

# The Impact of Acute Stress on the Neural Processing of Food Cues in Bulimia Nervosa: Replication in Two Samples

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The impact of acute stress on the neural processing of food cues in bulimia nervosa (BN) is unknown, despite theory that acute stress decreases cognitive control over food and hence increases vulnerability to environmental triggers for binge eating. Thus, the goals of this manuscript were to explore the impact of acute stress on the neural processing of food cues in BN. In Study 1, 10 women with *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association, 2013) BN and 10 healthy controls participated in an fMRI paradigm examining the neural correlates of visual food cue processing pre and post an acute stress induction. Whole brain analysis indicated that women with BN exhibited significant decreases in activation in the precuneus, associated with self-referential processing, the paracingulate gyrus, and the anterior vermis of the cerebellum. Healthy controls exhibited increased activation in these regions in response to food cues poststress. In Study 2, 17 women with *DSM-5* BN or otherwise specified feeding and eating disorder with BN symptoms participated in the same paradigm. A region of interest analysis replicated findings from Study 1. Replication of imaging findings in 2 different samples suggests the potential importance of these regions in relation to BN. Decreased activation in the precuneus, specifically, is consistent with models of BN that posit that binge eating serves as a concrete distraction from aversive internal stimuli.

### General Scientific Summary

Binge eating in bulimia nervosa is often triggered by acute stress and serves as a distractor from aversive thoughts about the self. This study indicates that women with bulimia nervosa (BN) experience dampened response in the precuneus and heightened response in other regions when presented with food cues following acute stress. The results suggest a neurobiological basis for escape theories of emotion regulation in BN.

**Keywords:** bulimia, neuroimaging, fMRI, stress, food cues

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Bulimia nervosa (BN) is a disorder classified by recurrent episodes of binge eating, compensatory behavior via purging, excessive exercise, or extreme caloric restriction, and self-evaluation strongly in-

fluenced by shape and weight (American Psychiatric Association, 2013). Emotion regulation models of BN suggests that binge eating reduces negative affect, and is thus negatively reinforced (Heatherton & Baumeister, 1991; Pearson, Wonderlich, & Smith, 2015). The act of binge eating allows an individual to focus on a concrete, present focused stimulus that reduces awareness of aversive cognitions about the self (Heatherton & Baumeister, 1991). Negative affect may be triggered by self-comparison or aversive self-related cognitions (Pearson et al., 2015). Consistent with these emotion regulation models, several laboratory and ecological momentary assessment studies demonstrate that stress and negative affect increase prior to binge eating, with several studies also demonstrating that negative affect decreases directly following binge eating (Becker, Fischer, Smith, & Miller, 2016; Berg et al., 2014; Cardi, Lepanen, & Treasure, 2015; Smyth et al., 2007; but see Haedt-Matt & Keel, 2011).

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Although this and other psychosocial models of binge eating are well-established, there is growing interest in the neurobiological substrates of BN (Berner & Marsh, 2014; Kaye et al., 2013). There are few studies that examine the impact of acute negative emotion or stress on the neural processing of food cues, however, and none that include individuals with BN (e.g., Born et al., 2010). This is surprising, as acute stress increases risk for binge episodes in individuals with BN, and the presence of food cues may increase risk for lapses in restraint (e.g., Smyth et al., 2007; Wallis & Hetherington, 2004). Thus, this pair of studies was designed to examine the impact of acute stress on the neural correlates of food cue reactivity and subjective response to food cues in women with BN. The goal of this research is to integrate premises from the emotion regulation theory of BN with neurobiological models, in order to help develop a more complete understanding of how brain function impacts psychopathology.

### Stress

Stress is understood to be “an experience in which the demands incurred by deviation from one’s normal state exceed one’s coping resources,” (Lazarus, 1993, p. 32). Acute stress may be a particularly important trigger for binge eating in women with BN (Goldschmidt et al., 2014; Smyth et al., 2007). There are several potential mechanisms via which acute stress may facilitate binge eating. Cognitive appraisals of stressful situations initiate a sequence of neurobiological events. These cognitive appraisals may be personally aversive, perhaps involving self-critical thinking regarding how one may handle the stressor. This, in turn, may motivate a desire to avoid. Although several brain regions are involved in the evaluation of stressful events, the precuneus plays an important role in self-referential processing (Cavanna & Trimble, 2006; Soares et al., 2013). Activity in this region is associated with body shape concern in BN and with rumination in non-ED samples (e.g., Hamilton, Farmer, Fogelman, & Gotlib, 2015; Lee et al., 2014). These, among other studies, indicate that this region plays a functional role in self-appraisal. Acute ego-threatening stress may trigger a dampening response in this region as resources are directed toward distracting external stimuli.

Following cognitive appraisal, the physiological response to acute stress is initiated in the hypothalamic pituitary adrenal (HPA) axis (Dickerson & Kemeny, 2004; Ulrich-Lai & Herman, 2009). The release of glucocorticoids following HPA axis activation facilitates increased release of dopamine into limbic regions, promoting increased activation (Born et al., 2010; Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009; Nieuwenhuizen & Rutters, 2008). In contrast, stress has a dampening effect on prefrontal regions, disrupting flexible problem solving, creativity, and other prefrontal cortex dependent processes (Arnsten, 2015). In sum, stress both invokes action and inhibits action (dopamine activation in sympathetic regions, quiet frontal regions). Thus, physiological responses to acute stress are associated with dampened activation in frontal regions and, plausibly, dampened response in the precuneus.

Behavioral studies suggest that both acute stress and the presence of food cues increases vulnerability to binge eating (Mills & Palandra, 2008; Tanofsky-Kraff, Wilfley, & Spurrell, 2000; Wallis & Hetherington, 2004). Although the neural correlates of acute stress itself have been studied (e.g., Pruessner et al., 2008), very

little is known about how viewing food cues during acute stress affects functional responses in the brain. Studies utilizing fMRI to examine responses to both stress and food cues indicate that changes in BOLD signals are present in similar regions across acute stress conditions and food cue conditions (Hommer et al., 2013; Jastreboff et al., 2013). Those studies that have examined BOLD response to food cues directly following acute stress have suggest that limbic regions exhibit decreased response while processing food cues under stress (Born et al., 2010).

