visual: high calorie, low calorie, neutral, eating utensils; olfactory; gustatory cue conditions (Brooks et al., 2011; Coletta et al., 2009; Haase, Cerf-Ducastel, & Murphy, 2009; LaBar et al., 2001; Ohla, Toepel, Le Coutre, & Hudry, 2012; Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Schienle, Schafer, Hermann, & Vaitl, 2009). This study design was novel for its inclusion of a stress induction in a food cue reactivity paradigm. The interaction of multiple neural systems involved in negative affect and food cue
processing is important to study given the gap in extensive mood and food cue reactivity literature regarding neurobiological correlates of maladaptive eating behavior. Our recruitment methods were stringent and served to better this specific study by limiting the confounding nature of other mental health conditions; however, comorbidity of mental health disorders in women with BN is the rule, not the exception. Future studies may seek to investigate neural functioning of women with BN who classically present with more symptomology than disordered eating pathology alone.

While the current study had many strengths, there are some limitations. Many a priori ROIs were identified based on previous food cue reactivity studies and our results did not yield consistent subcortical limbic system activation in many of those regions for food vs. neutral contrasts. As noted above, dissimilar results of food cue reactivity in the current study may be specific to the methodology, especially regarding the state of satiety in our participants during scanning (van der Laan et al., 2011). Diverse results could also be a result of the method utilized for ROI analyses. Despite documentation of subcortical limbic activation in food cue processing, it may be premature to identify ROIs by center of masses that are representative of food cue reactivity in various populations (healthy, eating disorder) and paradigm conditions (fasted, fed). Though the current study attempted to account for habituation, our limited number findings in a priori limbic system ROIs may be attributed to attenuated activation in participants who are exposed to repeated visual stimuli (Breiter et al., 1996; Holsen et al., 2005; Wright et al., 2001). A larger sample size would have been optimal for detecting effects of group, condition, and interactions of group x condition and might have led to more statistically significant effects and interactions in a priori ROIs. Menstrual cycle has been shown to affect limbic system functioning (Van Vugt, 2010; Dreher et al., 2007) and food cue reactivity (Frank, Kim,
Krzemien, & Van Vugt, 2010). In this study we did not match women on the stage of their cycle. Lastly, though brain region functions can be broadly classified by sensory modality, location, or other shared characteristics, results in the current study caution investigators to consider nuanced behavior of brain regions within a system under unique conditions.

There are still many unanswered questions regarding the interaction of multiple neural systems involved in stress and food cue processing. Future studies should attempt to induce acute psychosocial stress for periods long enough to provide sufficient fMRI data for further analysis. Understanding the temporal nature of BOLD signal response across stressful and food cue conditions would shed important light on alterations in corticolimbic activity in various populations and conditions. Additionally, future paradigms should aim to assess simultaneous experiences of stress and food cue processing in order to shed light on externally valid experiences of eating behavior in women with BN. As noted above, the state of hunger drastically affects food cue reactivity (Führer, Zysset, & Stumvoll, 2008; LaBar et al., 2001; O’Doherty et al., 2006; Smeets et al., 2006; van der Laan et al., 2011). Thus, state of hunger should be manipulated during acute stress inductions and food cue exposure. The addition of a feeding condition at the end of this study would provide behavioral data to examine in conjunction with the BOLD signal and other group variables, as expectancies for eating in the near future have also modulated neural activation (Malik et al., 2011). Future research should aim to recruit minority populations in eating disordered and healthy control groups. The anatomical and functional relationships between neural systems investigated in the current study are not well-understood regarding food cue reactivity. Future studies may begin to better understand the relationship between default mode network, visual, and limbic system by correlating cross-neural system BOLD signal responses. For example, the current study
employed post-hoc analyses to investigate the relationship between the inferior parietal lobule and middle occipital gyrus under conditions of stress. Our findings were likely limited by a relatively small sample size. Therefore, future investigations should continue this avenue of investigation.

