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Authors

Bischoff-Grethe, Amanda
Wierenga, Christina E
Bailer, Ursula F
et al.

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Satiety Does Not Alter the Ventral Striatum's Response to Immediate Rewards in Bulimia Nervosa

Amanda Bischoff-Grethe, Ph.D.[1], **Christina E. Wierenga, Ph.D.**[1,2], **Ursula F. Bailer, M.D.**[1,3], **Samuel M. McClure, PhD.**[4], **Walter H. Kaye, M.D.**[1]

[1]Department of Psychiatry, University of California, San Diego, La Jolla, CA

[2]VA San Diego Healthcare System, San Diego, CA

[3]Department of Psychiatry and Psychotherapy, Division of General Psychiatry, Medical University of Vienna, Vienna, Austria

[4]Department of Psychology, Arizona State University, Tempe, AZ

Abstract

Individuals with bulimia nervosa (BN) cycle between periods of binge-eating and compensatory behavior, and periods of dietary restraint, suggesting extremes of under- and over-control that may be metabolic-state related. This study examined the influence of hunger and satiety on impulsivity and neural responding during decision-making. Twenty-three women remitted from BN (RBN) and twenty healthy comparison women (CW) performed a delay discounting task after a 16-hour fast and following a standardized meal during functional neuroimaging. A dual-systems approach examined reward valuation (decision trials where the early reward option was available immediately) and cognitive control (all decision trials). Interactions of Group × Visit (Hungry, Fed) for immediate rewards revealed that CW had greater activation when hungry vs. fed in the ventral striatum and dorsal caudate, whereas RBN had greater response when fed vs. hungry in the dorsal caudate. Compared to CW, RBN showed decreased response when hungry within the left dorsal caudate and ventral striatum, and increased response when fed in bilateral dorsal caudate. No differences were found within cognitive control regions or with choice behavior. Reward sensitivity is normally increased when hungry and decreased when fed; our findings in CW provide further support of hunger-based reward sensitivity within the striatum. However, RBN showed no differences for hunger and satiety in the ventral striatum, and greater activation in the dorsal caudate when fed compared to hungry. This suggests RBN may be less sensitive to reward when hungry but do not devalue reward when satiated, indicating altered metabolic modulation of self-regulatory control.

General Scientific Summary:

Corresponding Author: Amanda Bischoff-Grethe, PhD, Associate Professor of Psychiatry, University of California, San Diego, 9500 Gilman Drive, MC 0738, La Jolla, CA 92093-0738, agrethe@health.ucsd.edu.

Author Note: Preliminary data and analyses associated with this manuscript were previously presented at the Society for Neuroscience and the American College of Neuropsychopharmacology conferences. The study (Neurobiology of Anorexia and Bulimia Nervosa, #080019) was conducted according to the IRB regulations of the University of California, San Diego Human Research Protections Program.

This study found that brain reward response in adult women remitted from bulimia nervosa remained elevated after a meal, whereas healthy women demonstrated the typical decrease in reward response that reflects satiety signaling a decreased drive to eat when full. This suggests that individuals with bulimia nervosa may not devalue reward when full and may help explain why individuals with bulimia nervosa may binge eat beyond satiation.

Keywords

Bulimia nervosa; fMRI; impulsivity; dorsal caudate; ventral striatum

INTRODUCTION

Bulimia nervosa (BN) is characterized by cycles of binge eating, defined as excessive food consumption over a short time period combined with a sense of “loss of control” over eating (Shoemaker et al., 2010; Wolfe, Baker, Smith, & Kelly-Weeder, 2009), and compensatory (e.g. self-induced vomiting) behavior. Between binge/purge episodes, individuals with BN commonly engage in dietary restraint (American Psychiatric Association, 2013; Weltzin, Hsu, Pollice, & Kaye, 1991). Theoretical models of BN have proposed these cyclical binge-purge behaviors serve to regulate emotions (Lavender et al., 2014), are reinforcing (Pearson et al., 2016), or may result from depleted energy stores and hunger (Fairburn, Cooper, Shafran, Bohn, & Hawker, 2008). For example, cognitive behavioral models posit that dietary restriction is a risk factor for binge-eating; thus, treatment may focus on regularizing meals to reduce periods of hunger. However, these models assume that hunger substantially increases impulsivity and reward seeking to drive binge-eating. Moreover, few models acknowledge the puzzling ability of individuals with BN to alternate between over- and under-control.

Individuals with BN may be both impulsive and less concerned with future consequences, yet also inhibited, obsessive, and inflexible (Cassin & von Ranson, 2005), suggesting dysregulated cognitive control (Marsh et al., 2011; Wu et al., 2013). Behaviorally, individuals with BN experience poor cognitive flexibility (Tchanturia et al., 2012) and may have impaired decision-making (Boeka, 2006; Brogan, 2010; Matsumoto et al., 2015). Neuroimaging studies of individuals with both active and remitted BN report frontostriatal perturbations (Marsh et al., 2009; Wagner et al., 2010) consistent with altered executive and inhibitory function and perturbed reward processing (Wagner, et al., 2010) that may contribute to disordered eating behavior. However, since individuals with BN experience these alternating periods of over- and under-control in the context of hunger and satiety, it is possible that metabolic signaling disrupts reward and motivation processing, thereby impairing their ability to inhibit eating when full, and failing to motivate eating when hungry.