### Current Study

Psychosocial models of binge eating in BN posit that acute stressors increase aversive self-related cognitions, negative affect, and avoidance of higher order cognition (Heatherton & Baumeister, 1991; Pearson et al., 2015). In turn, self-control is depleted and previously rewarding food stimuli may become more salient (Mather & Lighthall, 2012; Pearson et al., 2015). Given this, we anticipate that regions associated with self-referential cognition, cognitive control and reward may exhibit dampened response to food cues following acute stress, whereas regions associated with attention may exhibit increased response to these cues.

The goal of our current studies was to examine the neurobiological response to food cues under conditions of acute stress in women with BN. Two studies were conducted using the same fMRI paradigm. Briefly, participants viewed a series of neutral cues, followed by a series of highly palatable food cues. Following an acute stress induction in the scanner, participants were exposed to a different series of highly palatable food cues. Following each run, participants reported subjective levels of stress and craving for food. The first study included 10 women with *DSM-5* BN and 10 noneating disordered women. Whole brain analyses of within-subject and between-subjects responses were selected because of the exploratory nature of the research question. The second study included 17 women with *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association, 2013) BN or an otherwise specified feeding and eating disorder (OSFED) with BN symptoms. The regions showing significant results from Study 1 were used to create a priori regions of interest (ROI) for Study 2. Thus, we conducted analyses for the same paradigm on two different samples; a whole brain analysis in one sample, and an ROI analysis in the second sample.

### Study 1

The aim of Study 1 was to test neural responsivity to food cues following acute stress in women with BN. We examined the within participant response to food cues prior to and immediately following an acute stress induction, as well as compared the responses of BN participants to healthy noneating disordered controls. Acute ego threatening psychosocial stressors are associated with increased consumption of high fat/high sugar foods and snacking in daily life, with increased consumption of food in laboratory tasks, and thus are thought to be relevant to loss of control over eating behavior (O'Connor, Jones, Conner, McMillan, & Ferguson, 2008; Wallis & Hetherington, 2004). Individuals who restrain their eating appear to be most impacted by ego threatening stressors (e.g., Wallis & Hetherington, 2004). Thus, in our pair of studies, 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 and prepare and deliver a public speech on an unfamiliar topic, all while being socially evaluated on their performance. We used the same scan paradigm and assessments in both Study 1 and Study 2. A detailed synopsis of these methods is provided below.

Limbic regions involved in the regulation of cognitive control, attention and/or reward processing, such as the orbital frontal cortex (OFC) and the anterior cingulate cortex (ACC) may exhibit changes in activation during this task (e.g., Schienle, Schäfer, Hermann, & Vaitl, 2009). Hypoactivation in response to food cues in BN compared with controls in these regions is also reported (e.g., Kaye et al., 2013). As changes in BOLD response to food cues have been reported in these regions in previous ROI analyses, we hypothesized that women with BN would exhibit a within-subject decreased response to visual food cues in these regions following acute stress. We also hypothesized that they would exhibit a between-subjects decreased response to food cues following acute stress compared with noneating disordered women.

## Method

**Recruitment and inclusion/exclusion criteria.** Participants were recruited through advertisements in local newspapers and retail stores within the northeast Georgia region. All participants were screened via telephone for eligibility, and then invited to attend an assessment session if they met inclusion criteria (female sex, age 18 to 45 years, and BMI between 18.5–29.9 kg/m<sup>2</sup>). For the BN group, inclusion criteria also included the presence of at least four binge episodes and four purging episodes over the previous month. The presence of binge eating and purging for at least the past 3 months was confirmed during the assessment session. For the control group, the presence of eating disorder symptoms such as binge eating and purging was an exclusion criteria. Individuals with ferrous-based tattoos, contraindicated surgical or metal implants, women who were pregnant or possibly pregnant, women who were 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 were excluded from participation. The study was approved by the Institutional Review Board at the University of Georgia.

**Assessment session.** Participants were administered the following interviews: Structured Clinical Interview of *DSM Disorders-I* (SCID-I) for substance dependence, depression, and psychotic symptoms, and the Eating Disorder Examination (EDE) Interview. They also completed an assessment of conditions that would render them ineligible for scans, several self-report measures (not used in the current study) and a demographics questionnaire. Participant's height, weight, and waist measurements were collected to ensure eligibility for scanning. Following the prescanning assessment, participants were compensated for their participation in this portion of the study.

### Measures.

**Structured Clinical Interview of *DSM Disorders-I* (SCID-I; First & Gibbon, 2004).** The SCID-I modules for substance dependence, major depressive disorder, and psychosis were utilized. Because items from SCID-I was used for screening purposes via

telephone interview, participant scores from the assessment session were at or near zero.

**Eating disorder examination (EDE; Fairburn & Cooper, 1993).** The EDE was used to assess eating disorder symptoms and to assign eating disorder diagnoses. The EDE yields a frequency count of binge eating and purging behaviors within the past 28 days and throughout the past 6 months. The EDE composite score of four subscales (weight concern, shape concern, eating concern, and restraint) was used as a global score capturing levels of cognitive symptomatology and eating pathology. Cronbach's alpha for the Global score was .83. Each participant's EDE was reviewed by the PI and members of the research team to determine interrater agreement on objective versus subjective binges.

### Procedure.

**Scan session overview.** Following the assessment session, participants returned on a second day to acquire fMRI data. Each session began at approximately 1:30 p.m. as participants provided baseline ratings of subjective craving and stress. Each participant ate a standardized meal consisting of approximately 20% fat, 20% protein, and 60% carbohydrates. As some studies in non-BN populations have indicated that hunger and satiety may influence BOLD response to food cues (Siep et al., 2009) we wished to explore response to food cues without potentially confounding participants' response to food cues under stress with hunger. Participants waited an hour to begin the next portion of the study to allow for sufficient digestion. Participants rated their subjective levels of craving and hunger for a second time after the 1-hr waiting period. Participants were trained on three different tasks in the scanner; use of response button pads for subjective ratings for craving and stress, selection of picture stimulus orientation (horizontal vs. vertical), and selection of correct answers to arithmetic problems. We asked participants to select stimulus orientation throughout the scan in order to ensure that they were awake and attending to stimuli. Scanning began at approximately 3:00 p.m. After fMRI data acquisition, participants were debriefed and compensated for their participation.