In conclusion, our study provided preliminary evidence of how several neural systems (limbic, prefrontal, visual, and default mode) interact during multiple cognitive processes: appetitive cue processing under a state of satiety and additionally under acute stress. Participant responses to pre-stress food vs. neutral food cues replicated some previous findings of visual information processing of food cues, but were not consistent with previous findings in subcortical limbic areas (likely influenced by satiety). Comparisons of post-stress food to pre-stress food cues implicated the role of the default mode network in negatively activated regions (medial frontal gyrus, inferior parietal lobule, precuneus, posterior cingulate cortex) and the role of visual cue processing systems in hyperactivated regions (middle occipital cortex, lingual gyrus) commonly associated with heightened attentional biases. More investigation is needed to replicate finding of how acute stress affects default mode network, limbic, prefrontal, and visual systems processing of food cues.
References


Figure 1a. Neutral cue from IAPS (Lang, Bradley, & Cuthbert 2005).
Figure 1b. Food cue from IAPS (Lang, Bradley, & Cuthbert 2005).
Figure 2. ROI mask applied to functional data for *a priori* ROI analyses. Each color represents one of the 19 identified *a priori* ROIs (see Table 4). Center of masses were applied to both hemispheres. Axial slices $z = -22$ (top right) through $z = 54$ (bottom left). Spacing = 4mm. Images are radiologically oriented: right = left. Underlay is the average of all BN and HC anatomical images.
### Table 1

**Hypotheses for main effects in a priori ROIs**

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Main Effect</th>
<th><em>A priori</em> ROI</th>
<th>Hypothesized direction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cue-type x group</strong>&lt;br&gt;<em>(Neutral, Pre-stress food) x (HC, BN)</em></td>
<td>Cue-type</td>
<td>Prefrontal: IFG, IPFC, dlPFC, mPFC, ACC, OFC</td>
<td>Pre-stress food &gt; N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limbic: Amg, NAcc, caudate, putamen, insula, PMC, precentral gyrus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual: Precuneus, angular gyrus, fusiform gyrus, inferior occipital gyrus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>Prefrontal: IFG, IPFC, dlPFC, mPFC, ACC, OFC</td>
<td>HC &gt; BN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limbic: Amg, NAcc, caudate, putamen, insula, PMC, precentral gyrus</td>
<td>BN &gt; HC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual: Precuneus, angular gyrus, fusiform gyrus, inferior occipital gyrus</td>
<td></td>
</tr>
<tr>
<td><strong>Condition x group</strong>&lt;br&gt;<em>(Pre-stress food, Post-stress food) x (HC, BN)</em></td>
<td>Condition</td>
<td>Prefrontal: IFG, IPFC, dlPFC, mPFC, ACC, OFC</td>
<td>Pre-stress food &gt; post-stress food</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limbic: Amg, NAcc, caudate, putamen, insula, PMC, precentral gyrus</td>
<td>Post-stress food &gt; pre-stress food</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual: Precuneus, angular gyrus, fusiform gyrus, inferior occipital gyrus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>Prefrontal: IFG, IPFC, dlPFC, mPFC, ACC, OFC</td>
<td>HC &gt; BN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limbic: Amg, NAcc, caudate, putamen, insula, PMC, precentral gyrus</td>
<td>BN &gt; HC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual: Precuneus, angular gyrus, fusiform gyrus, inferior occipital gyrus</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* N = neutral cues, HC = healthy control, BN = bulimia nervosa, IFG = inferior frontal gyrus, IPFC = lateral prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, mPFC = medial prefrontal cortex, ACC = anterior cingulate cortex, OFC = orbitofrontal cortex, Amg = amygdala, NAcc = nucleus accumbens, PMC = premotor cortex.
Table 2

*Demographics.*

<table>
<thead>
<tr>
<th></th>
<th><strong>BN</strong></th>
<th></th>
<th><strong>HC</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Mean</strong></td>
<td>(Range)</td>
<td><strong>Mean</strong></td>
<td>(Range)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.7</td>
<td>(18-26)</td>
<td>24.0</td>
<td>(18-32)</td>
</tr>
<tr>
<td>BMI (index)</td>
<td>21.8</td>
<td>(18-23.5)</td>
<td>22.2</td>
<td>(20.6-24)</td>
</tr>
<tr>
<td>Highest lifetime weight (lbs.)</td>
<td>147.3</td>
<td>(105-180)</td>
<td>148.1</td>
<td>(117-170)</td>
</tr>
<tr>
<td>Lowest lifetime weight (lbs.)</td>
<td>117.4</td>
<td>(89-150)</td>
<td>125.1</td>
<td>(103-160)</td>
</tr>
<tr>
<td>BDI total (score)</td>
<td>15.2</td>
<td>(2-42)</td>
<td>5.2</td>
<td>(2-20)</td>
</tr>
<tr>
<td>Lifetime stressors (# of events)</td>
<td>10.1</td>
<td>2-21</td>
<td>7.8</td>
<td>(0-20)</td>
</tr>
<tr>
<td>Binge frequency (# of days)*</td>
<td>8.4</td>
<td>(4-20)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Binge frequency (# of episodes)*</td>
<td>9.8</td>
<td>(4-20)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Self-induced vomiting (# of episodes)*</td>
<td>8.6</td>
<td>(0-30)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Laxative use (# of episodes)*</td>
<td>9.1</td>
<td>(0-84)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Diuretic use (# of episodes)*</td>
<td>.1</td>
<td>(0-1)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Excessive exercise frequency (# of episodes)*</td>
<td>4.2</td>
<td>(0-26)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Fasting (# of episodes)*</td>
<td>.5</td>
<td>(0-3)</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note.* SD = standard deviation, BN = bulimia nervosa, HC = healthy control, BMI = body mass index. *a* = frequency of behavior in the last 28 days.
Table 3

