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Reward circuit function in high BMI individuals with compulsive overeating: Similarities with addiction

Francesca M. Filbey [a,*], Ursula S. Myers [b], Samuel DeWitt [a]

[a] Center for BrainHealth, School of Behavioral and Brain Sciences, University of Texas at Dallas, Dallas, TX 75235, USA
[b] SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA 92122, USA

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ABSTRACT

Context: The rising rate of overweight and obese individuals among developing countries despite focused efforts on prevention and treatment underscores not only the need to better define the physiological factors that contribute to weight problems, but also the need to elucidate the neurobiological mechanisms of the self-regulatory failure over eating that leads to weight problems. Emergent findings suggest an overlapping model of addiction and compulsive overeating.
Objective: Our goal was to examine whether neural hyper-responsivity to reward typically associated with substance abuse could also be seen in individuals exhibiting binge-eating behavior.
Design: Participants completed self-assessments of demographic information and eating behavior. Neurofunctional data were collected via functional MRI (fMRI) scans while participants were exposed to personally relevant high-calorie cues.
Setting: The participants were recruited from the general community.
Participants: Twenty-six individuals with high body mass index (BMI) > 25 and moderate binge-eating behavior as assessed by the Binge Eating Scale (BES) were recruited for this study.
Main Outcome Measures: fMRI BOLD response during exposure to high-calorie taste cues.
Results: The results showed that exposure to high-calorie taste cues elicited fMRI BOLD response in the reward system of individuals with high BMI, and, more importantly, that this hyper-responsivity increases with greater number of binge-eating symptoms (cluster-corrected $p < .05$, $z = 1.9$).
Conclusions: These findings support an overlapping neural model of addiction and self-regulatory failure over eating that may lead to problems with weight in humans. These findings offer insight into the prevention and treatment of disordered eating.

Introduction

Recent research has suggested that aspects of disordered eating share mechanisms associated with addiction (Gearhardt and Corbin, 2011), specifically with respect to craving (Haddock and Dill, 2000). Addiction is commonly defined as the presence of tolerance, physical dependence, loss of control over use, and/or craving (Gordis, 1990; Jonas, 1989). People who pathologically overeat, such as binge eaters, report similar experiences with abuse of food such as craving, loss of control after they start eating, impaired functioning, preoccupation with food, and the use of binge eating to regulate emotions and stress (Connors and Johnson, 1987; Jansen, 1998; Krahn, 1991). Aspects of tolerance in disordered eating have been demonstrated as decreased neural response during receipt of palatable food in obese individuals as compared to a lean population (Green et al., 2011), weight gain (Stice et al., 2010) and habitual consumption that is independent of weight status (Burger and Stice, 2012). These findings in humans are concordant with animal models of compulsive eating (Alsio et al., 2012). In the animal literature, exposure to foods with high fat and sugar content resulted in binge-eating behavior resulting in significant weight gain (Avena et al., 2012). Taken together, studies suggest a possible overlap in mechanisms that mediate appetitive motivation for alcohol and drugs and the mechanisms that mediate appetitive motivation for food (Kelley et al., 2005; Robinson and Berridge, 2000; Volkow et al., 2008). First, the rewarding properties of both food consumption and alcohol/drug use have been linked to increases in dopaminergic activity in brain reward circuits (Wise and Rompre, 1989). Second, as in chronic drug use that results in poor inhibitory control over drug intake, repeated exposure to certain foods (particularly those with a high fat and sugar content) in vulnerable individuals can also result in compulsive food consumption, poor food intake control, conditioning to food stimuli, and, over time, unhealthy weight gain (Kalivas and Volkow, 2005). Third, there are similarities in the types of medications shown to decrease drug and food consumption in animal models of drug abuse and obesity respectively (i.e., cannabinoid antagonists, baclofen, GABA agonists, and CRF antagonists). In a direct investigation of this overlapping model, it was found that rats that were

* Corresponding author at: UTD Center for BrainHealth, 2200 W. Mockingbird Lane, Dallas, TX 75235, USA. Fax: +1 214 905 3026.
E-mail address: Francesca.Filbey@utdallas.edu (F.M. Filbey).

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exposed to a cafeteria diet developed symptoms of compulsive feeding that resulted in obesity. This behavior was reported as "addiction-like," characterized by resistance to food consumption disruption by an aversive conditioned stimulus similar to drug-addicted animals. Further, post-mortem examinations found down-regulation of D2 receptors in the striatum (Johnson and Kenny, 2010), which is posited to be the underlying mechanism that leads to reward hyposensitivity in addiction. Current research suggests that this disruption in reward sensitivity serves as a combined vulnerability factor for substance abuse and obesity, and when coupled with environmental factors, may significantly increase the chance of obesity (Volkow and Wise, 2005). These findings provide strong evidence for the overlapping neural mechanisms between compulsive overeating (eating uncontrollably even when not physically hungry, commonly referred to as "binge eating") that leads to obesity and substance abuse, and further support the role of dopamine in this dysfunction.