**Stimuli.** Visual food and neutral cues were selected from the International Affective Picture Set (IAPS; Lang, Bradley, & Cuthbert, 2008). Additional photos were purchased from Shutterstock Photos (www.shutterstock.com) based on reference IAPS images. We selected the visual stimuli, photographs of high fat/high sugar (palatable) foods, based on previous research utilizing neuroimaging to study response to visual food cues. Foods that are viewed as highly rewarding/palatable are more likely to be those that are consumed in excess (e.g., Yeomans, Lee, Gray, & French, 2001). Additionally, individuals exhibit different BOLD responses when viewing photographs of high calorie foods versus low calorie foods (Killgore et al., 2003). An equal number of sweet and savory food cues were selected, and were pilot tested (data available upon request). Neutral cues were selected based on levels of visual complexity, brightness, and color composition consistent with the palatable food images.

**Stress induction.** Solving difficult arithmetic problems resulting in failure reliably induces stress (Dickerson & Kemeny, 2004; Kirschbaum et al., 1993; Pruessner, Hellhammer, & Kirschbaum, 1999), however, a 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. Serial subtraction tasks which include evaluative threat based on performance have been successfully adapted for the fMRI environment (Dedovic et al., 2005; Pruessner et al., 2008). Thus, we selected a publicly evaluated serial subtraction task for this series of studies. Before inducing stress, participants completed a series of simple subtraction problems under timed constraints (e.g.,  $9999 - 0 = 9999$ ). This was followed by serial 17 subtractions under timed conditions. Answers were selected from four options using a serial response pad and then subjects were informed of their accuracy. Participants were told that the accuracy of their performance was relayed to an audience consisting of members of the research team, who were recording their data.

#### fMRI data acquisition.

**Structural scan.** Data were acquired at the Bio-Imaging Research Center at the University of Georgia using a 3.0 T General Electric Signa Excite HDx System (Milwaukee, WI) and 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 (echo time [TE] < 3ms, time of repetition [TR] = 7.5, flip angle = 20°, matrix = 256<sup>2</sup>, field of view [fov] = 24 cm, in plane resolution of 0.9375 × 0.9375 mm, slice thickness = 1 mm, interscan spacing = 0). Following the structural scan, participants rated their subjective level of food craving and their subjective level of stress with a 4-button serial response pad which linked to a set of visual analog scales presented via the LCD goggles. The visual analog scales for subjective craving and stress ratings were analogous to those collected during the standardized meal.

**Functional scan.** Functional images were acquired sagittally using a T2\*-weighted gradient EPI pulse sequence in an oblique plane (TE = 25 ms, TR = 2000 ms, flip angle of 90°, a, FOV = 22 cm, in plane resolution of 3.75 × 3.75, 1 echo with interleaved slices of 4 mm thickness, 0.0 slice gap).

The study paradigm consisted of four functional runs. All visual cues were taken from or interpolated from the IAPS. In the first run, participants viewed eight blocks of three neutral cues ("neutral cues"; 18-s blocks, 6 s per cue). The second run consisted of eight blocks of three highly palatable foods cues ("pre-stress food cues"; 18-s blocks, 6 s per cue). 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-s blocks, 6 s per cue). Interspersed between all blocks of visual stimuli were baseline blocks of a centered crosshair for initial contrasts. Likewise, a centered crosshair was 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. To ensure participants were alert and attending to visual stimuli participants were instructed to respond to each visual cue by indicating stimulus orientation with the button response pad. No images were presented more than once in order to minimize habituation. Subjective ratings of in-scanner stress and craving were assessed immediately following each run using the button response pad.

**fMRI analyses.** Statistical analysis based on the General Linear Modeling (GLM) was used for fMRI analysis as implemented in the FMRIB Software Library (FSL). All MRI data were pre-processed and analyzed using fMRI Expert Analysis Tool (FEAT; v. 5.4) available as part of FSL (FSL; v .4.0) toolbox (fsl.fmrib.ox.ac.uk). Preprocessing procedures included separating images of the brain from the rest of the images using Brain Extraction Tool (BET). Preprocessing procedures included slice timing correction, high-pass temporal filtering (1/96Hz) to remove nonlinear drifts, and spatial smoothing with a Gaussian kernel (6 mm FWHM). Functional data were transformed into MNI-152 standard space (Montreal Neuroimaging Institute; MNI) using FLIRT (FSL).

First-level individual subject analyses were performed using FEAT. The first-level individual analysis modeled the three cue conditions (neutral cues, food cue prestress, food cue poststress) as explanatory variables and averaged across each run using a fixed effects model (Smith et al., 2004). Functional images were examined closely for motion or spike artifacts (motion >1.5 mm). Explanatory variables were created by convolving the stimulus onset times within each cue condition with a standard double gamma hemodynamic response function. Data were fitted to the model using FSL's implementation of the general linear model (GLM), with motion components included as confound EVs. In order to examine BOLD activation unique to food cues, at the second-level, contrasts of interests (food cue prestress—neutral cue, food cue poststress—neutral cue) were calculated for each participant using a fixed-effect analysis in FEAT. The resulting individual level contrasts represented BOLD activation prestress and poststress unique to food cues.

**Study 1 whole brain analysis.** Whole brain analyses were conducted to examine diffuse areas of activation in each group (BN, HC) for each condition (prestress food cues, poststress food cues) using a nonparametric repeated measures analysis of variance (ANOVA) for each group separately. The significance threshold for between-groups and time differences was set at  $p < .01$ , corrected for multiple comparisons across voxels using the threshold-free cluster-enhancement (TFCE) option in the randomize permutation-testing tool in FSL (Smith & Nichols, 2009).