*Between groups comparison of eating pathology and behavioral measures.*

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BN</td>
<td>HC</td>
<td>*</td>
<td>df</td>
<td></td>
</tr>
<tr>
<td>EDE Total</td>
<td>2.39</td>
<td>0.26</td>
<td>4.45</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.44)</td>
<td>(0.44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDE Shape</td>
<td>2.36</td>
<td>0.38</td>
<td>3.39</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.71)</td>
<td>(0.68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDE Weight</td>
<td>2.02</td>
<td>0.26</td>
<td>3.24</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.63)</td>
<td>(0.51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDE Eating</td>
<td>2.18</td>
<td>0.14</td>
<td>4.11</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.55)</td>
<td>(0.27)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDE Restraint</td>
<td>3.02</td>
<td>0.22</td>
<td>5.49</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.57)</td>
<td>(0.37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEI Total</td>
<td>157.6</td>
<td>93.40</td>
<td>4.52</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(28.27)</td>
<td>(34.92)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCI - Craving</td>
<td>74.00</td>
<td>51.3</td>
<td>3.60</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(11.89)</td>
<td>(16.04)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>FCI - Indulgence</td>
<td>56.20</td>
<td>54.10</td>
<td>0.24</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(11.13)</td>
<td>(25.85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEBQ</td>
<td>119.20</td>
<td>68.50</td>
<td>6.33</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(15.53)</td>
<td>(20.00)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMQ</td>
<td>68.60</td>
<td>48.80</td>
<td>4.09</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(11.80)</td>
<td>(9.75)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.* SD = standard deviation, BN = bulimia nervosa, HC = healthy control, *t* = *t*-statistic, *df* = degrees of freedom, EDE = Eating Disorder Examination, FCI = Food Craving Inventory, DEBQ = Dutch Eating Behavior Questionnaire, EMQ = Eating Motive Questionnaire. * *p < .05, ** *p < .01, *** *p < .001.
Table 4

Results for ROI and Whole brain analysis in a priori ROIs

<table>
<thead>
<tr>
<th>Brain ROI</th>
<th>ROI findings</th>
<th>Direction</th>
<th>Whole brain findings</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAcc</td>
<td>ROI: Condition x Group</td>
<td>HC &gt; BN</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Main effect of group</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Insula</td>
<td>ROI: Cue-type x Group</td>
<td>N &gt; Pre-Stress food</td>
<td>Contiguous</td>
<td>N &gt; Pre-stress food</td>
</tr>
<tr>
<td>anterior</td>
<td>Main effect of cue-type</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>medial</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Amg</td>
<td>-</td>
<td></td>
<td>Contiguous</td>
<td>HC &gt; BN</td>
</tr>
<tr>
<td>ACC</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>OFC</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>PFC</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>lPFC</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>dlPFC</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>mPFC</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Precuneus</td>
<td>-</td>
<td></td>
<td>Whole brain: Condition x Group</td>
<td>HC &gt; BN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Main effect of cue-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td>-</td>
<td></td>
<td>Whole brain: Cue-type x Group</td>
<td>N &gt; Pre-stress food</td>
</tr>
<tr>
<td>Angular</td>
<td>-</td>
<td></td>
<td>Main effect of group</td>
<td>(see Figure 12)</td>
</tr>
<tr>
<td>Lingual</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Inferior Occ</td>
<td>ROI: Cue-type x Group</td>
<td>HC &gt; BN</td>
<td>Whole brain: Condition x Group</td>
<td>BN &gt; HC</td>
</tr>
<tr>
<td></td>
<td>Main effect of group</td>
<td></td>
<td>Main effect of group</td>
<td></td>
</tr>
<tr>
<td>PMC</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>-</td>
<td></td>
<td>Contiguous</td>
<td>N &gt; Pre-stress food</td>
</tr>
<tr>
<td>Caudate</td>
<td>-</td>
<td></td>
<td>Contiguous</td>
<td>N &gt; Pre-stress food</td>
</tr>
<tr>
<td>Putamen</td>
<td>-</td>
<td></td>
<td>Contiguous</td>
<td>-</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>-</td>
<td></td>
<td>Contiguous</td>
<td>HC &gt; BN; also (see Figure 8)</td>
</tr>
<tr>
<td>IFG</td>
<td>-</td>
<td></td>
<td>Contiguous</td>
<td>N &gt; Pre-stress food</td>
</tr>
</tbody>
</table>