A dual-systems model may help explain the ongoing conflict between impulsive behavior and self-control in individuals with active BN. The Competing Neurobehavioral Decision Systems model proposes two neurobiological systems that reflect impulsivity vs. more deliberate control, and it is their interaction that drives choice behavior (Bickel et al., 2007;

Hofmann, Friese, & Strack, 2009). Delay discounting tasks are thought to capture these competing processes (McClure & Bickel, 2014). Participants must choose between smaller-sooner rewards and larger-later rewards; a preference for smaller-sooner rewards reflects impulsivity and increased delay discounting (i.e., the decline of a reward's value relative to how long one must wait to receive the reward). Studies in addictions research have supported the relationship between delay discounting and the dual-systems model (Bickel et al., 2019). For eating disorders, some behavioral studies in individuals with bulimic symptoms, as with BN, binge eating disorder, or the binge-purge subtype of anorexia nervosa, report a preference for early rewards (Kekic et al., 2016; Steward et al., 2017), suggesting increased impulsivity, although others report no significant differences relative to healthy controls (Bartholdy et al., 2017). Delay discounting neuroimaging studies in healthy individuals have consistently implicated regions associated with reward valuation/impulsivity and cognitive control. Reward processing regions include the striatum (Wittman, Movero, Lane, & Paulus, 2010) and rostral anterior cingulate cortex to valuate incentives (Noda et al., 2020), the dorsal anterior cingulate cortex, which processes difficult choices (Massar, Libedinsky, Weiyan, & Huettel, 2015), and the posterior cingulate, which may be sensitive to immediate rewards (Sripada, Gonzalez, Phan, & Liberzon, 2011) and discounting behavior (Miedl & Buchel, 2012). In comparison, cognitive control regions including the middle frontal gyrus, ventrolateral prefrontal cortex (VLPFC), and superior parietal cortex are engaged with inhibition, attention, and value accumulation (Massar, et al., 2015; Rodriguez, Turner, Van Zandt, & McClure, 2015; Schuller, Kuhn, Jessen, & Hu, 2019). As part of the salience network, the insula calculates incentive value and assists decision-making by triggering cognitive control signals (Menon & Uddin, 2010; Sellitto, Ciaramelli, Mattioli, & di Pellegrino, 2016; Wittman, et al., 2010). While studies have implicated frontostriatal regions as aberrant in individuals with BN (Berner & Marsh, 2014), there are no reported neuroimaging studies of delay discounting in association with BN and satiety.

Although delay discounting is a relatively stable trait, it can be manipulated by context (Peters & Buchel, 2011; Scholten et al., 2019). Hunger, for example, can increase delay discounting (Bartholdy, Cheng, Schmidt, Campbell, & O'Daly, 2016) and risk-seeking behavior (Levy, Thavikulwat, & Glimcher, 2013; Shabat-Simon, Shuster, Sela, & Levy, 2018) while decreasing self-control (Gaillot, 2013; Skrynka & Vincent, 2019) in healthy individuals. Thus, an important question is whether BN-associated impulsivity might be influenced by satiety, as binge episodes occur despite increasing levels of satiety.

This study examined the influence of hunger and satiety on impulsivity in women remitted from BN (RBN) relative to control women (CW). Participants performed a delay discounting task (McClure, Laibson, Loewenstein, & Cohen, 2004) during functional neuroimaging when fasted and when fed on two separate visits. We hypothesized that the RBN group would show an enhanced preference for immediate rewards relative to the CW group, as evidenced by more discounting and greater blood oxygen level-dependent (BOLD) response within the striatum. We also hypothesized that the CW group would show elevated BOLD response to immediate rewards when hungry relative to when fed, reflecting state-based differences in reward processing (Bartholdy, Cheng, Schmidt, Campbell, & O'Daly, 2016; Levy, et al., 2013; Shabat-Simon, et al., 2018). However, given that individuals with

BN tend to be impulsive regardless of consequences, we hypothesized the RBN group would show an elevated BOLD response regardless of satiety level.

METHODS

Participants

Twenty-six RBN (6 with a prior history of anorexia nervosa [AN] restricting type, and 8 with a prior history of AN binge-eating/purging type) were recruited nationally, and 22 healthy control women (CW) were recruited locally through advertisements. Seventeen CW were also part of a prior comparison with women remitted from AN (Wierenga et al., 2015), and all CW and RBN participants also took part in a study examining the effects of hunger and satiety on pleasant taste (Ely et al., 2017). Remittance was defined as maintaining more than 85% of average body weight, regular menstrual cycles, and no eating disorder behaviors for at least one year prior to study entry (Wagner et al., 2006). All participants were assessed for past DSM-IV Axis I diagnosis, but none had a current DSM-IV diagnosis, a history of alcohol or drug abuse or dependence 3 months prior to the study, or any medical or neurologic concerns contraindicative to MRI. The study was conducted according to the IRB regulations of the University of California, San Diego. All participants provided written, informed consent.

Assessments

Current and past psychiatric history was assessed with the Mini International Neuropsychiatric Interview (M.I.N.I. (Sheehan et al., 1998)) or the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I (First, Biggon, Spitzer, Williams, & Benjamin, 1997)). Groups were balanced across interviews (Table 1). The M.I.N.I. has been validated against the longer SCID Patient Version and is considered a more time-efficient alternative (Sheehan, et al., 1998).

Participant characteristics were assessed with the State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970), the Beck Depression Inventory-II (BDI-II) (Beck, Steer, & Brown, 1996), the Temperament and Character Inventory (Cloninger, Przybeck, Svrakic, & Wetzel, 1994), the Barratt Impulsiveness Scale-11 (Patton, Stanford, & Barratt, 1995), and the Eating Disorders Inventory-2 (Garner, 1991). At 1:30 pm one day prior to the first scan, blood samples were drawn to measure baseline levels of estradiol to confirm participants were in the follicular phase of their menstrual cycle. Participants also completed Likert scales rating anxiety and hunger ranging from 0 (not at all) to 7 (extreme) at 3:00 pm the day before a scan visit (baseline), and at 6:45 am (awakening), 8:45 am (pre-scan), and 11:00 am (post-scan) the day of a scan visit.

Imaging Procedures

Participants performed a delay discounting task (McClure, et al., 2004) during functional neuroimaging at 9 am on 2 visits 24 hours apart. Participants fasted for 16 hours prior to the hungry state scan. For the fed state, participants consumed a personalized, standardized breakfast, determined by the individuals' BMI, and containing 30% of overall daily caloric needs (~450 kilocalories, with a macronutrient distribution of 53% carbohydrates, 32% fat,

and 15% protein) 2 hours prior to the scan. All participants were housed and provided meals at the UCSD Clinical & Translational Research Institute to ensure 100% compliance. Visit order was randomized across participants.