Next, a fixed effects model was implemented to perform a  $2 \times 2$  (Group [BN, HC] × Condition [prestress, poststress food cues]) ANOVA on whole brain BOLD activation for examination of effects with FSL, with a conservative cluster mean threshold of  $Z > 2.3$  and a cluster-corrected significant threshold of  $p < .05$  (Beckmann, Jenkinson, & Smith, 2003). In order to correct for multiple comparisons, Monte Carlo simulations were performed on  $F$ -maps. In the occurrence of significant main effects and interactions,  $t$  tests were performed on surviving clusters to determine directionality of between-groups and within-group effects

## Results

**Participants.** Eighty-one participants were screened, 30 qualified, 27 completed an in-person assessment, and 21 completed this fMRI study. Due to technological difficulties, one participant's data were not included in analyses. The final sample consisted of 10 women with bulimia nervosa (BN group; mean age = 21 years,  $SD = 2.5$ ) and 10 healthy-weight, control women (HC group; mean age = 24 years,  $SD = 5.5$ ) all with normal or

corrected-to-normal vision. Women in the BN group reported an average of 8.4 binge days in the past month (range = 4–20;  $SD = 4.9$ ), an average of 8.60 (range = 0.0–30.0;  $SD = 8.9$ ) episodes of self-induced vomiting, an average of 9.1 (range = 0–50;  $SD = 26.4$ ) episodes of laxative use, an average of 4.2 (range = 0–26;  $SD = 8.3$ ) days of compensatory exercise, and an average of .5 (range = 0–3;  $SD = .97$ ) days of fasting. (See Table 1 for a comparison of EDE scores and BMI in BN and HC women). Women in the BN group predominantly described themselves as Caucasian (20% African American). All participants in the HC group described themselves as Caucasian.

**In-scanner craving and stress.** To examine between group differences for craving and stress on the day of the fMRI tasks, a series of repeated measures ANOVAs were carried out with group as the between-subjects factor and time as the within-subject factor. The main effect of group showed women with BN and HC women reported significant differences in craving,  $F(1, 19) = 12.72, p < .01$ . At each time point, women with BN reported higher levels of craving than HC women. (See online supplemental materials for a more detailed analysis of changes in craving throughout the paradigm.) The same design was utilized to examine changes in stress over the course of the scan session. A main effect of time indicated significant changes in stress for both groups from pre to post stress induction,  $F(1, 19) = 32.91, p < .001$ . There were no significant interaction effects, indicating that changes in stress over time did not differ by group status. A follow up paired samples  $t$  test indicated that stress levels increased following the induction,  $t(1,19) = 5.81, p < .001$ . Additionally, there were significant changes in stress levels for both groups following exposure to poststress food cues,  $F(1, 19) = 88.20, p < .001$ . A follow up paired samples  $t$  test indicated that stress levels significantly decreased following the post stress food cue exposure,  $t(1,19) = -9.20, p < .001$ . (More detailed descriptions of findings and figure are presented in the online supplemental materials.)

**Whole brain analysis results.** We first examined unique activation to food cues following stress within each group (BN and HC). Results are displayed in Tables 2–3 and Figures 1–3. The BN group exhibited increased BOLD signal to poststress food cues in occipital areas and decreased BOLD signal bilaterally in the anterior cingulate cortex (ACC), right orbitofrontal cortex (OFC) and bilaterally in the precuneus. The HC group exhibited increased BOLD signal for food cues following stress bilaterally in several

occipital regions (including the precuneus). The HC group did not exhibit decreased BOLD signal in any region.

We then conducted a  $2 \times 2$  (Group [BN, HC]  $\times$  Condition [prestress, poststress food cue]) ANOVA. There was a significant Group  $\times$  Condition interaction identifying regions of parietal (including precuneus and cuneus) and occipital cortices. Although the BN group exhibited decreased BOLD signal to food cues following stress in the right and left precuneus, left cuneus and right anterior vermis, the HC group demonstrated increased BOLD signal in the same regions.

## Discussion

Results of within-subject analyses suggest that both BN and HC women have increased visual processing of visual food stimuli following acute stress, consistent with previous findings of studies of response to food cues in nonclinical populations (Killgore et al., 2003; van der Laan, de Ridder, Viergever, & Smeets, 2011). Between-groups analyses indicated that women with BN exhibited decreased BOLD signal unique to the visual processing of food cues following stress bilaterally in the precuneus, left cuneus, and right anterior vermis of the cerebellum, whereas HC women exhibited increased signal in these regions.

Although we interpret these findings with caution given the exploratory nature of the study and the small sample size, there are several intriguing explanations for our findings. The precuneus may support higher-order cognitive functions, including self-referential cognitive processes, cognitive control, and default-mode network processing (Cavanna & Trimble, 2006; Soares et al., 2013). The BN group's decreased response in the precuneus for poststress food cues is consistent with reports of decreased BOLD signal in the default mode network during stress (Dagher, Tannenbaum, Hayashi, Pruessner, & McBride, 2009; Soares et al., 2013), which may indicate direction of attentional resources toward other stimuli, such as appetitive processing (Raichle & Snyder, 2007). Other studies document decreased BOLD signal in this region during cognitive control tasks (e.g., Fox et al., 2005; Spreng, 2012). We hypothesize that, consistent with emotion regulation theories of BN, decreased BOLD signal in this region represents a shift away from aversive self-related cognitions, instead of a focus on cognitive control. This is because the HC group exhibited increased signal in this region in the poststress food cue condition, suggesting that the response of the BN group to the task was unique. It is also important to note that the task was designed to include a social-evaluative component and induce ego-threatening stress. Consistent with theoretical predictions, we expect that women with BN may respond distinctly from noneating disordered women to food cues under these particular conditions. Another stress task, such as cold pressor task, might produce different results.

A significant interaction was observed in the anterior vermis, located within the cerebellum (Bapi, Miyapuram, Graydon, & Doya, 2006; Monte Bispo et al., 2010). Recently the role of the cerebellum in addiction has begun to be explored, although its role in processing of food is less well understood (e.g., Moulton, Elman, Becerra, Goldstein, & Borsook, 2014). The cerebellum may play a role in the modulation of emotional processes by integrating positive and negative affect inputs, similar to the way it modulates fine motor control by integrating sensory inputs (D'Angelo & Casali, 2013; Ito, 2006; Schmahmann, 2004). Food

Table 1  
Study 1 Between-Groups Comparisons of Eating Pathology

ED Symptoms and BMI	Group		$t(18)$
	BN (10)	HC (10)	
EDE Global	2.39 (1.44)	.26 (.44)	4.45****
EDE Shape	2.36 (1.71)	.38 (.68)	3.39**
EDE Weight	2.02 (1.63)	.26 (.51)	3.24**
EDE Eating	2.18 (1.55)	.14 (.27)	4.11**
EDE Restraint	3.02 (1.57)	.22 (.37)	5.49****
BMI	21.75 (1.59)	22.21 (1.28)	0.67

Note. BN = bulimia nervosa; HC = healthy-weight, control; EDE = Eating Disorder Examination; BMI = body mass index.

