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Greater anterior cingulate activation and connectivity in response to visual and auditory high-calorie food cues in binge eating: Preliminary findings

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Abstract

Obese individuals show altered neural responses to high-calorie food cues. Individuals with binge eating [BE], who exhibit heightened impulsivity and emotionality, may show a related but distinct pattern of irregular neural responses. However, few neuroimaging studies have compared BE and non-BE groups. To examine neural responses to food cues in BE, 10 women with BE and 10 women without BE (non-BE) who were matched for obesity (5 obese and 5 lean in each group) underwent fMRI scanning during presentation of visual (picture) and auditory (spoken word) cues representing high energy density (ED) foods, low-ED foods, and non-foods. We then compared regional brain activation in BE vs. non-BE groups for high-ED vs. low-ED foods. To explore differences in functional connectivity, we also compared psychophysiological interactions [PPI] with dorsal anterior cingulate cortex [dACC] for BE vs. non-BE groups. Region of interest (ROI) analyses revealed that the BE group showed more activation than the non-BE group in the dACC, with no activation differences in the striatum or OFC. Exploratory PPI analyses revealed a trend towards greater functional connectivity with dACC in the insula, cerebellum, and supramarginal gyrus in the BE vs. non-BE group. Our results suggest that women with BE show hyper-responsivity in the dACC as well as increased coupling with other brain regions when presented

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with high-ED cues. These differences are independent of body weight, and appear to be associated with the BE phenotype.

Keywords

neuroimaging; food cue reactivity; food reward; conflict processing; dietary restraint

Introduction

Binge eating (BE) is characterized by episodes of loss of control and excessive food consumption (1), which are often followed by feelings of shame and guilt (2). Binge eaters, compared to non-binge eaters, report greater impulsivity, which hinders inhibitory control and correlates with increased food intake, specifically of “binge-type” foods (3). Binge eaters also engage in emotional eating (4), report negative mood as a trigger of eating (5), and consume greater amounts of food when negative mood is induced in the laboratory (6). Individuals with binge eating are more likely to be overweight or obese than non binge eaters (7), and binge eating behavior often predates the onset of obesity, suggesting a causal relationship (8). Although binge eating has some phenotypic overlap with overweight/obesity, binge eaters as compared to weight matched controls commonly experience psychiatric symptoms such as negative self evaluation and depressive symptoms (9), suggesting that it may be caused and/or maintained by a related but distinct set of underlying neurobiological factors.

Few neuroimaging studies have been conducted on binge eating (BE) or the full-fledged disorder, Binge Eating Disorder (BED). However, existing reports have linked BED to increased activation in frontostriatal circuits in response to food cues. For example, in a study using PET to examine brain activation in response to exposure to real foods (i.e. smell, sight) in the scanner (vs. control pictures) in women with and without BED, it was found that obese BED vs. obese non-BED, and also obese BED vs. lean non-BED participants showed increased rCBF in left frontal and pre-frontal regions including the OFC (10). In an fMRI study, overweight BED participants exhibited greater reward expectancy scores based on the Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS) self-report questionnaire (11), and also showed a greater OFC response to food pictures, compared to both normal weight, and to obese/overweight non-binge eaters and BN patients, and reward sensitivity scores positively correlated with ACC/medial OFC activation (12). More recently, Wang et al (13) used PET to measure changes in extracellular dopamine in response to food stimulation following oral methylphenidate [MPH], a drug that enhances dopamine signals by blocking re-uptake, vs. placebo. During food stimulation and following MPH, vs. the baseline (no food stimulation+ placebo), obese people with BED had significantly more dopamine release (vs. non binge eaters) within the caudate, suggesting that dopaminergic activity in the striatum may play a role in BED. Furthermore, dopamine increases in the caudate were positively correlated with binge eating scores on the Binge Eating Scale (BES; (14)), but not BMI.