Despite the recent animal literature on parallels in behavior between compulsive overeating that could lead to obesity and addiction, research in the underlying neural processes in human remains sparse. We are only aware of one neuroimaging study by Gearhardt et al. (2011) that directly examined this relationship using a food addiction survey in lean to high BMI individuals (i.e., BMI = 23.8–39.2) (Gearhardt et al., 2011). This study utilized a novel 25-item scale, The Yale Food Addiction Scale (YFAS), to categorize individuals into two groups based on their addiction scores. The authors compared individuals with high food addiction scores (>3 items endorsed) to individuals with low food addiction scores (≤1 item endorsed) and found that individuals with high food addiction scores had attenuated response in lateral orbitofrontal cortex (OFC) during exposure to food cues (vs. control cues). Contrary to the authors' expectations, there were no differences in the reward areas between the two groups. Notably, the low frequency of food addiction symptoms in this cohort based on their scale (i.e., maximum number of items endorsed was 4 out of 25) suggests that this study's sample may not adequately capture all behavior related to addiction. As the authors cautioned, none of the participants met the clinical diagnosis for food addiction based on this novel scale. By the standards of their scale (YFAS), clinically significant impairment or distress is a criterion for food addiction. These symptoms are often seen in eating disorders, which this particular study used as exclusion criteria. Another potential explanation for the absence of difference in reward areas may be due to the non-specificity of the cue used. All participants were provided chocolate milkshake during the task, which may have dampened the reward circuitry response due to variable levels of cue salience across participants. Thus, in the present study, we utilized cues of personal relevance and a Binge Eating Scale (BES) (Gormally et al., 1982) to test an overlapping model of compulsive overeating that leads to obesity and addiction by examining reward system function in high BMI individuals who exhibit loss of control over eating (i.e., moderate binge-eating behavior). We operationalized compulsive overeating in terms of having moderate binge-eating behavior based on the BES. Further, to validate the involvement of the reward circuit in response to taste cues in this population, we also determined functional connectivity between areas in the reward system.

Materials and methods

Participants

Thirty-two individuals with BMI≥25 were recruited through flyers and media advertisement in the Albuquerque, NM metro area and provided informed consent to participate in this study. Our decision to require high BMI was to maximize the recruitment of a homogeneous group of individuals with moderate binge-eating behavior whose loss of control over eating was associated with problems with increased weight (vs. binge eaters who purge). Binge eating was assessed using the Binge Eating Scale (BES) and participants with a minimum score of 8 were included in the study. All participants were right-handed and free of MRI contraindications (i.e., no metallic implants, claustrophobia, pregnancy, etc.). Participants were compensated for their participation. The University of New Mexico Human Research Review Committee approved all procedures used. Six of whom were excluded from further analyses due to problems with their data (e.g., incomplete scans, movement > 2 mm). Table 1 describes the 26 who completed the fMRI session and were included in these analyses.

Procedure

The participants were required to be right-handed, between 18 and 50 years of age, English speaking, and to have BMI≥25. Participants who met these inclusion criteria were invited to participate in the study, which took place at The Mind Research Network in Albuquerque, NM. Participants were instructed to eat a typical meal 4 h prior to the scan time, but to abstain from eating after that in order to capture the typical hunger level as one approaches their next meal. Hunger rating was measured on a Likert scale between 1 and 10 (1 = not at all hungry, 10 = very hungry). Participants were also instructed to abstain from caffeine for 4 h prior to the scan. During the experiment, participants completed pen and paper questionnaires and were administered a neuropsychological battery (not reported here). Prior to scanning, participants were weighed on-site, and BMI was calculated using the NIH National Heart Lung and Blood Institute's BMI calculator (www.nhlbisupport.com/bmi). Once in the MRI scanner, we collected a high-resolution anatomical scan for registration and localization of the fMRI data, and a Stop-Signal fMRI Task (not reported here). Participants were then administered a gustatory high-calorie cue exposure task similar to that described in Filbey et al. (2008). Specifically, each trial consisted of a continuous delivery (approximately 1 ml per trial) of either a high-calorie taste cue or water for 20 s (2×8-s periods of cue exposure with a 2-s swallow period intervening) followed by a 16-s washout period where no tastes were delivered (see Fig. 1). The participants were then asked to rate their level of urge (6 s). Each trial ended with a 2-s prompt for the proceeding trial. Thus, for 2 runs (8 min and 48 s each) with 12 trials (44 s each) each, the total length of this task was 17 min and 36 s, resulting in a total of 24 ml (1.6 tablespoons) of tastes (.8 per cue type).