\*\*  $p < .01$ . \*\*\*\*  $p < .001$ .

Table 2  
Brain Regions Significantly Activated Poststress in Each Group in Study 1

	Cluster size (no. of voxels)	Brain regions	Max Z	MNI max Z
Pre > Post				
BN	1,068	Bilateral precuneus, bilateral cuneus	3.98	-4, -84, 28
	1,039	Right middle frontal gyrus, right frontal pole	4.8	32, 40, 30
	589	bilateral cingulate gyrus, bilateral paracingulate gyrus,	3.91	2, 24, 36
Controls	All <i>ns</i>			
Post > Pre				
BN	2,502	Right occipital pole, Right lateral occipital superior cortex, Right lingual gyrus	7.43	38, -96, 16
	1,023	Left occipital cortex, Left lateral occipital superior cortex	5.51	-8, -104, 24
Controls	10,366	Lingual gyrus, occipital fusiform gyrus, occipital pole	7.79	-8, -94, 2

*Note.* Voxels encompass the brain regions listed in column 3. Max Z indicates maximum  $z$  score (or peak) for the cluster value of those brain regions. Montreal Neuroimaging Institute (MNI) max Z indicates the coordinates of the maximum  $z$  values of the  $x$ -,  $y$ -, and  $z$ -coordinates of the cluster peak location in MNI space. BN = bulimia nervosa.

cues may have increased emotional salience for BN women, and decreased activation may perhaps indicate difficulty with discrimination of positive and negative emotional responses to food. Hypoactivation to food cues in the areas of the cerebellum has also been observed in women with anorexia (AN; Uher et al., 2004).

Taken together, results suggest that brain response to food cues under stress may be functionally related to diverting attentional control away from acute stressors for women with BN. Given the constraints of the current study, we conducted a replication study in a second, larger sample.

## Study 2

In Study 2, we recruited a new sample of BN participants, at a different institution, who underwent the same fMRI procedure. We did so because of the need to replicate the findings from Study 1, which was based on a small sample (Bakker, van Dijk, & Wicherts, 2012; Open Science Collaboration, 2015). There were two differences in the study design. First, we only recruited participants with BN or BN symptoms. We created regions of interest (ROIs) for Study 2 based on both significant within-subject BOLD response in the BN group from Study 1 whole brain analysis and from BOLD responses that were distinct from the HC group. Second, we did not ask participants to eat a standardized meal prior to the scan. Instead, we asked participants to complete a timeline follow back meal calendar with an interviewer. We entered time since last meal as a covariate in our analyses. We hypothesized that we would observe significantly increased BOLD signal in occipital regions, and significantly decreased BOLD signal in the precuneus and anterior vermis.

## Method

**Inclusion and exclusion criteria.** Inclusion criteria were:  $\geq$  one episode of binge eating and compensatory behavior (self-induced vomiting, laxative use, fasting for 24 hours, excessive exercise) in the past month, female sex, age 18 to 45 years, and BMI between 18.5 and 29.9 kg/m<sup>2</sup>. Exclusion criteria were: active substance use disorder (SUD) within past 12 months, psychotic disorder, left-handedness, and contraindications for scanning (e.g., metal implants).

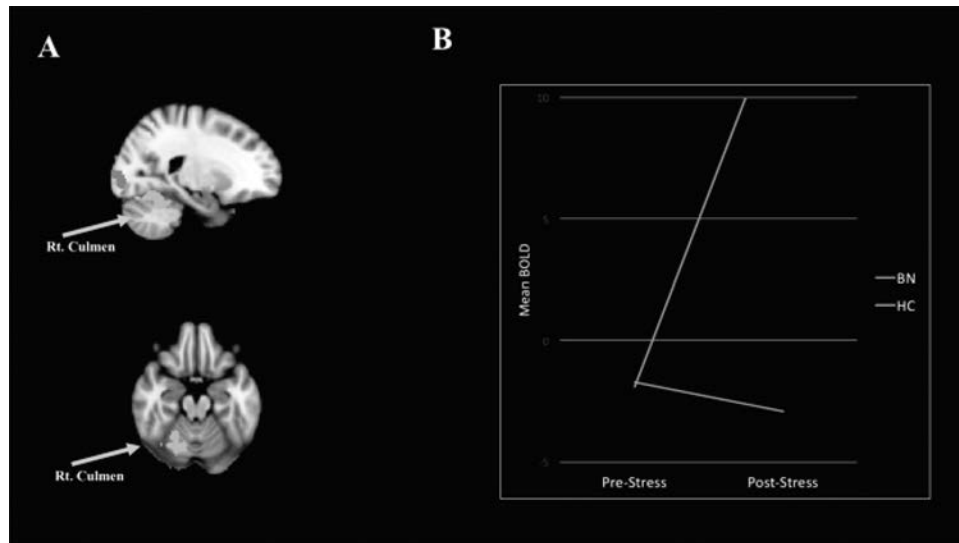
**Recruitment.** Participants were recruited via flyers from a large, Mid-Atlantic university, an outpatient eating disorder clinic, and Internet advertisements in the greater Washington, DC area. The goal of recruitment was to obtain a sample with a range of frequency of binge eating and compensatory behaviors. A total of 279 people responded to study advertisements, with 211 completing diagnostic telephone screens. Subsequently, 36 participants were invited to the laboratory to complete structured clinical interviews, 19 of which were ruled out (three with active SUD; one with a BMI below the minimum; nine with too infrequent episodes of binge eating and/or compensatory behaviors; two without significant eating pathology; one who elected to withdraw following the assessment; and three who were unable to complete the study due to complications surrounding their fMRI scans). Seventeen participants met inclusion criteria and completed the MRI session.