Delay discounting task.—Trials lasted 15 sec. Two choices were presented, with each choice including a monetary amount and a time delay for receiving that amount (Figure 1). The first two trials were fixed to allow participants to acclimate to the task: participants chose between the same dollar amount available at two different delays (i.e., $27.10 available in 1 week vs $27.10 available in 1 month), followed by one where the earlier, smaller dollar amount was less than 1% of the larger, delayed amount (i.e, $0.16 today vs. $34.04 in 6 weeks). The remaining 30 trials per run were random. The delay to the early reward, *d*, was selected from the set {today, 2 weeks, 4 weeks}. The delay between the late reward, *d'*, and the early reward (i.e., *d'-d*) was selected from the set {2 weeks, 4 weeks}, provided that the late reward occurred no more than 6 weeks from the study date. The reward percent difference (i.e., (*$R'-$R*)/*$R*) was selected from the set {3%, 5%, 10%, 15%, 25%, 35%}. Participants completed two 488 sec runs during each visit. Upon study completion, one trial was randomly chosen, and the participant received their selected reward at the specified temporal delay.

Image acquisition.—Data were collected using an 8-channel head coil on one of two 3T scanners (GE Medical Systems, Milwaukee, WI): a Signa HDx (TR = 2000 ms, TE = 30 ms, flip angle = 80°, 64×64 matrix, ASSET factor = 2, 40 2.6-mm axial slices with a 0.4-mm gap, 244 volumes) and a Discovery MR750 (TR = 2000 ms, TE = 30 ms, flip angle = 80°, 64×64 matrix, ASSET factor = 2, 40 3.0-mm axial slices, 244 volumes). The first four volumes of each run were discarded to discount T1 saturation. Field maps were acquired to correct for susceptibility-induced geometric distortions. High-resolution T1-weighted fast spoiled gradient echo (FSPGR) anatomical images (Signa HDx: TR = 7.7 ms, TE = 2.98 ms, flip angle = 8°, 192×256 matrix, 172 1-mm slices; MR 750: TR = 8.1 s, TE = 3.17 ms, flip angle = 8°, 256×256 matrix, 172 1-mm slices) were obtained sagittally for spatial normalization and activation localization.

Image preprocessing.—Data were preprocessed using Analysis of Functional NeuroImages (AFNI) (Cox, 1996), FreeSurfer (Fischl, 2012), and FSL software (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Functional images were slice-time corrected, motion-corrected, and aligned to high-resolution anatomical images using AFNI's align_epi_anat.py (Saad et al., 2009). Time points with isolated head movements not corrected by coregistration were censored. T1-weighted images were skull-stripped with FreeSurfer's mri_watershed (Segonne et al., 2004) and aligned to the MNI-152 template via linear, followed by nonlinear, registration with FSL's FLIRT and FNIRT (Andersson, Jenkinson, & Smith, 2010; Jenkinson & Smith, 2001). Following standard space alignment, functional data were resampled to 3 mm isotropic voxels and smoothed to a 6.0 mm FWHM Gaussian kernel.

Data Analysis

Behavioral analysis.—The probability of selecting the earlier reward was calculated as the percent of trials where participants selected the early option for all trials. Data were submitted to a 2 Group (RBN, CW) × 2 Visit (Hungry, Fed) × Temporal Delay (i.e., the time period between the early and late choice; 2 weeks, 4 weeks) linear mixed effects (LME) analysis in R (Pinheiro et al., 2013) to determine whether there were differences in preferences for early rewards due to diagnosis, visit, or the delay for the higher payout.

Participant choice data was fit to a hyperbolic discounting function (Mazur & Coe, 1987) to calculate each subject's discount factor, k. Higher k values correspond to greater discounting, reflecting greater impulsivity. Several data points were excluded due to poor estimates of choice behavior ($p > .1$, determined by likelihood-ratio test), or were outliers (i.e., cook's distance greater than four times the mean (Cook, 1977)), reducing the number of usable datasets (CW: 12 hungry, 19 fed; RBN: 21 hungry, 20 fed). Discounting data were log-transformed and submitted to a 2 Group (RBN, CW) × 2 Visit (Hungry, Fed) LME analysis. Post hoc analyses were performed using R's emmeans and false discovery rate corrected, and standardized effect sizes (ES) were reported.

Neuroimaging analysis.—Statistical analyses were performed using two separate general linear models, consistent with the dual-systems model of decision-making (McClure, et al., 2004). To model reward *valuation* (i.e., incentive of immediate rewards, or impulsivity), the first model only included regressors for trials where a reward available immediately (i.e., "Today"). To model *cognitive* control (i.e., deliberate decision-making), a second model included all trials. Regressors were based on the choice decision period, defined as the time from when the choice was presented until the participant made a selection, and convolved with AFNI's SPMG3 basis function. Six motion parameters (3 rotations, 3 translations) were included as nuisance regressors.

Regions of interest (ROIs) were based on the Harvard-Oxford atlas. Reward valuation ROIs included the ventral striatum, dorsal caudate, anterior cingulate (ACC), and posterior cingulate (Figure S1A). The ventral striatum was defined as the nucleus accumbens extending into the rostroventral caudate and ventrolateral putamen, and the dorsal caudate was defined as the caudate nucleus lying anterior to the anterior commissure in the coronal plane (Martinez et al., 2003; Mawlawi et al., 2001). The ACC was comprised of the rostral ACC, known to project to the limbic striatum (Haber & Knutson, 2010), and the cognitive zone of the dorsal ACC, which projects to executive striatal and prefrontal regions. The posterior cingulate was used in its entirety. Cognitive ROIs included the middle frontal gyrus (a core region of the dorsolateral prefrontal cortex), insula, superior parietal cortex, and VLPFC (Figure S1B). The middle frontal gyrus, insula, and superior parietal were used in their entirety. The VLPFC was defined by combining the three subdivisions of the inferior frontal gyrus (pars opercularis, pars triangularis, and pars orbitalis) and removing areas medial to the most medial aspect of the inferior frontal sulcus (to avoid including the operculum). The edges of the middle frontal gyrus and VLPFC masks were eroded by one voxel to minimize the potential influence of signal dropout (Leung & Cai, 2007).

We employed a Group (RBN, CW) × Visit (Hungry, Fed) LME analysis in R for the valuation and cognitive models. Subjects were nested within scanner and treated as random effects (Glover et al., 2012), with Group and Visit as fixed effects. Intrinsic smoothness was estimated using AFNI's 3dFWHMx (acf option). Minimum cluster sizes were calculated with AFNI's 3dClustSim (acf option) for multiple comparisons correction across eight ROIs, corresponding to a voxel-wise probability of $p < .002$ and a clusterwise probability of $\alpha < .00625$ (two-sided). Post hoc analyses were performed using R's emmeans and false discovery rate corrected. Exploratory whole-brain voxel-wise analyses were also performed (see supplement).