Note. N = neutral cues, HC = healthy control, BN = bulimia nervosa, IFG = inferior frontal gyrus, PFC = prefrontal cortex, lPFC = lateral prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, mPFC = medial prefrontal cortex, ACC = anterior cingulate cortex, OFC = orbitofrontal cortex, Amg = amygdala, NAcc = nucleus accumbens, PMC = premotor cortex, Occ = occipital. – indicates no finding from whole brain analyses.
Table 5

*ROI ANOVA results for cue-type (neutral, pre-stress food cue) x group (BN, HC)*

<table>
<thead>
<tr>
<th>Effect</th>
<th>Region</th>
<th>Direction</th>
<th>Hemisphere</th>
<th>x (/-)</th>
<th>y</th>
<th>z</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main effect of group</strong></td>
<td>Inferior occipital cortex</td>
<td>HC &gt; BN</td>
<td>Bilateral</td>
<td>26</td>
<td>86</td>
<td>-14</td>
<td>11.10**</td>
</tr>
<tr>
<td><strong>Main effect of condition</strong></td>
<td>Anterior insula</td>
<td>N &gt; Pre-Stress Food</td>
<td>Bilateral</td>
<td>32</td>
<td>-15</td>
<td>8</td>
<td>10.16**</td>
</tr>
</tbody>
</table>

*Note.* HC = healthy control, BN = bulimia nervosa, N = neutral cue-type. * p < .05, ** p < .01, *** p < .001.
Figure 3. Main effect of group for group x cue-type ANOVA in the inferior occipital cortex. HC = healthy control, BN = bulimia nervosa. Y-axis denotes beta-weight value of the BOLD signal in response to neutral and pre-stress food cues (x-axis).

Figure 4. Main effect of cue-type for group x cue-type ANOVA in the anterior insula. HC = healthy control, BN = bulimia nervosa. Y-axis denotes beta-weight value of the BOLD signal in response to neutral and pre-stress food cues (x-axis).
Table 6

ROI ANOVA results for condition (pre-stress food cue, post-stress food cue) x group (BN, HC)

<table>
<thead>
<tr>
<th>Effect Region</th>
<th>Direction</th>
<th>Hemisphere</th>
<th>x (+/-)</th>
<th>y</th>
<th>z</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main effect of group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>HC &gt; BN</td>
<td>Bilateral</td>
<td>12</td>
<td>-8</td>
<td>-8</td>
<td>5.35*</td>
</tr>
</tbody>
</table>

Note. HC = healthy control, BN = bulimia nervosa. * p < .05, ** p < .01, *** p < .001.

**Figure 5.** Main effect of group for group x condition ANOVA in the nucleus accumbens. HC = healthy control, BN = bulimia nervosa, BN No Outlier = BN group with one participant’s data removed, as this participants data was an outlier. Y-axis denotes beta-weight value of the BOLD signal in response to neutral and pre-stress food cues (x-axis).
Table 7

*Whole brain ANOVA results for cue-type (neutral, pre-stress food cue) x group (BN, HC)*