We determined personally relevant cues based on each participant's response when asked, "What is your most frequently consumed high-calorie drink?" Examples of the personally relevant high-calorie tastes delivered include Pepsi (100 cal, 0 g fat, 28 g sugar), chocolate milk (210 cal, 9 g fat, 26 g sugar) and cream soda (190 cal, 0 g fat, 31 g sugar). To eliminate carbonation from beverages that could cause erratic delivery of the tastes through the delivery tubes, we followed a procedure of freezing and thawing the beverages prior to the experiment. This procedure thoroughly eliminates carbonation and allows for uninterrupted delivery of the liquids during the experiment. We presented water as a control cue for all of the participants due to the inherent incentive value of water, which makes it a potent control for salience as observed differences between it and the high-calorie cue would be suggestive of an even greater reward value of the high-calorie

Table 1
Characteristics of the participants.

	All (*N* = 26)
Age, mean (SD)	32.88 (11.04)
Male, *n* (%)	12 (46%)
BMI, mean (SD), range	32.72 (5.98), 25.10–51.50
BES, mean (SD)	18.91 (9.59)
Hunger rating, mean (SD)*	6.4 (2.8)

* Data available for only 15 participants, 1 (not at all hungry) – 10 (extremely hungry).

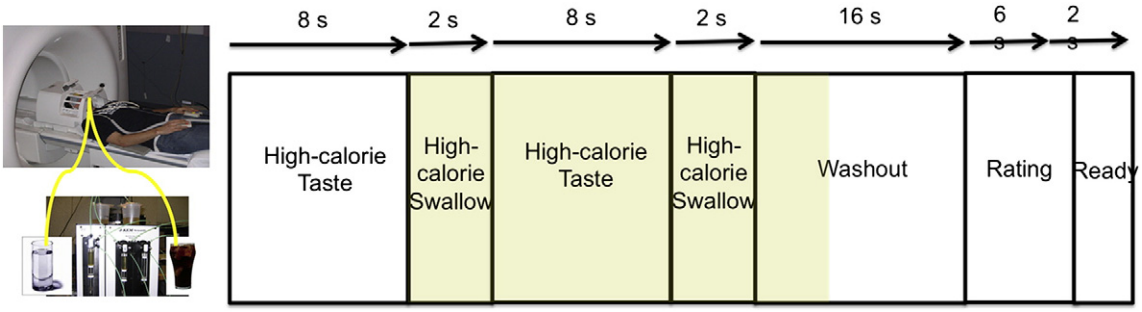

Fig. 1. Schematic of a single trial. For each trial, the participants were presented with a cue exposure period, during which the participants were shown visual prompts. This was followed by a washout period. The trial ended with an urge rating period during which participants were asked to rate their urge to consume food via right-handed button press. The visual presentations, timing of each event (in seconds) and regressor (i.e., highlighted in yellow).

cue. The task was presented using a front projection to a mirror system mounted on the head coil. Responses were recorded using a fiber-optic pad. Stimulus presentations were delivered using E-Prime (Psychology Software Tools, Inc.). The timing of the stimulus presentation was synchronized with trigger pulses from the magnet in order to ensure precise temporal integration of stimulus presentation and fMRI data acquisition.

MRI images were collected using a 3T Siemens Trio. fMRI scans were collected using a gradient echo, echoplanar sequence with ramp sampling correction using the intercommissural line (AC-PC) as a reference (TR: 2.0 s, TE: 27 ms, α: 70°, matrix size: 64×64, 32 slices, voxel size: 3×3×4 mm^3). Because the orbitofrontal cortex (OFC) is involved in the craving/reward system and can suffer from severe signal drop-out caused by susceptibility effects, a tilting acquisition was applied. The high-resolution anatomical MRI scan was collected with a multi-echo MPRAGE (MEMPR) sequence with the following parameters: TR/TE/TI = 2300/2.74/900 ms, flip angle = 8°, FOV = 256×256 mm, slab thickness = 176 mm, matrix = 256×256×176, voxel size = 1×1×1 mm, number of echos = 4, pixel bandwidth = 650 Hz, total scan time = 6 min.