Related eating disorders and disordered eating behaviors have been associated with irregular activation in anatomically and functionally related brain regions. For example, compared to adolescents of similar healthy body weights, those currently diagnosed with the binge eating and purging type of anorexia nervosa [AN] or bulimia nervosa [BN] showed greater activation in the ACC, precentral gyrus, middle and superior temporal gyri, hypothalamus and dorsolateral prefrontal cortex during a go/no-go task (15). In another study, Schienle et al (12) reported increased activation in the ACC as well as the insula in current BN patients (vs. similar weight controls or those with higher body weight, including obese BED and obese controls), while Uher et al (16) found that in response to visual food (vs. non-food) stimuli, both current AN and BN individuals, compared to age-matched, but not weight matched, controls, had greater activation in the ACC as well as the OFC, and less activation in the lateral and apical prefrontal cortex. A study of female emotional eaters vs. non-emotional eaters with similar BMI (mean BMI = 24.4), showed greater activation in the ACC as well as the parahippocampal gyrus during anticipation of a milkshake, and greater activation in the ACC, pallidum, and thalamus in response to receipt of a milkshake during a negative mood (17). Across these studies, a consistently activated structure is the ACC, primarily the dorsal region, a brain area which is known to play a role not only in reward-based decision making and learning (18) but also in conflict processing (19) – a cognitive phenomenon which may be particularly salient for those attempting but often failing to restrict their eating.

Notably, although the above studies of BED all compared obese or overweight BED subjects to obese or overweight non-BED subjects (10, 12, 13), none of them included normal-weight binge eaters. Although about 40% of binge eaters are obese, about 60% are either normal-weight or overweight (20), with the WHO World Mental Health Survey Initiative finding that among those with lifetime or 12-month BED, 1.3 and 1.5% respectively were underweight, 31.7 and 25.0% respectively were normal weight, 30.7 and 31.8% respectively were overweight, and 36.2 and 41.7% respectively were obese (21). Evidence suggests that normal-weight binge eaters are similar in associated eating disorder psychopathology to obese binge eaters (e.g. general distress, depressive symptoms (22), and are as likely to seek treatment and exhibit distress about binge eating and shape and weight overvaluation, although they are also more likely to use healthy and unhealthy weight control behaviors (23). Further, although all of the cues used within the studies contained a visual element, none included two types of cues, a design that enables the extraction of fundamental, modality-independent cue responses (24). Furthermore, these studies (along with most other studies of appetite) did not investigate differences in functional connectivity within appetite networks, which could be especially relevant for complex behaviors such as binge eating (25).

To address some of the issues raised above namely, use of more than one modality and inclusion of lean binge eaters, and assessment of functional connectivity, we measured brain activation in response to visual and auditory high-ED binge-type food stimuli in binge eaters and non-binge eaters, half of whom were lean, and half of whom were obese (counter-balanced). Although neglected in the food reward literature, auditory food cues are fairly common in everyday life, e.g., radio commercials and oral presentations of restaurant specials by waiters. The classic Pavlovian response to a bell can also be considered an

auditory cue, analogous to the lunch bell in schools. We have used this dual modality paradigm to investigate changes in neural responsivity pre and post obesity surgery (26).

By contrasting group-level activation in BE vs. non-BE individuals across a range of body weight groups, this study builds upon a preliminary analysis which suggested increased premotor activation in obese individuals with BE (27). To focus our analysis, we selected a priori regions of interest that consistently emerged from the few existing studies of binge eating in the context of BED – the OFC and the striatum. We also selected the ACC, due to its consistent implication in studies of binge eating and emotional eating outside of BED, and due to its role in reward-based decision making/learning and conflict processing (18) (19). Conflict processing is particularly relevant to binge eaters, who struggle to reconcile conflicting urges to a) consume food due to reward value, and b) restrict eating due to weight-related goals, subsequently experiencing shame and guilt. This conflict may be even more salient to normal-weight binge eaters, who are more likely than obese treatment-seeking individuals with BE, to struggle with dieting and skipping meals, and to avoid certain foods and feel more distressed about binge eating (23). To help illuminate functional relationships between regions, specifically the possibility of differential interactions with higher-order cognitive structures mediating food-related conflict, we additionally conducted psychophysiological interaction (PPI) analyses using a functionally derived ACC seed region.