<table>
<thead>
<tr>
<th>Effect Region</th>
<th>Direction</th>
<th>Hemisphere</th>
<th>Talairach coordinates (CM)</th>
<th>Cluster size (voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main effect of group (Figure 6)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Declive extending through: fusiform gyrus and lingual gyrus</td>
<td>HC &gt; BN</td>
<td>R</td>
<td>-15</td>
<td>-20</td>
</tr>
<tr>
<td>2. Declive extending through: lingual gyrus</td>
<td>HC &gt; BN</td>
<td>L</td>
<td>18</td>
<td>84</td>
</tr>
<tr>
<td><strong>Main effect of condition (Figure 7)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Middle Frontal gyrus extending through: precentral gyrus, BA 9, BA 6, caudate, cingulate gyrus, superior frontal gyrus</td>
<td>N &gt; Pre-stress food</td>
<td>R</td>
<td>-35</td>
<td>-1</td>
</tr>
<tr>
<td>2. Superior temporal gyrus extending through: BA 13, insula, postcentral gyrus, inferior parietal lobule, middle temporal gyrus</td>
<td>N &gt; Pre-stress food</td>
<td>L</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>3. Precentral gyrus extending through BA 6, middle frontal gyrus, cingulate gyrus, medial frontal gyrus, postcentral gyrus and inferior parietal lobule</td>
<td>N &gt; Pre-stress food</td>
<td>L</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>4. Lingual gyrus extending through: cuneus, middle occipital gyrus, declive</td>
<td>Pre-stress food &gt; N</td>
<td>L</td>
<td>16</td>
<td>83</td>
</tr>
<tr>
<td>5. Lingual gyrus extending through: cuneus, middle occipital gyrus, declive</td>
<td>Pre-stress food &gt; N</td>
<td>R</td>
<td>-20</td>
<td>84</td>
</tr>
<tr>
<td>6. Supramarginal gyrus extending through: inferior parietal lobule</td>
<td>N &gt; Pre-stress food</td>
<td>R</td>
<td>-42</td>
<td>46</td>
</tr>
<tr>
<td>7. Precentral gyrus extending through: IFG, BA 44, insula, BA 13, superior temporal gyrus</td>
<td>N &gt; Pre-stress food</td>
<td>L</td>
<td>46</td>
<td>-7</td>
</tr>
<tr>
<td><strong>Two-way interaction (Figure 8)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a. Cuneus</td>
<td>(see Figure 9)</td>
<td>L</td>
<td>6</td>
<td>78</td>
</tr>
<tr>
<td>1b. extending through fusiform gyrus, 1c. lingual gyrus, middle occipital gyrus (not pictured)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*Note.* BA = Brodmann area, HC = healthy control, BN = bulimia nervosa, N = neutral cues, R = right, L = left, CM = center of mass.
Figure 6. Main effect of group in the cue-type x group whole brain ANOVA ($F = 4.41, p = .05$). Red = HC > BN, blue = BN > HC. A: coronal slices $y = -55$ through $y = -83$, B: axial slices $z = -35$ through $z = -15$. Spacing for A and B = 4mm. 1 & 2 correspond to significant clusters surviving whole brain analyses presented in Table 7. 1 & 2 = declive. Images collected radiologically: right = left. Underlay is the average of all BN and HC anatomical images.
Figure 7. Main effects of cue-type in the cue-type x group whole brain ANOVA ($F = 5.55, p = .03$). Red = neutral cues > pre-stress food cues, blue = pre-stress food cues > neutral cues. Axial slices $z = -17$ through $z = 59$. Spacing = 4mm. 1-7 correspond to significant clusters surviving whole brain presented in Table 7. 1 = middle frontal gyrus, 2 = superior temporal gyrus, 3 = precentral gyrus, 4 = lingual gyrus, 5 = lingual gyrus, 6 = supramarginal gyrus, 7 = precentral gyrus. Images collected radiologically: right = left. Underlay is the average of all BN and HC anatomical images.
Figure 8. Two-way interaction for cue-type x group ANOVA ($F = 4.41, p = .05$) in the cuneus extending to fusiform gyrus. Color scale represents intensity of the $F$-statistic. A: sagittal slices $x = -18$ through $x = -2$, B: axial slices $z = -7$ through $z = 21$, C: coronal slices $y = -58$ through $y = -86$. Spacing for A, B, and C = 4 mm. $1a$ & $1b$ correspond to a significant cluster surviving whole brain presented in Table 7. Images collected radiologically: right = left. Underlay is the average of all BN and HC anatomical images.
Figure 9. Two-way interaction for cue-type x group ANOVA in the cuneus ($F = 4.41, p = .05$). HC = healthy control, BN = bulimia nervosa. Y-axis denotes beta-weight value of the BOLD signal in response to neutral and pre-stress food cues (x-axis).
Table 8