Analyses

Pre-processing of fMRI data followed a standard procedure. First, all slices were interpolated to a common time point (i.e., slice-time correction) to correct for differences in slice acquisition. The images were realigned using INRIalign, a motion correction algorithm unbiased by local signal changes. As mentioned above, participants who had translational movement greater than 2 mm were excluded from further analyses. Next, using FEAT (fMRI Expert Analysis Tool) Version 5.98, part of FSL (fMRIB's Software Library, FMRIB Analysis Group, The University of Oxford, UK), the following pre-statistics processing was performed: non-brain tissue/skull removal using BET (Brain Extraction Tool); spatial smoothing using a Gaussian kernel of FWHM 8 mm^3; mean-based intensity normalization of all volumes by the same factor; and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction. The first seven volumes of all EPI runs were discarded to allow the MR signal to reach steady state.

Explanatory variables were created by convolving the stimulus timing files with a double gamma hemodynamic response function in FEAT. A multiple linear regression analysis was performed to estimate the hemodynamic parameters for different explanatory variables (i.e., active condition for high-calorie cues, active condition for control cues) and a corresponding t-statistic indicates the significance of the activation of the stimulus. Because we were interested in the brain's response to high-calorie tastes that were above and beyond the brain's response to water, contrast maps were created by subtracting the exposure periods of the high-calorie tastes and water. Statistical maps were registered to the Montreal Neurological Institute (MNI) template with a two-step process. First, EPI images were registered to the high-resolution MPRAGE image, which was subsequently registered to the 152 brain average MNI template. These registration steps were performed using FLIRT (FMRIB's Linear Image Registration Tool). After transformation into MNI space, group-level analyses were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects). How compulsive overeating, and overweight and obesity are associated with the BOLD response to high-calorie tastes were examined by adding the total BES and BMI scores, respectively, as additional covariates. We set our threshold and multiple comparison correction using FEAT's cluster-thresholding method, which first defines contiguous clusters using a Z statistic maximum height threshold. Then, each cluster's estimated significance level (from Gaussian random field theory) is compared with the cluster probability threshold. Only clusters that meet these two levels of threshold are considered significantly active.

As a secondary analysis, we examined whether the reward pathway is a functional network involved in response to high-calorie taste cues. To determine how regions within the reward network are correlated in their activation to the taste cues, we performed psychophysiological interactions (PPI) analysis (Friston et al., 1997), see tutorial O'Reilly et al., 2012). PPI analysis finds areas across the whole brain whose activity is modulated by both task and the ongoing activity in the NAc (i.e., the interaction effect of the two). To that end, we extracted the time course of an anatomically defined mask for the nucleus accumbens (NAc; a key region in the reward circuit, Filbey et al., 2008) from all of the participants and added it to our model as a physiological regressor. Additional regressors were defined by the interaction (PPI) of the physiological regressor with the primary task regressors (high-calorie taste cue and water). These regressors were used to fit a GLM for the contrast between the interaction regressors where the main effect of NAc timecourse and task regressors are terms of no interest (i.e., PPI is most sensitive to the modulatory effects of task and NAc). Second level analyses generated t-maps within group for the PPI regressors. Resulting maps represent the variance over and above the main effects of the BOLD response to the high-calorie taste cue and correlations with NAc (Friston et al., 1997). In other words, the PPI analysis indicates how synchronous the BOLD response is of the NAc with other areas of the brain during high-calorie taste cues (vs. water). We expect that similar to the addiction literature, response of the NAc will be synchronous with other areas of the reward circuit, such as the orbitofrontal cortex (OFC) and striatum, therefore suggesting stronger connectivity within reward areas during high-calorie taste cues vs. water in our sample of high BMI individuals with moderate binge-eating behavior.

Results

Main effects of high-calorie taste cues

As expected, contrasts between exposure to high-calorie taste cues and exposure to water showed greater activation in a large cluster (cluster size = 44,767 voxels) encompassing several areas that underlie reward processes such as the medial OFC, ventral tegmental area (VTA), insula, caudate, putamen, NAc, and precuneus (cluster-corrected $p<.05$, $z=1.9$) (peaks are listed in Table 2). There was also greater activation in other areas such as the cingulate gyrus, supplementary motor area, thalamus and temporal lobe, as well as visual processing areas in the occipital lobe (cluster-corrected $p<.05$, $z=1.9$). Additionally, greater neural response was also found in areas underlying emotional processes such as the amygdala and hippocampal areas (cluster-corrected $p<.05$, $z=1.9$) (peaks are listed in Table 2 and Fig. 2).