Exploratory robust regression analyses.—Exploratory Huber robust regression analyses (Huber, 1964) examining the relationship between valuation or cognitive control neural activation with illness severity (worst past binge eating frequency, self-induced vomiting frequency, illness duration), k-value, trait anxiety, and harm avoidance in RBN are described in the supplement.

Exploration of prior diagnostic history.—As several individuals had a prior history of either AN restricting or AN binge-purge subtypes, we also examined behavioral and neural response for potential differences between RBN with a prior history of AN (AN+) in comparison to RBN who never had an AN diagnosis (AN−). Smaller sample sizes precluded a comparison based on AN subtype.

RESULTS

Demographics

Two CW and two RBN were excluded due to unusable neuroimaging data, and one RBN was excluded due to only selecting the larger-later reward (final sample: 23 RBN, 20 CW). Groups were of similar age, body mass index, and education, with similar lifetime histories of anxiety, alcohol use disorder, and substance use disorder (Table 1). RBN reported higher levels of state/trait anxiety, harm avoidance, and perfectionism relative to CW. Although RBN scored higher on the BDI-II compared to CW, no participants met criteria for depression. Relative to CW, RBN reported a higher rate of lifetime major depressive disorder.

Behavioral Analysis

Pre- and post-scan assessments.—Participants reported greater hunger during the Hungry condition relative to the Fed condition (Figure 2A), with greater hunger at the post-scan interval relative to the pre-scan interval overall. Similarly, participants reported greater thirst during the Hungry condition relative to the Fed condition (Figure 2B), as well as greater thirst at the post-scan interval relative to the pre-scan interval. The main effect of Group and all interactions were not significant for either hunger or thirst ratings.

Task performance.—There was a main effect of percent difference (Figure S2A); participants were less likely to choose the early option as the percent monetary difference between choices increased [$F(2,205) = 220.6$, $p < .001$; from 3%–5% to 10%–15%, $t =$

7.8, $p < .001$, ES = 3.55; from 3%–5% to 25%–35%, $t = 20.8$, $p < .001$, ES = 9.42; from 10%–15% to 25%–35%, $t = 13.0$, $p < .001$, ES = 5.87]. No main effect of Group, Visit, or interactions were observed. For the response time analysis, CW responded more quickly than RBN [($F(1,41) = 4.3$, $p = .045$]. All participants responded more quickly when hungry [$F(1,123)=8.8$, $p = .004$], and all participants responded more quickly for easy decision trials relative to hard decision trials [$F(1,123)=5.9$, $p = .017$]. No interactions were observed (Figure S2B). A Group × Visit LME analysis for the discounting rate did not detect a main effect of Group, Visit, or an interaction (RBN hungry: M = 0.068, SD = 0.05; RBN fed: M = 0.063, SD = 0.05; CW hungry: M = 0.066, SD = 0.04; CW fed: M = 0.074, SD = 0.03; all ps > .26).

Exploration of task performance in association with a prior AN diagnosis.— There was a main effect of percent difference [$F(2,205) = 220.64$, $p < .001$]. There was no main effect of Group, or Visit, and no interactions were significant (all ps > .68). Similarly, the reaction time analysis demonstrated only a main effect of choice difficulty [$F(1,63) = 5.56$, $p = .02$], with no other main effects or interactions significant (all ps > .11).

Imaging Analysis

Valuation Model.—We detected a Group × Visit interaction within the left ventral striatum and bilateral dorsal caudate in relation to immediate (i.e., “Today”) trials (Table 2, Figure 3). Within these regions, CW responded more during immediate trials when hungry relative to when fed, and CW also responded more than RBN when hungry. RBN had greater BOLD response relative to CW when fed in the left ventral striatum and left dorsal caudate. RBN also responded more when fed relative to when hungry in the bilateral dorsal caudate. There was a significant main effect of Visit, with a larger BOLD response within the left ventral striatum and bilateral dorsal ACC when hungry relative to when fed (Table 2, Figure 4). No main effect of Group was observed.

Cognitive Model.—No significant main effects of Group, Visit, or their interaction were detected in association with decision-making across all trials.

Exploration of prior diagnosis of AN

Valuation Model.—There were no significant main effects of Group, Visit, or their interaction in relation to immediate (“Today”) trials.

Cognitive Model.—There was a Group × Visit interaction within the right VLPFC [$F(1,21) = 27.91$, $p < .001$] for all decision-making trials. Post hoc analysis suggested this was due to greater activation in the RBN AN- subgroup relative to the RBN AN+ subgroup when hungry [$t(21) = 2.61$, $p = .03$, ES = 0.71], and greater activation in the RBN AN− subgroup when hungry relative to when fed [$t(21) = 5.24$, $p < .001$, ES = 0.70].

Results of the whole brain analysis and exploratory robust regression analyses are presented in the Supplement.

DISCUSSION

This is the first known neuroimaging study demonstrating that RBN have altered brain activation during a decision-making task under conditions of hunger and satiety. While groups did not differ in terms of discounting rates or choice behavior, RBN responded more slowly than CW. As expected, CW exhibited greater BOLD responses when hungry relative to when fed in both the ventral striatum and dorsal caudate. In contrast, RBN showed no differences for hunger and satiety in the ventral striatum, and RBN had greater activation in the dorsal caudate when fed compared to hungry. Taken together, these results suggest RBN may be less sensitive to rewards when hungry but do not devalue reward when fed.