We hypothesized that the BE group would show increased OFC, striatal and ACC activation compared with non-BE. We additionally predicted that the BE group would show greater functional connectivity between the ACC and brain structures known to be associated with food reward, reflecting the simultaneous experience of anticipatory food reward and cognitive goal conflict when exposed to high-ED, binge-type food cues.

Materials and Methods

Participants

Ten women with binge eating [BE] (5 normal-weight, 5 obese) and ten women without binge eating [non-BE] (5 normal-weight, 5 obese) participated (aged 20–27). Exclusion criteria included left-handedness, smoking, consuming more than 3 alcoholic drinks per day, substance use, claustrophobia and presence of metallic implants and non-removable metallic dental retainers or pacemakers. All women were pre-menopausal, not pregnant or lactating, had no significant health problems and were not on any medications influencing weight. Binge eating status was assessed using the Questionnaire on Eating and Weight Patterns [QEWP] (28) and confirmed by a clinical interview focusing on the key questions from the QEWP, concerning overeating and binge episodes with loss of control. All of those classified as BE reported overeating and loss of control but did not meet full criteria of BED (DSM-5) and were therefore considered subthreshold. The non-binge eaters did not report episodes of either overeating or loss of control. Participants also filled out a questionnaire packet including the Binge Eating Scale [BES; (14)] to assess behaviors indicative of BED, the Dutch Eating Behavior Questionnaire [DEBQ; (29)] to assess restraint, emotion and external eating behaviors, and the Zung Self-Rating Depression Scale (30). Height and

weight were measured to obtain body mass index [BMI], and bioelectrical impedance analysis [BIA] was used to measure body fat percentage.

Procedures

Three hours prior to scan start time, participants consumed a 650 kcal meal made up of tuna, chicken or egg salad sandwich, juice or non-diet soda and a piece of fruit. The scan was 45 minutes long and took place between 1 and 3 pm. During the scan, participants were presented with blocks of visual (pictures) and auditory (spoken word) food and non-food stimuli. Stimuli represented high energy density [high-ED] binge type foods (desserts, high fat snacks), low energy density [low-ED] non-binge type foods (fruits and vegetables), and neutral non-foods (office supplies). High-ED foods contained 3.5 kcal/g and the low-ED foods contained 1 kcal/g. Visual stimuli were photographs of foods transmitted through eye goggles presented for 4 seconds each; auditory stimuli were recorded 2-word names similar in content to the visual stimuli, transmitted through a headset and repeated twice to fill the 4 second epoch (e.g. “chocolate brownie, chocolate brownie”). The session was made up of 12 runs, 6 visual and 6 auditory, each containing one block. Each block was comprised of 10 stimuli of the same type, and each block type occurred twice in the session (i.e. 2 visual high-ED, 2 auditory high-ED, 2 visual low-ED, 2 auditory low-ED, 2 visual non-food, 2 auditory non-food), with similar but non-identical stimuli comprising each block of the same type. Blocks were each preceded by a 52 second baseline period, and followed by a 40 second baseline period, resulting in a total of 2 minutes and 12 seconds per run. The six visual blocks were presented first, followed by the 6 auditory blocks. This order was maintained in order to more validly compare the results across individuals in this small study. The blocks within each modality were presented in a pseudorandom order generated separately for each subject, such that there were no consecutive blocks with the same stimulus type (e.g., high-ED followed by high-ED).

After each block, participants verbally rated hunger and desire to eat separately on a scale from 1 to 10 (1=not hungry at all, 10=extremely hungry/1= no desire to eat, 10= extreme desire to eat). Once outside the scanner, participants filled out a questionnaire in which they rated color-printed images of the high-ED, low-ED, and non-food stimuli for liking on a scale ranging from -100 to 100 (-100=extreme dislike, 100=extremely like), and the food stimuli for binge eating likelihood (“How likely would you be to binge on this food?”) on a scale ranging from -100 to 100 (-100=extremely unlikely, 100=extremely likely).