**Whole brain ANOVA results for condition (pre-stress food cue, post-stress food cue) x group (BN, HC)**

<table>
<thead>
<tr>
<th>Effect Region</th>
<th>Direction</th>
<th>Hemisphere</th>
<th>r</th>
<th>y</th>
<th>z</th>
<th>Cluster size (voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main effect of group (Figure 10)</strong></td>
<td></td>
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</tr>
<tr>
<td>1. Medial frontal gyrus extending through: anterior cingulate, BA 10</td>
<td>HC &gt; BN</td>
<td>L</td>
<td>0</td>
<td>-53</td>
<td>7</td>
<td>119</td>
</tr>
<tr>
<td>2. Culmen extending through: tuber</td>
<td>HC &gt; BN</td>
<td>R</td>
<td>-23</td>
<td>53</td>
<td>-19</td>
<td>101</td>
</tr>
<tr>
<td>3. Lingual gyrus (Peak) extending through: BA 19, BA 18, middle occipital cortex</td>
<td>BN &gt; HC</td>
<td>L</td>
<td>31</td>
<td>65</td>
<td>-1</td>
<td>59</td>
</tr>
<tr>
<td>4. Cingulate gyrus extending through: medial frontal gyrus middle frontal gyrus, BA 8, superior frontal gyrus</td>
<td>HC &gt; BN</td>
<td>L</td>
<td>14</td>
<td>-24</td>
<td>39</td>
<td>58</td>
</tr>
<tr>
<td>5. Posterior cingulate gyrus extending through: parahippocampal gyrus cingulate, precuneus</td>
<td>HC &gt; BN</td>
<td>L</td>
<td>7</td>
<td>47</td>
<td>13</td>
<td>55</td>
</tr>
<tr>
<td><strong>Main effect of condition (Figure 11)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Inferior parietal lobule extending through superior parietal lobule, angular gyrus, supramarginal gyrus, BA 7, BA 39</td>
<td>Pre-stress food &gt; post-stress food</td>
<td>R</td>
<td>-45</td>
<td>59</td>
<td>38</td>
<td>145</td>
</tr>
<tr>
<td>2. Middle occipital gyrus extending through middle temporal, cuneus, BA 19</td>
<td>Post-stress food &gt; pre-stress food</td>
<td>L</td>
<td>33</td>
<td>78</td>
<td>9</td>
<td>93</td>
</tr>
<tr>
<td>3. Middle occipital gyrus extending through: middle temporal gyrus, cuneus, BA 19</td>
<td>Post-stress food &gt; pre-stress food</td>
<td>R</td>
<td>-33</td>
<td>75</td>
<td>9</td>
<td>68</td>
</tr>
<tr>
<td>4. Inferior parietal lobule extending through: superior parietal lobule, angular gyrus, BA 39</td>
<td>Pre-stress food &gt; post-stress food</td>
<td>L</td>
<td>40</td>
<td>63</td>
<td>41</td>
<td>60</td>
</tr>
<tr>
<td><strong>Two-way interaction (Figure 12)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Culmen extending through: parahippocampal gyrus, lingual gyrus, BA 18</td>
<td>(see Figure 13)</td>
<td></td>
<td>14</td>
<td>51</td>
<td>-2</td>
<td>55</td>
</tr>
<tr>
<td>2. Precuneus extending through: BA 7</td>
<td>(see Figure 14)</td>
<td></td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>54</td>
</tr>
</tbody>
</table>