Associations between BOLD response to high-calorie and compulsive overeating

Lastly, tests of how the neural response to high-calorie tastes is associated with compulsive overeating indicated a significantly positive correlation between BOLD response to high-calorie tastes and BES scores in a cluster (cluster size = 12,144 voxels) that includes the amygdala, putamen, insula, posterior cingulate gyrus, precuneus, hippocampus, thalamus, cingulate gyrus, VTA, medial frontal gyrus as well as other areas in the occipital and temporal lobes (cluster-corrected $z>1.9$, $p<.05$) (see Table 3 and Fig. 3). There was no significant correlation between BMI and neural response to high-calorie tastes. One explanation for this could be the limited range of BMI scores for our sample as all participants were required to have a BMI > 25.

Functional connectivity in reward circuit during high-calorie taste cues

The results of the PPI analysis showed that the seed region, namely, the NAc, is significantly more correlated with several areas within the reward system including medial OFC and dorsal striatum in response to high-calorie taste cues vs. water (see Fig. 4) (maximum Z-score = 3.1; cluster-corrected $p<.05$, $z=1.9$). These findings provide evidence for stronger associations between these reward processing areas in response to high-calorie taste cues vs. water.

In order to determine how these stronger correlations with NAc are associated with problems with weight and compulsive overeating, we correlated the PPI interaction with BMI and BES scores separately. Our results showed a positive correlation between NAc and posterior cingulate/precuneus area and occipital lobe and BES scores, such that the stronger the correlation between these regions, the more binge-eating symptoms (cluster size = 4,130; maximum Z-score = 3.1; cluster-corrected $p<.05$, $z=1.9$). There were no correlations in the negative direction.

Table 2
Main effects of high-calorie cues. Greater BOLD response was found in a large cluster during personally relevant high-calorie tastes vs. water. This table describes this activation in terms of local maxima derived using FSL's cluster program. BA = Brodmann area, R = right, L = left.

Max *z*-score	*x*, *y*, *z*	Localization	BA area
1 cluster (size = 44,767 voxels)			
5.47	−16, −78, −2	L lingual gyrus	18
5.23	2, −82, 8	R precuneus	8
5.22	2, −86, 6	R lingual gyrus	17
5.06	−24, −70, −14	L fusiform gyrus	19
4.79	24, −76, −10	R fusiform gyrus	19
4.75	−10, −94, 16	L cuneus	18
4.29	2, −10, 58	R precentral gyrus	6
3.85	6, 10, 52	R paracingulate gyrus	6
3.45	4, −24, 58	R medial frontal gyrus	6
3.42	−40, 6, 26	L inferior frontal gyrus	9
3.41	4, 24, 50	R superior frontal gyrus	8
3.38	−4, 10, 38	L anterior cingulate gyrus	32
3.16	−16, 6, −18	L parahippocampal gyrus	34
3.04	22, 20, −18	R orbitofrontal gyrus	47
2.93	−20, −4, −18	L amygdala	–
2.90	−38, 6, 16	L insula	13
2.75	16, −4, 24	R caudate	–
2.72	20, 16, −16	R orbitofrontal gyrus	47
2.63	−18, 22, −8	L ventral striatum	–
2.35	10, −30, 20	R thalamus, pulvinar	–
2.33	12, 4, 16	R caudate	–

Discussion

Several studies have characterized the neural mechanisms that underlie food intake and/or response to food cues (for review see Volkow et al., 2011). How these mechanisms are related to weight problems, however, has been inconsistent (for review see Burger and Stice, 2011; Zhang et al., 2011). In this study, we focused not on problems with weight, but on possible overlapping mechanisms between compulsive overeating and addiction in high BMI individuals. Concordant to previous studies using food cues, we found that personally relevant high-calorie tastes elicited greater activation in reward areas of the brain compared to water (Bassareo and Di Chiara, 1999; Berns et al., 2001; Frank et al., 2003; Grabenhorst et al., 2010; James et al., 2001; Pagnoni et al., 2002) and that these areas form a functionally connected circuit as determined by PPI analysis. The PPI analysis showed that there was stronger correlation between the NAc and the OFC, important regions within the reward pathway, in response to the high-calorie taste cues (vs. water). The NAc projects to the OFC (via the mediodorsal nucleus of the thalamus) and, in turn, has dense projections back to the NAc. Involvement of the OFC may reflect the integration of input regarding stimulus response associations for appetitive stimuli (Rolls, 2000; Tremblay and Schultz, 1999). The OFC also receives input from limbic structures such as the amygdala and hippocampus. Thus, the OFC may integrate limbic information and modulate the system's response to appetitive stimuli. In addition, the top-down connections between the OFC and limbic structures may be involved in inhibitory control and impulsive behavior, which has important implications for the loss of control over food consumption (Goldstein and Volkow, 2002; Volkow et al., 2002). Response in the dorsal striatum may be due to processes related to the initiation of feeding (Rolls, 1993). In an $H_2^{15}O$-PET study in healthy self-proclaimed "chocolate-lovers" (Small et al., 2001), it was also found that rCBF in the dorsal striatum decreased along with decreased motivation to eat, providing further evidence for its role in the initiation of feeding behavior. Indeed, in a review by Balleine et al. (2007), they reported that the dorsal striatum is important in aspects of decision-making, particularly those related to goal-directed behavior based on expected reward value (Balleine et al., 2007). However, to date, the way in which this relates to disordered eating has not yet been examined. Our findings also showed large activation in the occipital lobe in response to the high-calorie taste cues (vs. water). In the current study, the delivery of the tastes was concurrent with visual instructions ("high-calorie taste" and "high-calorie swallow"; see Fig. 1). Thus, it is possible that greater response in the visual cortex during high-calorie taste cues may be due to top-down modulation associated with increased arousal during the high-calorie taste cues. Anticipation of rewards following exposure to conditioned visual stimuli with reward has been reported in occipital areas, suggesting a role of the primary visual cortex in higher cognitive functions (Shuler and Bear, 2006).