Image Acquisition—All scanning was conducted using a 1.5 Tesla twin-speed scanner with quadrature RF head coil. Participants lay in a supine position in the scanner with their heads in a padded restraint, with tape strapped across the forehead. Three-plane localization was used to verify head position. Functional T2*-weighted images with a gradient echo pulse sequence (echo time = 60 msec, repetition time = 4 sec, flip angle = 60°) were obtained. During each block, 36 whole brain scans were made, each consisting of 25 contiguous slices, parallel to the AC/PC line (19x19 cm field view, 128x128 matrix size, 1.5x1.5 mm in plane resolution). High-resolution anatomical scans were acquired with a T1-weighted SPGR sequence (TR=19 ms, TE= 5 ms, flip angle = 20°, FoV = 220x220 mm),

recording 124 slices at a slice thickness of 1.5 mm and in-plane resolution of 0.86 x 0.86 mm.

Statistical analysis

Rating analysis—Group comparisons of post-block hunger and desire to eat ratings during the scan, as well as of post-scan liking and binge eating likelihood ratings, for high-ED, low-ED and non-food cues, were conducted using repeated measures ANOVA. These analyses were conducted first unadjusted, then including weight group as an additional factor, or BMI as a covariate. Two tailed $\alpha=0.05$ was used to determine significance. Analyses were performed using SPSS v.20.

1st level fMRI analysis—For pre-processing, realigned T2-weighted volumes were slice-time corrected, spatially transformed to a standardized brain (Montreal Neurologic Institute) and smoothed with an 8-mm full-width half maximum Gaussian kernel. The 12 blocks for each subject's 1st level analysis were concatenated to create a single block (396 total time points). To account for the mean of each block within each subject's session, block regressors were included in the GLM. Additional nuisance covariates included global signal and spikes computed using the `scn_session_spike_id.m` script available in Diagnostics Tools for MATLAB (<http://wagerlab.colorado.edu/tools>). Regressors-of-interest were created by convolving the onset of each block (auditory and visual high-ED, low-ED, and non-food) with the canonical HRF with duration of 40 seconds. The following contrasts were then created from the resulting estimated parameters and passed to 2nd level analysis (see below): 1) visual high-ED > visual low-ED and 2) auditory high-ED > auditory low-ED. Because our hypotheses focused on high vs. low-ED food processing, non-food conditions were not included in 2nd level analyses and hence will not be presented.

PPI analysis—We applied Psychophysiological Interactions (PPI) analysis using a functionally defined seed in the dACC (31). We selected our MNI coordinates based on local maxima within the cluster for the group activation contrast (binge > non-binge, high-ED > low-ED, 59 voxels, 1208 mm³ with center of mass at MNI = [-2, 36, 28]): activity was extracted from suprathreshold voxels ($p<0.05$ uncorrected) within each subject (high-ED > low-ED). The BOLD signal throughout the whole-brain was then regressed on a voxel-wise basis against the product of this time course (physiological variable) and the vector of the psychological variable of interest, (i.e. 1* high-ED + -1*low-ED in the visual and auditory conditions separately), with the physiological and the psychological variables serving as regressors of no interest. The psychological regressor was included to remove any covariation between regions due to differences in activation, and PPI regressors for auditory and visual modalities (high-ED vs. low-ED) were kept separate. Both auditory and visual PPI beta maps were subsequently passed to 2nd level random effects analysis (see below).

2nd level analysis—A 3-way ANOVA (independent factors: BE vs. non-BE (factor of interest) and obese vs. lean (factor of no interest), dependent within-subject factor: visual vs. auditory) was conducted separately on the contrast, and beta images generated from the 1st level activation and PPI analysis. Based on prior research, we designated the caudate, putamen, OFC and ACC as a priori regions of interest [ROI] for activation analyses, with