**Participants.** Participants were 17 right-handed women with symptoms of BN and normal or corrected-to-normal vision. Participants ranged in age from 18 to 40 years ( $M = 22.85$ ,  $SD = 5.42$ ). BMI ranged from 20.0–29.4 with a mean of 24.47 ( $SD = 3.25$ ). Two participants did not report additional demographic

Table 3  
Brain Regions Significantly Activated in the Group  $\times$  Condition Interaction in Study 2

No. of voxels	Brain regions	Max Z	MNI Max Z
2,152	Bilateral Precuneus, Bilateral Cuneus, Left occipital superior	6.53	-8, -94, 6
790	Right cerebral cortex, Right culmen, Right lingual gyrus	3.91	18, -52, -2
770	Right middle occipital gyrus, Right occipital superior	5.73	36, -94, 20

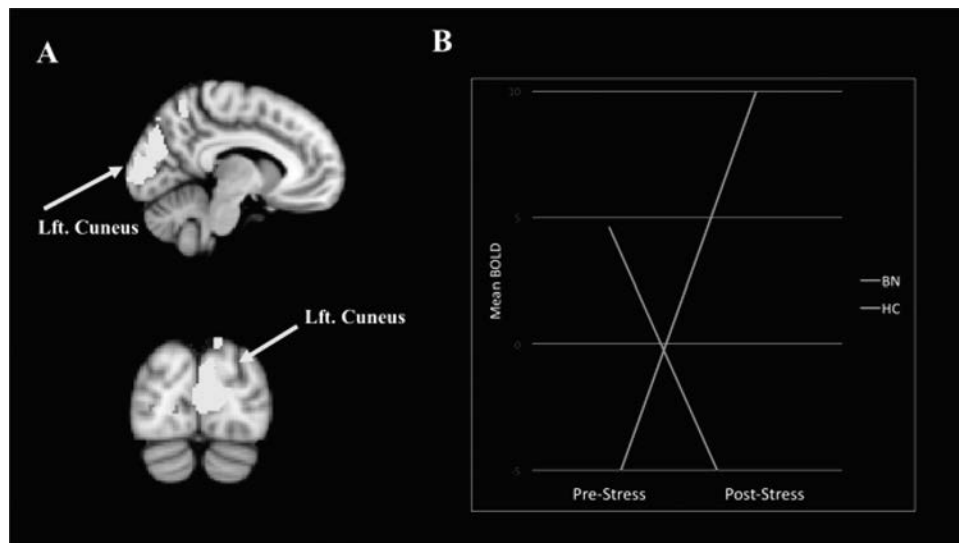
*Note.* Voxels encompass the brain regions listed in Column 3. Max Z indicates maximum  $z$  score (or peak) for the cluster value of those brain regions. MNI max Z indicates the coordinates of the maximum  $z$  values of the  $x$ -,  $y$ -, and  $z$ -coordinates of the cluster peak location in Montreal Neuroimaging Institute (MNI) space.



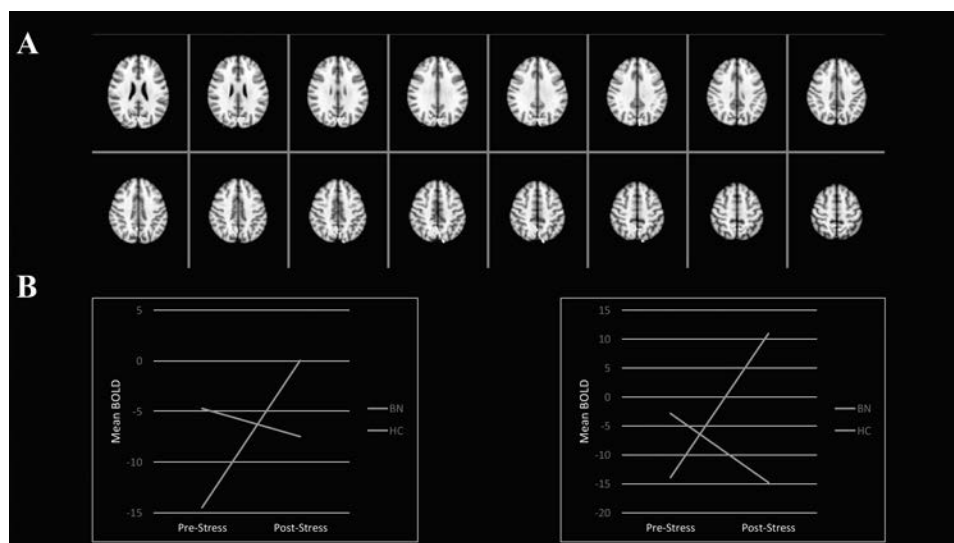
**Figure 1.** (A) Sagittal (top) and axial (bottom) planes of the significant clusters from the Group  $\times$  Condition interaction. The arrow pointing to the shaded area indicates significant clusters in the right culmen. (B) Post hoc analyses indicated that individuals in the bulimia nervosa (BN) group exhibited a decreased BOLD signal to food cues following stress in the culmen, whereas individuals in the healthy-weight, control (HC) group exhibited an increase in BOLD response to post stress food cues. See the online article for the color version of this figure.

information. Of the remaining participants, 71% (10) described themselves as Caucasian, 14% (2) as Hispanic American, and 14% (2) as Asian American. A total of 50% of the sample reported ever receiving treatment for an eating disorder, and only 2 participants reported being in treatment at the time of the study. Participants reported a mean number of 7.1 objective binge episodes in the past

month (OBEs; range = 1–15;  $SD = 3.8$ ), a mean number of 4.4 purging episodes (vomiting, laxative use, or diuretic use; range = 0–16,  $SD = 5.0$ ), a mean number of 6.6 excessive exercise episodes (range = 0–25,  $SD = 6.1$ ), and a mean of 1.0 days of fasting (range = 0–4,  $SD = 1.5$ ). The presence of binge eating and compensatory behaviors over a three month period was confirmed



**Figure 2.** (A) Sagittal (top) and coronal (bottom) planes of the significant clusters from the Group  $\times$  Condition interaction. The arrow pointing to the shaded area indicates significant clusters in the left cuneus. (B) Post hoc analyses indicated that individuals in the bulimia nervosa (BN) group exhibited a decreased BOLD signal to food cues following stress in the left cuneus, whereas individuals in the healthy-weight, control (HC) group exhibited an increase in BOLD response to post stress food cues. See the online article for the color version of this figure.