Further, we investigated how this activation in the reward pathway is associated with compulsive overeating as seen in binge-eating behavior. We found that reward system hyper-responsivity was

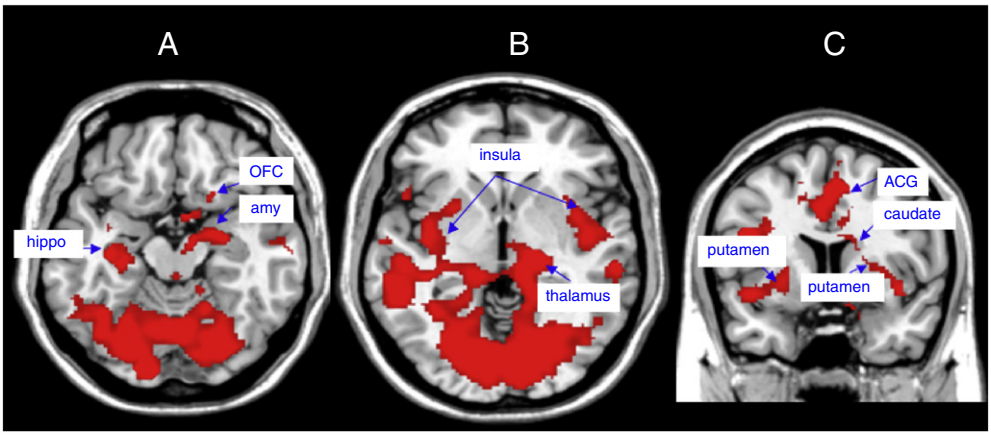

Fig. 2. Greater activation in several areas of interest during high-calorie food cues compared to control cues (cluster-corrected $z = 1.9$, $p < .05$). (A) Orbitofrontal cortex, hippocampus and amygdala. (B) Insula and thalamus. (C) Anterior cingulate gyrus and dorsal striatum (caudate, putamen). Right side of the image reflects left hemispheric activations.

associated with binge-eating behavior such that the greater binge-eating behavior symptoms, the greater the BOLD response to high-calorie tastes in areas that underlie goal-oriented behavior based on reward salience (putamen), interoceptive awareness of craving (insula, posterior cingulate gyrus), and affective evaluation (amygdala) (for review see Tsuchiya and Adolphs, 2007). Reviews of the current neuroimaging data support our claim that compulsive overeating resulting in obesity is a result of dysregulation of the human reward system and is similar to what is seen in other forms of substance abuse. These findings of hyper-responsivity in reward areas of individuals who report loss of control over eating support the incentive-sensitization hypothesis. The incentive–sensitization hypothesis posits that exposure to cues associated with addictive substances enhance dopamine function that is attributable to the incentive salience or the 'wanting' (vs. 'liking') of the substance. This notion also states that repeated exposure to addictive substances leads to changes in the reward system's homeostasis rendering it sensitized to the associated stimuli or cues (Robinson and Berridge, 1993). These findings are in accord with other studies of the effects of food cues in reward areas including greater OFC (Stice et al., 2010), NAc, limbic structures and anterior cingulate (Stoeckel et al., 2008) response in obese versus lean individuals. Taken together, these findings provide strong evidence for an overlapping model of neural mechanisms that underlie symptoms of craving that lead to addiction and obesity, which is in accord with the recent animal study that highlights addiction-like responses in behavior and activation seen in striatal areas of obese rats (Johnson and Kenny, 2010).