ROI masks created using wfupickatlas. To obtain regions common to both modalities, we conducted a conjunction (conjunction null hypothesis) analysis of the positive effects of binge eating across both visual and auditory cues. Statistical maps for conjoined activation were displayed at $p < 0.05$ uncorrected, cluster size $[k] > 30$. For small volume correction (ROI analysis), we then determined whether each region, which appeared in the conjoint analyses above, also appeared in a separate analysis that tested against the global null hypothesis (of 1 or more effects) and corrected for multiple comparisons using cluster-extent thresholding. For this we used the 3dClustSim program in AFNI (v.2010) to generate 1000 Monte Carlo simulations using parameters from our data to determine the cluster size at which the false positive probability was below a desired alpha level of $p < 0.05$ (i.e. effective threshold of $p < 0.05$ corrected). Input parameters to 3dClustSim included the masks used for all analyses (i.e. OFC, caudate, putamen and ACC for ROI analysis, or whole-brain mask for whole-brain analyses (PPI only)) and inherent smoothness estimated from data (obtained from SPM.xVol.FWHM). For ROI analyses, using an uncorrected threshold of $p=0.01$, this simulation yielded a cluster threshold of 43.7 for OFC, 13 for caudate, 26.9 for putamen and 26.4 for ACC. For whole-brain PPI analyses, using an uncorrected $p=0.005$, the cluster threshold was 58. Regions that survived these thresholds are denoted in Table 3. Finally, in order to compare group-level statistical parametric mapping results with a preliminary study which applied t-tests at the single-subject level (27), the precentral gyrus was designated as an additional ROI. This region was included for validation purposes and was not considered an a priori ROI. Clusters in the whole-brain analysis were labeled using labels available in the wfu_pickatlas (<http://fmri.wfubmc.edu/software/pickatlas>) and using xjview. (<http://www.alivelearn.net/xjview8/>).

To disambiguate the direction of activity for the primary analyses of i) conjoined visual and auditory activation in BE vs. non-BE groups and ii) conjoined visual and auditory PPI analyses in BE vs non-BE groups, we plotted beta estimates plus 90% confidence intervals for peak voxels in clusters surviving $p < 0.05$, for high-ED food responses alone and low-ED food responses alone, for both the BE and non-BE groups separately. 1st level, 2nd level and PPI analyses were conducted using SPM8.

Results

Participants

There were no significant differences in BMI, body weight or body fat percentage between the BE and non-BE groups (Table 1) and no group differences in depression score. However, the BE group had significantly higher scores on the BES and all of the DEBQ scales (restraint, emotional eating, external eating). Analyses including weight group or BMI as a covariate revealed no main effects of body weight, or interaction effects between body weight and binge eating category.

Ratings

Repeated measures ANOVAs comparing high-ED, low-ED, and non-food conditions, demonstrated significant effects of cue condition on ratings of hunger ($F(2,32) = 6.4$, $p=0.004$), desire to eat ($F(2, 34) = 45.6$, $p<0.001$), liking ($F(2, 32)=15.4$, $df=$, $p<0.001$) and

binge likelihood ($F(2,32) = 4.7, p = 0.017$), but no evidence for BE vs. non-BE differences on any variable (Table 2). These results were largely unchanged when analyses were repeated including weight group as another between-subjects factor.

fMRI results: activation

ROI analyses for the striatum (caudate, putamen) and OFC revealed no evidence for greater activation in the BE compared to the non-BE group. ROI analysis for the ACC revealed greater dorsal ACC activation in response to high-ED (vs. low-ED) food cues in binge eaters compared to non-binge eaters. Plots of parameter estimates indicated that group differences resulted from BE showing relatively increased responses to high-ED cues in parallel with decreased responses to low-ED cues, and non-BE showing the inverse pattern (Figure 1, Table 3).

ROI analysis for the precentral gyrus revealed no evidence for BE vs. non-BE group differences in response to visual and auditory stimuli conjoined, or visual and auditory cues separately. To more fully explore our previous finding, we also used ROI analysis to examine visual and auditory activation for the positive effect of binge eating in obese and lean groups separately, although these results should be considered purely preliminary due to small sample size in each subgroup. This revealed that obese BE (vs. obese non-BE) showed increased precentral responses to both visual and auditory cues, while lean individuals with BE showed increased precentral responses to visual cues only (Supplementary Figure 1, Supplementary Table 1).