Valuation Circuitry

As expected, CW had a greater BOLD response when hungry relative to when fed, whereas RBN showed no differentiation between hunger and satiety. Neuroimaging studies have reported elevated striatal response to high calorie foods following a fast in healthy individuals (Goldstone et al., 2009), while satiety decreased reward-related neural activation (Fletcher et al., 2010; Thomas et al., 2015). The ventral striatum perceives stimuli as pleasant or aversive depending upon the context in which they were presented (Nieuwenhuis et al., 2005), responding to anticipation (Kim, Shimojo, & O'Doherty, 2011; Knutson, Adams, Fong, & Hommer, 2001) and outcome (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001) of appetitive as well as aversive stimuli (Jensen et al., 2007). Prior work has shown that individuals with RBN have altered neural discrimination of positive and negative monetary feedback within this region, suggesting contextual implications may be impaired (Wagner, et al., 2010). Notably, the same RBN participants as in the present study completing a taste paradigm did not differentiate ventral striatal response to pleasant taste when hungry vs. when fed (Ely, et al., 2017). This ventral striatal insensitivity to the influence of hunger for both monetary and food-based rewards suggests individuals with BN could have difficulties with using contextual cues to evaluate stimuli.

We found significant group differences in the BOLD response to immediate rewards in the dorsal caudate, with CW and RBN showing opposite patterns. The CW group responded more strongly when hungry than when fed, and CW also responded more than RBN when hungry. The dorsal caudate is sensitive to the associations between response and outcome (Balleine, Delgado, & Hikosaka, 2007), and is generally more engaged with valuating immediate outcomes during delay discounting (McClure, Ericson, Laibson, Loewenstein, & Cohan, 2007; McClure, et al., 2004). Increased activation within the caudate to immediate outcome trials when hungry in CW support the notion that metabolic state influences reward processing circuitry (Zhao et al., 2018) during action planning. In contrast, RBN had greater BOLD response in the bilateral dorsal caudate when fed relative to when hungry. Other studies have reported reduced caudate responding during self-regulatory control (Marsh, et al., 2009) and inhibition (Skunde et al., 2016), but increased responding during implicit learning. These findings suggest individuals with BN may have altered goal-directed behavior when fed; when combined with reduced reward valuation when hungry, it may lead to the occurrence and maintenance of dysregulated eating behavior.

Finally, we detected an elevated response to immediate rewards in the ACC in association with hunger in both groups. As part of the salience network, the ACC has been associated with a number of cognitive and emotional functions, including motivation, conflict monitoring, attention, and cognitive control (Berridge & Kringelbach, 2011; Klein-Flugge, Kennerley, Friston, & Bestmann, 2016). Previously, the ACC has shown a preference for immediate rewards during delay discounting in healthy individuals (McClure, et al., 2004). However, while both CW and RBN in this study had higher BOLD responses to immediate rewards when hungry, reflecting increased salience, this was not similarly reflected in the striatum for the RBN group, suggesting that RBN struggle to associate salience with motivation. Individuals with BN may thus experience a generalized impairment in the ability to discriminate the appetitive value of stimuli, particularly under conditions where context, such as hunger/satiety, should render them more/less appealing.

Implications

These results raise the possibility that there is impaired neural functioning in individuals with BN to the motivational drives of food deprivation or to the inhibitory influences of being fed. Consequently, this could lead to exaggerated food restriction and other behaviors, alternating with extremes of overeating, impulsivity, and labile moods. An impaired ability to integrate metabolic signals with reward valuation could help explain why individuals with BN are often able to engage in periods of restrained eating when hungry, yet also binge beyond satiation. This is consistent with the hypothesis of a dysfunctional, metabolically-signaled “switch” mechanism regulating inhibitory control that fails to activate eating based on reward and motivation when hungry, and likewise fails to inhibit eating based on reward devaluation when fed. As we found a similar dysfunctional response to taste with satiety in the same participants in a prior study (Ely, et al., 2017), it’s possible that hunger and satiety signaling may also influence economic decision-making in individuals with BN. Taken together, these data may help explain maladaptive periods of over- and under-control and lack of self-regulatory feedback when fasted or eating in BN.

Counter to our hypothesis, both RBN and CW showed similar choice response behavior and similar discounting rates that were insensitive to satiety level. The literature on delay discounting in individuals with BN is mixed; while some suggest individuals with active BN show impaired decision-making relative to healthy controls (Kekic, et al., 2016), others find no difference (Bartholdy, et al., 2017). It is possible a lack of a behavioral finding was due to our study participants being remitted. This could also be due to task-related differences: other versions have immediately available early rewards for all trials, use a consistent temporal interval between early and late rewards, or anchor a reward to a specific value, making comparison across studies difficult. Performance differences between groups can mask whether differences in brain activation reflect biological differences vs. the ability to perform the task. It is therefore preferable that groups perform similarly to aid interpretation of differences in neural responsivity (Gazzaley & D’Esposito, 2007). The RBN group responded more slowly than CW, regardless of satiety or difficulty of the decision. This is consistent with studies in BN demonstrating slower response times for tasks which involve making a decision (Ferraro, Kramer, & Weigel, 2018) and suggests motor slowing may occur even with remittance.

Cognitive Circuitry

There were no significant differences within cognitive ROIs during decision-making. Neuroimaging studies of cognitive control in participants with active BN have implicated frontostriatal regions as particularly relevant to the disorder (Marsh, et al., 2011; Marsh, et al., 2009; Skunde, et al., 2016). However, these alterations may be associated with symptom severity (Skunde, et al., 2016). As our participants were remitted, it is possible the remitted state may have mitigated differences in cortical regions associated with decision-making. Alternatively, it is possible that the effects of interest were small, and thus our sample size was ill equipped to detect group differences. Additional studies with larger sample sizes may help address this question.

Comparison to Findings in Anorexia Nervosa

Our exploratory analyses of prior AN history did not detect any significant differences in either the ventral striatum or caudate to immediate rewards. Given the role of the caudate in decision-making (Grahn, Parkinson, & Owen, 2008) as well as action-outcome contingencies (Yin & Knowlton, 2006), these data suggest that women with BN, whether or not they have previously been ill with AN, may experience dysregulated striatal functioning in association with rewarding stimuli, and this difficulty may thus lead to cycles of binging and purging behavior. This is consistent with studies reporting individuals with AN or BN have similar striatal responses to reward and punishment (Wagner, et al., 2010; Wagner et al., 2007) and could point to altered reward processing in general. Intriguingly, there were differences associated with cognitive control, as the RBN AN- subgroup exhibited greater brain response in the VLPFC relative to the RBN AN+ subgroup when hungry. Although underpowered, these exploratory findings could support behavioral studies reporting differences in decision-making in individuals with active BN who have previously had AN (Degortes, Tenconi, & Santonastaso, 2016; Strumila et al., 2020). Alternatively, cognitive control in individuals with AN, binge-purge type may be more similar to individuals with BN than to individuals with AN, restricting type (Lock, Garrett, Beenhakker, & Reiss, 2011; Wu, Hartmann, Skunde, Herzog, & Friederich, 2013). Larger studies are needed to better explore these relationships.