Table 3
Brain–behavior correlations. There was a significant cluster of activation with significant correlation between BOLD response and Binge Eating Scale. This table describes this activation in terms of local maxima derived using FSL's cluster program. BA = Brodmann area, R = right, L = left.

Max *z*-score	*x*, *y*, *z*	Localization	BA area
1 cluster (size = 12,144 voxels)			
4.35	42, −72, −8	R inferior lateral occipital gyrus	18
4.34	38, −74, −4	R inferior lateral occipital cortex	19
3.87	32, −64, −14	R fusiform gyrus	19
3.82	40, −76, 18	R middle occipital cortex	19
3.64	52, −60, 14	R inferior lateral occipital cortex	39
3.64	54, −54, 0	R middle temporal gyrus	37
3.59	12, −44, 34	R precuneus	31
3.56	8, −42, 34	R posterior cingulate gyrus	31
3.44	8, −36, 36	R posterior cingulate gyrus	31
3.42	−16, −42, 32	R posterior cingulate gyrus	31
3.36	2, −44, 34	R cingulate gyrus	31
3.02	−30, −14, −10	L amygdala	–
2.85	0, −30, 30	cingulate gyrus	23
2.82	48, −16, −6	R insula	13
2.95	−32, −26, 4	L lentiform nucleus, putamen	–
2.95	−28, −18, −10	L hippocampus	–
2.92	8, 24, 12	R anterior cingulate	24
2.70	10, −6, −4	R thalamus	–
2.69	20, 10, 10	R lentiform nucleus, putamen	–
2.66	0, −64, 44	L precuneus	7
2.65	12, 6, 8	R caudate body	–
2.64	6, −16, −10	R substantia nigra/VTA	–
2.47	−36, −4, −2	L insula	–
2.46	−32, −6, −4	L lentiform nucleus, putamen	–
2.42	−18, −6, 56	L medial frontal gyrus	6

With regards to BMI, our results did not corroborate previously reported associations between response to food cues and BMI (Stice et al., 2010; Tetley et al., 2009; Yokum et al., 2011). However, this absence of correlation between neural response to food cues and BMI has been shown in previous studies (Gearhardt et al., 2011; Wang et al., 2004) and suggests that this pattern of neural response is specific to compulsive eating, which in turn may contribute to future weight problems not completely captured by BMI. Additionally, BMI may not be an accurate predictor of one's propensity to overeat as other factors could lead to high BMI such as a predisposition toward high body weight not necessarily related to food consumption (for review see Choquet and Meyre, 2011).

Because this study presented personally relevant cues (vs. standard cue consistent across participants), it is possible that differences in the characteristics of food cues may have confounded the BOLD response. To address this possibility, we first determined how differences in these content factors may be related to binge-eating behavior. We did not find a significant correlation between BES scores and calorie-, sugar- or fat-content of the high-calorie cues. As a second test, we performed correlations between the BOLD response to high-calorie cues and content factors. These analyses did not show significant correlations between BOLD response to high-calorie cues and calorie- or fat-content. However, sugar content was found to be positively correlated with BOLD response to cues in areas related to executive control (cingulate gyrus) and self-awareness (precuneus) (for review see Maddock, 1999) (see Supplement). This suggests that the higher the sugar content of the cue, the greater neural response in self-monitoring areas during cue exposure. No significant negative correlations were found. This finding corroborates previous studies that used chocolate milkshake across participants. However,

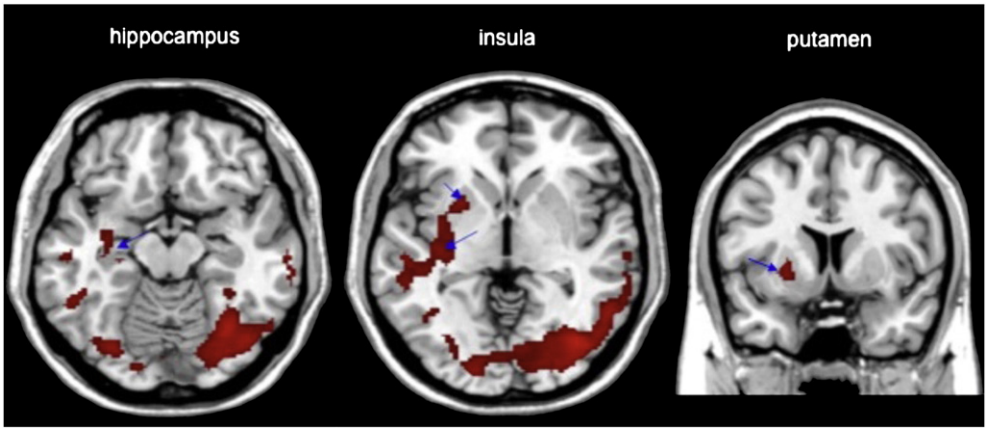

Fig. 3. Significantly positive areas of correlation between BOLD response to high-calorie tastes (vs. water) and BES in hippocampal area, insula, and putamen (cluster-corrected $z = 1.9$, $p = .05$). Right side of the image reflects left hemispheric activations.