fMRI results: functional connectivity

PPI analyses, using the functionally defined dorsal ACC region as a seed, in response to high-ED (vs. low-ED) food cues, in BE vs. non-BE suggested greater connectivity with dACC in the insula, cerebellum, and supramarginal gyrus (Figure 2, Table 3). Contrast plots revealed that all group differences resulted from a pattern of increased dACC coupling among BE, together with decreased dorsal ACC coupling among non-BE, for the high-ED cues, and vice versa for the low-ED cues. However, the cerebellum effects appeared to be primarily driven by a relative decoupling to high-ED cues in the non-BE group, while the supramarginal gyrus effect was more strongly driven by a relatively greater coupling to low-ED cues in the non-BE group. Note that no regions survived $p < 0.05$ corrected in the whole-brain PPI analysis, therefore PPI results presented above should be regarded as exploratory and provisional upon replication in an independent sample.

Discussion

Our results indicate that women with BE show hyper-responsivity in the ACC, as well as relatively increased ACC functional connectivity, in response to visual and auditory modalities of high-ED binge type food cues as compared to low-ED non-binge food cues. We found that the BE (vs. non-BE) group showed increased activation in response to high-ED binge food cues in a dorsal region of the ACC, which plays an important role in conflict processing as well as reward-based decision-making and emotion (32), and overlaps geographically with the ACC region identified in previous neuroimaging studies of eating

disorders characterized by binge eating (12, 15–17). Given the experimental control of weight we employed here, as well as our inclusion of normal-weight as well as overweight binge eaters, the pattern of activation we observed may be associated specifically with binge eating behavior.

A primary characteristic of binge eating is consumption of greater amounts of food than most people would consume within a discrete period of time, even if after eating a meal and feeling sated, and, greater ACC responsivity has also been positively correlated with food addiction scores in response to anticipated milkshake receipt (33), and in obese vs. lean individuals in response to visual food cues (34, 35). Murdaugh et al (36) additionally found that increased ACC activation in response to high-calorie (vs. control) pictures in obese individuals prior to weight loss treatment predicted less successful weight loss. Together these studies suggest that the increased ACC activation we observed in BE could be associated with the heightened desire for food that is exhibited by all of the above groups.

Binge eating is also characterized by a sense of loss of control while eating, i.e. a failure to execute the goal of inhibiting intake due to being overwhelmed by a strong parallel experience of motivation to eat. The ACC has been demonstrated to subserve detection of error (37) and incongruent trials in the Stroop task, in which individuals must choose an answer that conflicts with an intuitive answer (38). The ACC also plays a role in the bingeing and craving aspects of drug addiction, as well as in the motivation salience of reinforcers such as monetary gains, and the ability to control responses (39). Indeed, increased ACC activation has been observed in cocaine addicts (vs. healthy controls) viewing cocaine cues (vs. control) cues (40), in cigarette smokers viewing smoking (vs. neutral) cues (41), and in problem gamblers viewing gambling (vs. control) cues as well as during inhibition within a go-no/go task (42). Our results could therefore reflect a similar process of increased desire paired with ineffective inhibition occurring in relation to palatable food in BE.

Another key feature of binge eating is affective disturbance and emotional eating (43). Many studies have observed increased ACC activation in healthy individuals in response to negative emotional stimuli (sad faces) (44), and also in individuals with depressive symptoms or those dealing with social rejection manipulations such as exclusion during a ball toss game (45, 46). Increased ACC activation, has also been observed in emotional eaters (12), who have similar traits to BE, and in individuals with BN, a disorder similar to BE (47).

Nevertheless, the several other imaging studies of BED did not note differences in ACC function. For example, Schienle et al (12) found increased ACC responses to food cues in BN individuals but not in the three other reference groups, including overweight BED patients, overweight healthy control subjects, and normal-weight healthy control subjects. However, all the scans took place after an overnight fast, raising the possibility that hunger across all the groups could have diminished activation differences between BED and non-BED individuals. Our results therefore suggest that abnormal ACC function may contribute not only to obesity, emotional eating, addictive behaviors, and emotionality, but also towards binge eating. Our study also includes both obese and lean binge eaters, which might

tease out brain specific differences in reward and conflict processing in binge eating that is not related to weight, which might even be more salient in lean binge eaters, as mentioned above in the introduction.