Limitations

This is the first neuroimaging study examining the effects of hunger and satiety on decision-making in BN. The sample size was relatively small, and more studies are needed with larger samples to replicate the findings and to determine whether other moderators, such as anxiety, may influence decision-making. BN participants were also remitted, preventing us from drawing broad conclusions on how decision-making differences may be associated with satiety in individuals with active BN, and how this may relate to active symptomatology. Those who achieve remittance may have less neural disturbances than those who experience a more severe, protracted illness course. Physiological measures, such as leptin or ghrelin, may provide additional clues beyond self-report of hunger and satiety in interpreting how energy homeostasis contributes to evaluating rewarding stimuli.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Implications

Our results may have important implications for our understanding and effective treatment of BN. Individuals with BN may not sufficiently devalue appetitive rewards when eating, and this dysregulated reward valuation may help explain why individuals with BN binge beyond satiation. Enhancing our understanding of the neurocircuitry contributing to BN symptoms may help us to better address dysregulated reward processing. Our findings are consistent with models positing altered self-regulatory control, eating expectancy, and reward function as critical components of BN behavior. Approaches which help individuals with BN devalue rewarding food during a meal, such as learning strategies that use external, rather than internal, cues to guide eating behavior, may therefore be helpful in maintaining control.

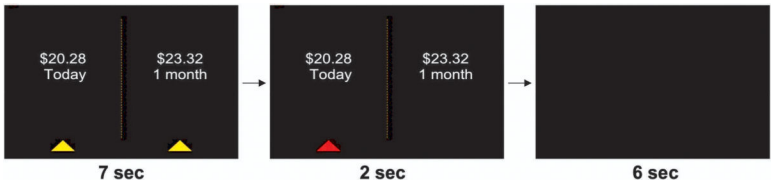

Figure 1.

Task design. Participants had 7 s to choose between two potential options. The smaller-sooner option was always presented on the left. Yellow triangles at the bottom of the screen indicated that participants must choose one of the two options. Once selected, the triangle under the preferred choice turned red for 2 s. Participants then experienced a 6 s delay period until the onset of the next trial.

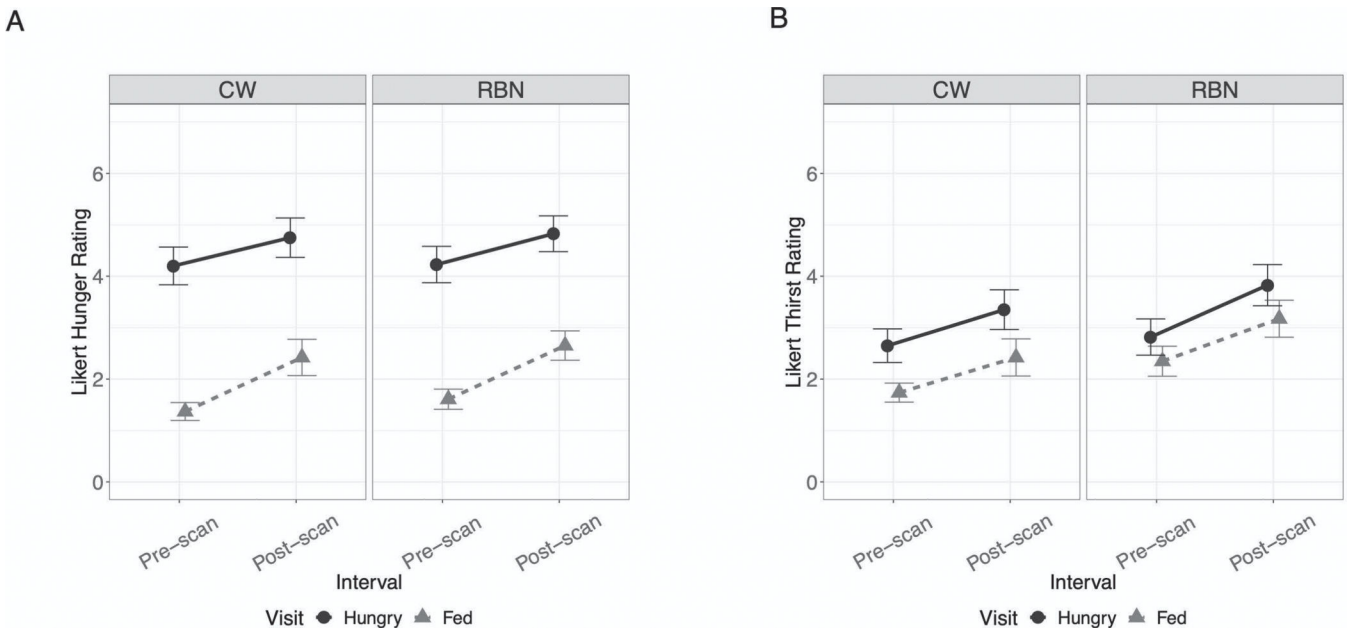

Figure 2.

Line graph of self-report measures. A) Participants reported a main effect of Visit [$F(1,120) = 221.1$, $p < .001$], with greater hunger during the hungry condition relative to the fed condition [$t = 14.9$, $p < .001$]. Participants also reported a main effect of interval [$F(1,120) = 23.6$, $p < .001$], with participants reporting greater hunger at the post-scan interval relative to the pre-scan interval [$t = 4.9$, $p < .001$]. B) Participants reported a main effect of Visit [$F(1,120) = 26.5$, $p < .001$], with greater thirst during the hungry condition relative to the fed condition [$t=5.2$, $p < .001$]. Participants also reported a main effect of interval [$F(1,120) = 31.8$, $p < .001$], with greater thirst at the post-scan interval relative to the pre-scan interval [$t = 5.6$, $p <.001$].