*Note. BA = Brodman area, HC = healthy control, BN = bulimia nervosa, R = right, L = left, CM = center of mass.*
Figure 10. Whole brain contrast for significant clusters with a main effect of group in the condition x group ANOVA ($F = 4.41$, corrected $p = .05$). Red = HC > BN, blue = BN > HC. Axial slices $z = -33$ through $z = 43$. Spacing = 4mm. 1-5 correspond to significant clusters surviving whole brain analyses presented in Table 8 (4 not pictured). 1 = medial frontal gyrus, 2 = Culmen, 3 = lingual gyrus, 4 = cingulate gyrus, 5 = posterior cingulate gyrus. Images collected radiologically: right = left. Underlay is the average of all BN and HC anatomical images.
Figure 11. Whole brain contrast for significant clusters with a main effect of condition in the condition x group ANOVA ($F = 4.41$, corrected $p = .05$). Red = pre-stress food cues > post-stress food cues, blue = post-stress food cues > pre-stress food cues. A: axial slices $z = 3$ through $z = 47$, B: coronal slices $y = -51$ through $y = -83$. Spacing for A and B = 4 mm. 1-4 correspond to significant clusters surviving whole brain analyses presented in Table 8. 1 & 4 = inferior parietal lobule, 2 & 3 = middle occipital gyrus. Images collected radiologically: right = left. Underlay is the average of all BN and HC anatomical images.
Figure 12. Two-way interaction for cue-type x group ANOVA ($F = 4.41, p = .05$) in the culmen and precuneus. Color scale represents intensity of the $F$-statistic. A: sagittal slices $x = -24$ through $x = -4$, B: coronal slices $y = -41$ through $y = -61$. Spacing for A and B = 4mm. 1 & 2 correspond to significant clusters surviving whole brain presented in Table 8. 1 = culmen, 2 = precuneus. Images collected radiologically: right = left. Underlay is the average of all BN and HC anatomical images.
**Figure 13.** Two-way interaction for the condition x group ANOVA in the culmen. HC = healthy control, BN = bulimia nervosa. Y-axis denotes beta-weight value of the BOLD signal in response to pre- and post-stress food cues (x-axis).

**Figure 14.** Two-way interaction for the condition x group ANOVA in the precuneus. HC = healthy control, BN = bulimia nervosa. Y-axis denotes beta-weight value of the BOLD signal in response to pre- and post-stress food cues (x-axis).
Figure 15a. Linear relationship of inferior parietal lobule and middle occipital gyrus activation for the HC group. Blue = pre-stress food cues, green = post-stress food cues. Y-axis denotes beta-weight values of the BOLD signal. Each participant is in the HC group is represented twice on the plot, one diamond and one triangle for each participant.

Figure 15b. Linear relationship of inferior parietal lobule and middle occipital gyrus activation for the BN group. Red = pre-stress food cues, orange = post-stress food cues. Y-axis denotes beta-weight values of the BOLD signal. Each participant is in the BN group is represented twice on the plot, one diamond and one triangle for each participant.
Figure 16. Trajectory of subjective craving levels during scan session. Y-axis = reported value of craving level on a scale of 0-6. Pre-Meal = craving rating before provision of standard meal, Post-Meal = craving rating 1 hour following meal consumption, Baseline = craving rating upon entering fMRI environment and following structural scan, Neutral = craving rating following neutral cues, Pre-Stress Food = craving rating following pre-stress food cues, Stress = craving rating following stress induction, Post-Stress Food = craving rating following post stress food cues. * = significant two-way interaction. Thicker, bold lines indicate significant increase or decrease in craving rating. Thin lines indicate no significant change in craving rating.
Figure 17. Trajectory of subjective stress levels during scan session. Y-axis = reported value of stress level on a scale of 0-6. Pre-Meal = stress rating before provision of standard meal, Post-Meal = stress rating 1 hour following meal consumption, Baseline = stress rating upon entering fMRI environment and following structural scan, Neutral = stress rating following neutral cues, Pre-Stress Food = stress rating following pre-stress food cues, Stress = stress rating following stress induction, Post-Stress Food = stress rating following post-stress food cues. * = significant two-way interaction. Thicker, bold lines indicate significant increase or decrease in stress rating. Thin lines indicate no significant change in stress rating.
Table 9