Although we did not observe precentral gyrus activation differences in conjoint analyses, we did find some evidence for increased precentral activation in obese binge eaters in response to visual and auditory cues separately, as well as in the lean binge eaters in response to visual cues only, consistent with our preliminary individual analyses (32). Increased precentral gyrus activation has been observed in individuals with BN in response to food (vs. non-food) images (48), in restrained (vs. unrestrained) eaters in response to highly palatable food pictures during a fed state (49), and in individuals who are food deprived (50), suggesting that binge eaters, along with other disordered eaters, may activate motor planning areas in response to high-ED food stimuli, reflecting readiness for intake. Although the analyses should be considered exploratory due to the small sample sizes of the subgroups, the fact that precentral activation was observed in both modalities for obese binge eaters, but only in the (possibly more salient) visual modality for lean binge eaters may reflect differences in the relative severity of the phenotype.

A relatively novel feature of our study was the inclusion of functional connectivity analyses, which examine statistical dependencies between regions based on their time-series data. The results suggested increased crosstalk between the dACC, a region of the ACC which has been specifically implicated in the processing of negative emotion (51) and cognitive control (52), and regions involved in food reward and action planning (insula, cerebellum/vermis, supramarginal gyrus), when the BE group was presented with binge food cues. The insula is involved in emotional saliency and craving (53), and shows responsivity to visual food cues as well as anticipation and consumption of food tastes in obese individuals (54), and environmental drug cues in drug abusers (55). The increased dACC-insula connectivity that we observed may therefore reflect integration of top-down cognitive control and conflict processing with food reward related insular activation among the BE group. The cerebellum, which is implicated in sensory attention and reinforcement learning as well as motor learning (56), has been previously reported to show increased responses to food cues in obese vs. lean individuals (57), BN vs. healthy controls (16), and restrained vs. unrestrained eaters (49). The heightened dACC-cerebellar connectivity we saw in BE could therefore reflect the triggering of attention and motor memory processes by food cues, in parallel with efforts to regulate eating. The supramarginal gyrus is classically implicated in word-related processing and recollection but has also been shown to activate during food tastes, possibly due to emotional valence of taste perception (58).

The main limitation of the study is the relatively small sample size, especially for interactions within subgroups, e.g., obese binge eaters ($n=5$), which should be viewed as exploratory. The more valid comparisons are between the binge vs. non-binge eaters with $n=10$ per group. Nevertheless, even with $n=10$ per group, the study findings should be viewed as preliminary. Another limitation is that we did not monitor the menstrual cycle, and it has been reported that binge eating behavior can be influenced depending on the menstrual phase (59).

In summary, our results revealed that a dorsal region of the ACC shows heightened activation in BE when viewing and/or listening to words representing high-ED foods, as well as increased connectivity with other brain regions associated with food reward. The circuitry implicated overlaps with that observed in other eating behaviors and disorders including BN, and the regions identified appear to be specific for BE rather than body weight. The brain regions identified could be further studied to determine if their responsivity to food cues could serve as biomarkers for binge eating behavior, the degree to which activity changes after remission, and as potential neuropharmacological targets for treating binge-eating behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We examine neural responses to visual and auditory food cues in binge eaters [BE].
- BE show increased dACC responses to high vs. low-energy density [ED] cues.
- BE show greater dACC functional connectivity with other regions for high-ED cues.
- dACC hyper-responsivity and altered functional connectivity may help maintain BE.

Figure 1.

Slices depict areas where there was greater activation in response to high-ED (vs. low-ED) food cues in binge eaters compared to non-binge eaters. Figure shows region of interest (ROI) activation, conjunction of both visual and auditory modalities, in the dorsal anterior cingulate cortex (dACC; cluster size = 59, peak MNI coordinate: $-2,36,28$, $p < 0.05$ corrected). Bar graphs show beta estimates for voxels of each region in binge (BE) and non-binge (non-BE) eaters for high-ED (vs. baseline) and low-ED (vs. baseline).