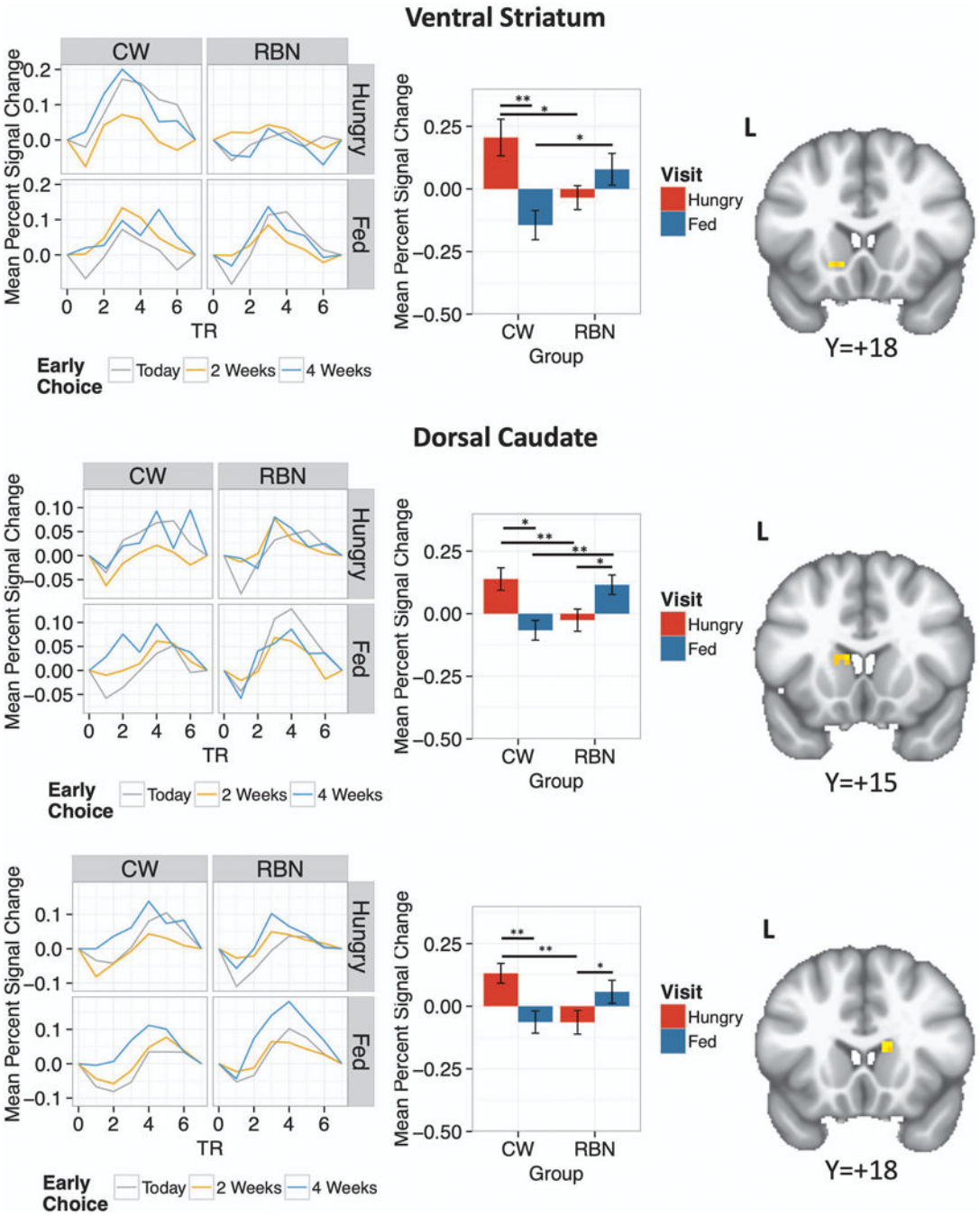

Figure 3.

Regions showing a significant Group (CW, RBN) × Visit (Hungry, Fed) for the Valuation Model where the early choice was "Today." Top row: left ventral striatum; middle row: left dorsal caudate; bottom row: right dorsal caudate. Shown are the BOLD response timecourses for trials where the early choice was today, 2 weeks, or 4 weeks; bar plots of the interaction; and peak cluster activation maps. Within all three regions, CW responded more during immediate trials when hungry relative to when fed, and CW also responded more than RBN when hungry. In comparison, RBN had greater BOLD response relative to

CW when fed in the left ventral striatum and left dorsal caudate. RBN also responded more when fed relative to when hungry in the bilateral dorsal caudate. CW: healthy comparison women; RBN: women remitted from bulimia nervosa; L: Left *$p < .05$; **$p < .01$

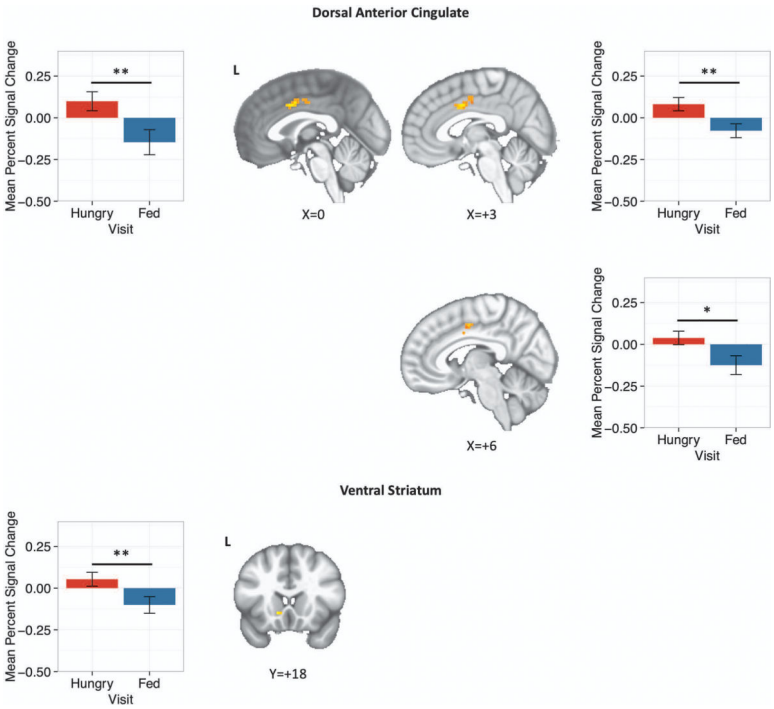

Figure 4.