**Figure 3.** (A) Axial slices of significant clusters from the Group  $\times$  Condition interaction. The shaded area indicates significant clusters in the right and left precuneus. (B) Post hoc analyses indicated that individuals in the bulimia nervosa (BN) group exhibited a decreased BOLD response to food cues following stress in the left (bottom left graph) and right (bottom right graph) precuneus, whereas individuals in the healthy-weight, control (HC) group exhibited an increase in BOLD response to post stress food cues in the left (bottom left graph) and right (bottom right graph) precuneus. See the online article for the color version of this figure.

during the assessment section. Of the 16 participants, 12 met *DSM-5* criteria for BN, and the remainder were diagnosed with Otherwise Specified Feeding and Eating Disorder (OSFED).

**Procedural overview.** Following an assessment session, eligible participants returned to campus to acquire fMRI data at the George Mason University Krasnow Center. Upon arrival, participants rated their baseline levels of stress and food craving and completed a timeline follow back food log. Time in hours since the participant had last eaten was calculated. Participants were familiarized and trained on the scanner tasks and button response pad. Participants then completed the same assessments (SCID-I; EDE; questionnaires) and scan task as fully described in Study 1.

**fMRI data acquisition.** Data for Study 2 were acquired at the George Mason University MRI facility on a Siemens (Erlangen, Germany) 3.0 Tesla Allegra MRI scanner and a single channel birdcage head coil. Visual stimuli were displayed on a rear projection screen and viewed by participants on a coil mounted angled mirror. Functional images were acquired during four runs using a gradient echo  $T2^*$ -weighted interleaved echo planar imaging (EPI) pulse sequence for a total of 168 volumes. The imaging parameters for all functional scans were as follows: repetition time  $TR = 2350$  ms;  $TE = 30$  ms; flip angle =  $70^\circ$ ; FOV =  $192 \text{ mm}^2$ ; in-plane resolution =  $64 \times 64 \text{ mm}$ ; and 3 mm slices (1-mm gap) with axial acquisition. The first three volumes of each run were discarded to discount T1 saturation. Following each scan, one T1 whole-head structural scan was acquired to correct for spatial normalization and activation localization using a three-dimensional, magnetization prepared rapid-acquisition gradient echo pulse sequence. The following parameters were used for the structural scan:  $TR = 2300$  ms;  $TE = 3.37$  ms; flip angle =  $7^\circ$ ; FOV =  $1260 \text{ mm}^2$ ; in-plane resolution =  $256 \times 256 \text{ mm}$ ; and 1-mm slices with sagittal acquisition.

**ROI analysis.** A priori hypotheses were based on the location of regions of interest to food cues following stress reported in Study 1. The predetermined ROIs for analysis were the calcarine sulcus, anterior vermis of the cerebellum, cuneus, lingual gyrus, midoccipital gyrus, occipital superior gyrus, paracingulate gyrus, and precuneus. Significant clusters from Study 1 whole-brain results were matched with MNI coordinates of the Automated Anatomical Labeling (AAL) atlas. From these coordinates, ROI masks were created based on the AAL atlas (Tzourio-Mazoyer et al., 2002).

Data were preprocessed in FSL using the same methods as Study 1, including brain extraction, slice timing correction, high pass filtering, motion correction, and warping to the MNI template. First-level estimation of the response to the different stimuli were calculated using GLM within the FEAT module of FSL. Average estimates of the response to each condition (prestress food cues and poststress food cues) were calculated from the ROI regions for each subject. Paired sample  $t$  tests were used to compare activation in each region from the prestress food cue condition to the post-stress food cue conditions. As hunger and satiety may influence BOLD response to food cues (Siep et al., 2009), we conducted repeated measures ANOVAs with time since last meal as a covariate. Coordinates of activated voxels were transformed and calculated in Talairach space.

## Results

**In-scanner craving and stress.** A series of repeated measures ANOVAs were conducted to examine the effect of time and cue type on subjective ratings of craving and stress within the BN subjects. Consistent with Study 1, there was a significant change in subjective ratings of food craving from the presentation of neutral



cues to prestress food cues,  $F(1, 16) = 26.47, p < .001$ . A follow up paired sample  $t$  test indicated that craving significantly increased,  $t(1,16) = 5.19, p < .001$ . There were no significant differences in craving following the stress induction,  $F(1, 16) = .17, p < .68$ . There was a significant change in subjective ratings of stress following the stress induction,  $F(1, 16) = 17.56, p < .001$ . A follow-up paired sample  $t$  test indicated that stress increased,  $t(1,16) = 4.19, p < .001$ , suggesting that the stress induction activity was successful. (See the online supplemental material for more detailed analyses and figures.)

**ROI analysis results.** As in Study 1, we isolated activation specific to visual food cues by contrasting activation in response to neutral cues with activation in response to prestress food and poststress food in a prior ROI's identified from Study 1. (Analyses available upon request). Paired sample  $t$  tests and repeated measures ANOVAs with time since last meal entered as a covariate were then conducted in each a priori ROI to compare poststress and prestress activation in response to visual food cues. For all analyses, time since last meal ( $M = 2.5$  hours; range = .50–12.0 hours) did not alter the results nor did it account for significant variance in changes in BOLD values.

Several results from Study 1 were replicated. Participants exhibited significantly decreased BOLD response to food cues following the stress induction in the right anterior vermis of the cerebellum,  $F(1, 16) = 2.96, p < .01$ , right,  $F(1, 16) = 2.33, p < .05$  and left,  $F(1, 16) = 2.53, p < .05$  paracingulate gyrus, and left precuneus,  $F(1, 16) = 2.23, p < .05$ . Decreased BOLD response in the right precuneus approached significance,  $F(1, 16) = 2.06, p = .056$ .