Figure 2.

Slices depict areas where there was greater connectivity with the dACC in response to high-ED (vs. low-ED) food cues in BE compared to non-BE. Whole brain maps of the conjunction of both visual and auditory modalities are shown in the supramarginal gyrus (SG; coronal view, $y=-22$), the cerebellum (sagittal view $x=-4$), the vermis (sagittal view, $x=6$), and the insula (axial view, $z=-2$) ($p<0.05$). Bar graphs show beta estimates for voxels of each region in binge (BE) and non-binge (non-BE) eaters for high-ED (vs. baseline) and low-ED (vs. baseline).

Table 1

Participant characteristics*

	BE (n=10)	Non-BE (n=10)
Age	22.1 ± 2.3	21.3 ± 0.6
Body mass index	27.4 ± 5.8	27.7 ± 7.2
Weight (kg)	71.1 ± 11.8	73.8 ± 16.2
Body fat (%)	36.4 ± 8.6	33.8 ± 9.5

*
No significant differences between groups

Table 2

Hunger, desire to eat, liking and binge likelihood ratings (mean $\pm$ SD) for BE and non-BE groups.

		BE	Non-BE	Combined
Hunger [*]	High-ED	5.16 $\pm$ 2.68	3.92 $\pm$ 2.40	4.47 $\pm$ 2.53
	Low-ED	4.68 $\pm$ 2.80	3.65 $\pm$ 2.19	4.10 $\pm$ 2.46
	Non-foods	4.30 $\pm$ 2.74	3.37 $\pm$ 2.0	3.78 $\pm$ 2.34
Desire to eat [*]	High-ED	6.13 $\pm$ 2.79	5.63 $\pm$ 2.47	5.84 $\pm$ 2.54
	Low-ED	3.75 $\pm$ 1.56	3.63 $\pm$ 2.10	3.68 $\pm$ 1.84
	Non-foods	1.38 $\pm$ 0.53	1.25 $\pm$ 0.42	1.30 $\pm$ 0.46
Liking [*]	High-ED	45.24 $\pm$ 12.08	42.67 $\pm$ 24.09	43.67 $\pm$ 19.86
	Low-ED	13.39 $\pm$ 25.85	19.63 $\pm$ 32.18	17.21 $\pm$ 29.24
	Non-foods	-7.97 $\pm$ 45.44	-4.02 $\pm$ 33.17	-5.56 $\pm$ 37.15
Binge likelihood [*]	High-ED	10.12 $\pm$ 28.42	-13.31 $\pm$ 41.45	-4.20 $\pm$ 37.87
	Low-ED	-42.70 $\pm$ 27.88	-43.71 $\pm$ 34.63	-43.32 $\pm$ 31.30

Hunger and desire to eat ratings obtained in the scanner following each run; liking and binge likelihood ratings based on images and words presented after the scan ended.

* Significant effect of cue condition ($p < 0.05$), no significant differences between groups.

Table 3

Brain regions showing greater activation (conjunction of visual and auditory modalities) in response to high-ED vs. low-ED food cues in BE compared with non-BE group

Analysis method	Region	Side	Peak coordinates			K size	t value (df = 32)
			x	y	z		
ROI	ACC (dorsal) <i>a,b</i>	L	-2	36	28	59	2.29
	OFC	R	26	56	-2	1	1.81
	Striatum (putamen)	L	-32	0	4	1	1.73
Functional connectivity with dACC as a seed <i>a</i>	Supramarginal gyrus	R	66	-22	20	43	2.72
	Cerebellum	L	-4	-56	-12	39	2.30
	Cerebellum (vermis)	R	6	-58	-2	35	2.46
	Insula	L	-34	-10	-2	35	2.37

ROI = region of interest analysis; x,y,z=Montreal Neurological Institute coordinates; K=cluster size, i.e. number of voxels.

a Significant at $p < 0.05$ uncorrected, $k > 30$ testing against conjunction null hypothesis;

b Significant at $p < 0.05$ corrected (see Methods).