Regions showing a main effect of Visit for the Valuation model. Overall, participants responded more strongly to immediate trials when hungry relative to when fed. CW: healthy comparison women; RBN: women remitted from bulimia nervosa; L: Left *$p < .05$; **$p < .01$

Table 1.

Participant demographics and characteristics.

Measure	CW (N=20)	RBN (N=23)	*t* or χ^2	*P*	*Effect Size*
Age (years)	25.8 (6.6)	28.1 (5.3)	−1.29	.20	0.40
Current BMI	22.2 (2.1)	22.3 (1.6)	−0.16	.87	0.05
Education (years)	15.7 (1.3)	16.5 (2.4)	−1.35	.19	0.40
Illness Duration (years)		7.7 (3.2)			
Remission (years)		4.1 (3.7)			
Worst Binge Frequency (episodes/week)		20.1 (13.6)			
Worst Vomiting Frequency (episodes/week)		21.6 (22.2)			
Beck Depression Inventory II[a]	0.3 (0.5)	1.5 (1.8)	−2.90	.01	0.85
State Anxiety[a]	23.7 (3.4)	27.9 (8.2)	−2.21	.03	0.66
Trait Anxiety[a]	23.6 (3.4)	27.5 (7.2)	−2.28	.03	0.68
Temperament and Character Inventory					
Harm Avoidance[a]	6.4 (4.4)	10.8 (6.6)	−2.56	.01	0.78
Novelty Seeking[a]	20.1 (6.0)	19.8 (5.4)	0.16	.87	0.05
Reward Dependence[a]	18.1 (3.7)	18.0 (2.8)	0.09	.93	0.03
Barratt Impulsiveness Scale					
Motor[b]	20.4 (3.1)	19.6 (2.7)	0.76	.45	0.25
Cognition[b]	12.2 (2.8)	13.0 (4.5)	−0.66	.52	0.20
Nonplanning[b]	18.6 (5.0)	19.7 (3.6)	−0.75	.46	0.25
Eating Disorder Inventory-2					
Body Dissatisfaction[a]	0.8 (1.6)	1.5 (1.6)	−1.24	.22	0.39
Drive for Thinness[a]	0.1 (0.2)	0.4 (1.4)	−1.17	.25	0.34
Bulimia[a]	0.0 (0.0)	0.3 (0.8)	−1.67	.11	0.48
Ineffectiveness[a]	0.3 (0.8)	0.1 (0.3)	0.88	.39	0.29
Perfectionism[a]	3.9 (2.8)	6.5 (3.8)	−2.51	.02	0.77
Interoceptive Awareness[a]	0.1 (0.5)	0.4 (1.1)	−1.01	.32	0.30
Maturity Fears[a]	1.1 (1.7)	0.8 (1.3)	0.61	.55	0.19
Impulse Regulation[a]	0.1 (0.2)	0.5 (1.3)	−1.47	.16	0.43
Lifetime Diagnoses					
Major depressive disorder (N)	0	13	13. 63	<.001	0.56
Any anxiety disorder	1	4	0.62	.43	0.12
Alcohol use disorder	0	4	2.05	.15	0.22
Substance use disorder	0	3	1.15	.28	0.16
Scanner					

Measure	CW (N=20)	RBN (N=23)	*t* or χ^2	*P*	*Effect Size*
GE Signa Excite 3T	8	9	0	1	0
GE MR750 3T	12	14			
Assessment Method					
MINI	14	18	0.07	.79	0.04
SCID	6	5			

Note: Entries are of the form mean (sd). Statistical comparisons were either by means of Welsh t-tests (effect sizes reported as Cohen's d) or χ^2 test (φ) for equality of proportions. Any anxiety disorder defined as having had at least one prior episode of panic disorder, phobia, post-traumatic stress disorder, generalized anxiety disorder, or any anxiety disorder not otherwise specified. Any alcohol or substance use were defined as any history of abuse or dependence per DSM-IV criteria. BMI: body mass index; CW: healthy comparison women; RBN: women remitted from bulimia nervosa.

[a] one CW and one RBN are missing from this measure;

[b] three CW and one RBN are missing from this measure.

Table 2.

Significant BOLD activation within regions of interest for the Group (CW, RBN) × Visit (Hungry, Fed) linear mixed effects analysis for the Valuation model where the early choice was “Today.”

Structure	Volume (μL)	X	Y	Z	*F*(peak)	Post hoc comparison	*t*	*P*	*Effect Size*
Main Effect of Group									
None									
Main Effect of Visit									
Left Ventral Striatum	270	−12	18	−6	15.4	Hungry > Fed	2.9	.006	0.27
Left Dorsal Anterior Cingulate Cortex	378	0	9	36	19.6	Hungry > Fed	3.0	.005	0.41
Right Dorsal Anterior Cingulate Cortex	324	3	6	36	22.5	Hungry > Fed	3.2	.003	0.34
	270	6	3	45	16.4	Hungry > Fed	2.7	.01	0.32
Group × Visit Interaction									
Left Ventral Striatum	135	−18	18	−6	15.8	CW: Hungry > Fed	3.9	.001	0.66
						Hungry: CW > RBN	2.8	.02	0.45
						Fed: RBN > CW	2.6	.02	0.42
Left Dorsal Caudate	459	−9	15	12	16.4	CW: Hungry > Fed	3.4	.005	0.42
						RBN: Fed > Hungry	2.5	.01	0.29
						Hungry: CW > RBN	2.8	.01	0.34
						Fed: RBN > CW	3.1	.008	0.37
Right Dorsal Caudate	162	12	18	15	17.6	CW: Hungry > Fed	3.5	.004	.36
						RBN: Fed > Hungry	2.4	.03	.23
						Hungry: CW > RBN	3.1	.007	.36

Note: Center of mass coordinates reported in MNI space. Small volume correction was determined with Monte-Carlo simulations (via AFNI’s 3dClustSim) to guard against false positives. CW: healthy comparison women; ES: standardized effect size; RBN: women remitted from bulimia nervosa.