**HC Bivariate correlations of self-report data and subjective craving and stress during fMRI procedure**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Neutral</th>
<th>Pre-Stress</th>
<th>FCI Crave</th>
<th>Indulge</th>
<th>Baseline</th>
<th>Neutral</th>
<th>Pre-Stress</th>
<th>FCI Crave</th>
<th>TSST Stress</th>
<th>Post-Stress</th>
<th>Stressors</th>
<th>Restraint</th>
<th>Eating Concern</th>
<th>Shape Concern</th>
<th>Weight Concern</th>
<th>EDE Total</th>
<th>DEBQ External</th>
<th>EEI Affect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Crave</strong></td>
<td>* .68**</td>
<td>.81**</td>
<td>.87**</td>
<td>.87*</td>
<td>.69**</td>
<td>-.58</td>
<td>-.58</td>
<td>-.65*</td>
<td>-.70**</td>
<td>-.48</td>
<td>-.18</td>
<td>.82**</td>
<td>-.10</td>
<td>.69**</td>
<td>.61**</td>
<td>.65**</td>
<td>.10</td>
<td>.28</td>
<td>.75**</td>
</tr>
<tr>
<td><strong>Neutral Crave</strong></td>
<td><em>.99</em>*</td>
<td>.84**</td>
<td>.94**</td>
<td>.97**</td>
<td>.71**</td>
<td>-.37</td>
<td>-.37</td>
<td>-.22</td>
<td>-.35</td>
<td>-.30</td>
<td>.09</td>
<td>.76**</td>
<td>.40</td>
<td>.74**</td>
<td>.74**</td>
<td>.76**</td>
<td>.48</td>
<td>.66**</td>
<td>.75**</td>
</tr>
<tr>
<td><strong>Pre-Stress Crave</strong></td>
<td>* .84**</td>
<td>.57</td>
<td>.51</td>
<td>-.48</td>
<td>-.65**</td>
<td>-.47</td>
<td>-.46</td>
<td>-.40</td>
<td>.06</td>
<td>.67**</td>
<td>.18</td>
<td>.64**</td>
<td>.69**</td>
<td>.65**</td>
<td>.27</td>
<td>.43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TSST Stress</strong></td>
<td>* .58</td>
<td>.55</td>
<td>-.33</td>
<td>-.33</td>
<td>-.05</td>
<td>-.20</td>
<td>-.27</td>
<td>.22</td>
<td>.67**</td>
<td>.58</td>
<td>.74**</td>
<td>.80**</td>
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<td>.55</td>
<td>.76**</td>
<td></td>
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</tr>
<tr>
<td><strong>Post-Stress Crave</strong></td>
<td>* .91**</td>
<td>-.31</td>
<td>-.21</td>
<td>-.58</td>
<td>-.68**</td>
<td>-.43</td>
<td>-.08</td>
<td>.50</td>
<td>-.19</td>
<td>.38</td>
<td>.34</td>
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<td>.09</td>
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<tr>
<td><strong>FCI Crave</strong></td>
<td>* -.44</td>
<td>-.16</td>
<td>-.48</td>
<td>-.57</td>
<td>-.34</td>
<td>-.03</td>
<td>.41</td>
<td>-.20</td>
<td>.28</td>
<td>.23</td>
<td>.25</td>
<td>.34</td>
<td>.11</td>
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</tr>
<tr>
<td><strong>Indulge</strong></td>
<td>* .83**</td>
<td>.51</td>
<td>.65**</td>
<td>.82**</td>
<td>.25</td>
<td>-.37</td>
<td>.10</td>
<td>-.35</td>
<td>-.38</td>
<td>-.33</td>
<td>-.33</td>
<td>-.20</td>
<td>.20</td>
<td>.47</td>
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<td></td>
</tr>
<tr>
<td><strong>Baseline Stress</strong></td>
<td>* .64**</td>
<td>.65**</td>
<td>.82**</td>
<td>.27</td>
<td>-.37</td>
<td>.10</td>
<td>-.35</td>
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<tr>
<td><strong>Pre-Stress Stress</strong></td>
<td>* .90**</td>
<td>.63</td>
<td>.34</td>
<td>-.24</td>
<td>.76**</td>
<td>-.08</td>
<td>-.08</td>
<td>-.02</td>
<td>.20</td>
<td>.47</td>
<td>.24</td>
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</tr>
<tr>
<td><strong>TSST Stress</strong></td>
<td>* .79**</td>
<td>.50</td>
<td>-.49</td>
<td>.47</td>
<td>-.36</td>
<td>-.32</td>
<td>-.30</td>
<td>.03</td>
<td>.22</td>
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<td></td>
</tr>
<tr>
<td><strong>Post-Stress Stress</strong></td>
<td>* .26</td>
<td>-.36</td>
<td>.13</td>
<td>-.39</td>
<td>-.46</td>
<td>-.37</td>
<td>-.22</td>
<td>-.10</td>
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</tr>
<tr>
<td><strong>Stressors</strong></td>
<td>* -.27</td>
<td>.28</td>
<td>.01</td>
<td>.14</td>
<td>.02</td>
<td>-.08</td>
<td>.24</td>
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</tr>
<tr>
<td><strong>Restraint</strong></td>
<td>* .28</td>
<td>.92**</td>
<td>.80**</td>
<td>.90**</td>
<td>.11</td>
<td>.58</td>
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</tr>
<tr>
<td><strong>Eating Concern</strong></td>
<td>* .51</td>
<td>.59</td>
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Table 10

**BN Bivariate correlations of self-report data and subjective craving and stress during fMRI procedure**

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