The remaining significant findings from the whole brain analysis in Study 1 were not replicated. Participants did not exhibit significant changes in BOLD signal in the left ( $F(1, 16) = 1.59, p = .131$  and right,  $F(1, 16) = 1.44, p = .170$  calcarine sulcus, left anterior vermis,  $F(1, 16) = 1.24, p = .232$ , left,  $F(1, 16) = 1.61, p = .127$  and right,  $F(1, 16) = 0.94, p = .361$  cuneus, left,  $F(1, 16) = 0.71, p = .491$ , and right,  $F(1, 16) = 0.46, p = .649$  lingual gyrus, left middle occipital gyrus,  $F(1, 16) = 0.17, p = .868$ , and left,  $F(1, 16) = 1.14, p = .273$ , right,  $F(1, 16) = 0.71, p = .489$  superior occipital gyrus, nor right middle occipital gyrus,  $F(1, 16) = -0.27, p = .794$ .

## Discussion

Consistent with the results of Study 1, women with BN in Study 2 exhibited significantly decreased BOLD signal to food cues following stress in the right cerebellum, right and left paracingulate gyrus, and left precuneus. Replication of these findings in two separate samples of women with BN or BN symptoms, at two separate institutions, on two different MRI scanners, increases confidence in the reliability of the findings. The theoretical significance of these findings is that activation in these regions may be relevant to the pathology of BN. The theoretical significance of these findings, as well as the general limitations of these studies are discussed further below.

### General Discussion

To our knowledge, the current study is the first investigation of the neural correlates of food cue reactivity following a stress

induction in women with BN. In two separate samples of women with BN, we identified a unique response to visual food cues following an acute period of stress. During Study 1, we identified hyperactivation in cuneus (among other regions) and hypoactivation in the cerebellum (anterior vermis), limbic regions (paracingulate gyrus), and precuneus in women with BN. Healthy control women exhibited the opposite pattern of effects. In Study 2, using a within-subject design we again observed statistically significant hypoactivation in the right anterior vermis, bilateral paracingulate gyrus, and left precuneus.

Our findings are consistent with the characterization of binge eating as an escape from self-awareness, first proposed by Heatherton and Baumeister (1991). Hypoactivation in the precuneus was present in both samples of women with BN while viewing food cues following stress, and hyperactivation in this region was observed in control women during the same task. Several lines of research have converged to suggest that the precuneus plays a central role in self-referential processing and is functionally associated with mental representations of the self, including self-descriptions of personality and appearance (Cavanna & Trimble, 2006). First, it appears to play an important role in default mode network (DMN) processing (Fransson & Marrelec, 2008; Utevsky, Smith, & Huettel, 2014). The DMN is active when individuals are engaged in cognitive tasks that involve self-referential processing, such as autobiographical memory (Spreng, 2012). Functional connectivity analyses in large samples indicate that the precuneus demonstrates increased connectivity with the DMN while at rest (Utevsky et al., 2014). Increased connective density in this network is associated with rumination, further supporting hypotheses that this network is involved in self-referential cognitive processing (Hamilton et al., 2015).

Based on this literature, one hypothesis regarding the hypoactivation of the precuneus in BN during our task is that participants experienced decreased mental focus on the self when exposed to food cues. The stress induction task was designed to provide negative, ego-threatening feedback, and participants reported significant increases in subjective stress immediately following the task. This hypothesis is consistent with emotion regulation theories that suggest that women with BN shift away from self-awareness because of aversive cognitions regarding performance or negative social comparison, and shift focus to a more concrete stimulus, such as food (Heatherton & Baumeister, 1991; Pearson et al., 2015).

It is notable that we did not observe significant changes in limbic regions, with the exception of the paracingulate gyrus. Limbic regions have been identified in several studies using ROI analyses to examine response to food cues, both in BN and non-BN samples (Killgore et al., 2003). These analyses are based on the consistent findings in literature on cue reactivity in addictions, which indicates that activity in limbic regions differentiates clinical samples from controls (Zhang, Berridge, & Aldridge, 2012). However, several authors have suggested that whole brain analysis may yield different findings, which is what occurred in the current study (Engelmann et al., 2012; Schacht, Anton, & Myrick, 2013). In our studies, findings yielded through whole brain analysis were consistent with recent literature indicating that the precuneus, cerebellar regions, and occipital regions may play a larger role in appetitive, maladaptive behavior patterns than previously hypothesized (e.g., Engelmann et al., 2012; Schacht et al., 2013).

These results should be considered within the context of the following. First, only in Study 1 did we collect data in a control group as well as a BN group. We hypothesized that our results suggest that decreased precuneus response is associated with decreased self-awareness, in part because the control group exhibited the opposite response to our task. However, because we did not collect data from a control group in Study 2, we were not able to replicate this finding. Second, only in Study 1 did participants consumed a standardized meal prior to the scan session. Instead, we entered time since last meal as a covariate in analyses in Study 2. Hunger and satiety may influence BOLD response to food cues (e.g., Killgore et al., 2003) so it is possible that some of the results obtained in Study 1 that were not replicated in Study 2 are due to these variables. Third, in Study 2, half of the participants had been in treatment and we did not assess for the number of individuals seeking treatment in Study 1. Subtle clinical differences between the two groups may exist that we were not aware of and may contribute to differences in results. Additionally, only in Study 1 did all participants complete the scan at the same time of day. Thus, diurnal fluctuations in hunger and satiety may also influence findings.

Finally, the sample size in both studies was relatively small and only included females, increasing risk of spurious findings due to sample specific individual differences and lack of generalizability to males with BN. However, given that we replicated several of the primary findings from Study 1 to Study 2, there is reason to feel confident that these results are meaningful and relevant to the pathology of BN. An additional concern regarding small sample sizes is the risk of Type II error, in which true effects are not identified or replicated (Lieberman & Cunningham, 2009). We obtained several significant results in Study 1 (such as increased BOLD response in BN women in occipital regions) that were not replicated in Study 2. Due to power limitations, we cannot know whether this failure to replicate was due Type II error or reflects the absence of a true finding.

In sum, the current study provides support for a unique neural response to visual food cues following an acute stress induction in women with BN. In two separate studies, women with BN showed unique patterns of hypoactivation to visual food cues following stress. These results indicate that at the neurobiological level, there is dampened response in women with BN to food cues following acute ego-threatening stress in regions associated with thoughts about the self, and increased response in regions associated with attention. This suggests a possible neurobiological basis for the increased salience of food cues and use of food as a distractor during periods of acute stress in BN.

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