because sugar content and BES were not associated, it is postulated that the higher responsivity with higher BMI is not due to sugar content alone. Future studies should test the specificity of this response to highly potent stimuli by determining if this difference is observable between less disparate cues, i.e., high- vs. low-calorie cues. Lastly, the process of removing carbonation from some of the high-calorie stimuli (e.g., soda) required freezing and subsequent thawing that could have resulted in a form of the beverage that may somewhat be different from what participants are familiar with. However, given that the participants had high accuracy in recognizing their provided taste stimuli (verified following the experiment), any potential effect may be minimal.

Conclusions

In this study, we focused on aspects of food consumption that parallel primary behavioral symptoms of addiction, such as craving, and found significant correlations with response to high-calorie food cues and compulsive overeating with activation in reward pathway similar to what is shown in the presence of other addictive substances. Our findings underline the need to define the different etiologies that lead to obesity, with specific focus on psychophysiological risk factors that contribute to the hedonic aspects of overeating. The concept of "food addiction" remains highly debatable. For example, the parallels described here may more accurately reflect disorders of abuse rather than dependence (which is a

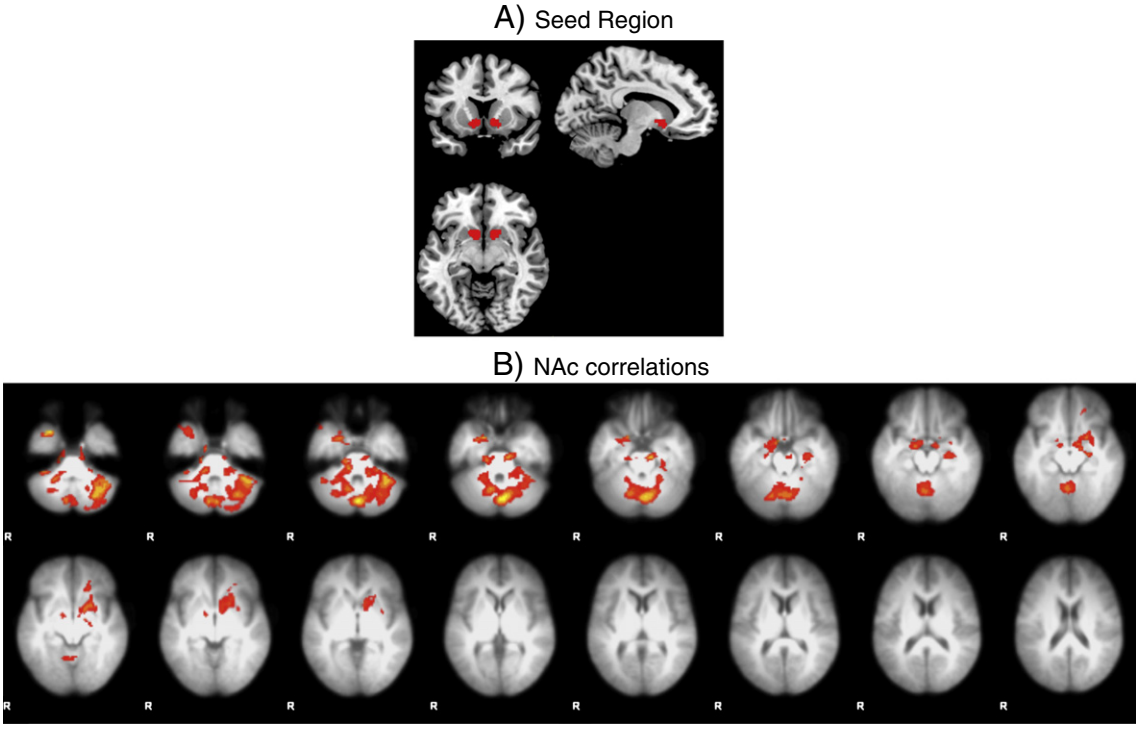

Fig. 4. Whole brain correlations with NAc (seed region) during exposure to high-calorie tastes using PPI analysis (cluster-corrected $z = 1.9$, $p < .05$). Right side of the image reflects left hemispheric activations.

necessary criteria for addiction) as all humans are dependent on food. On the other hand, others suggest that psychological disturbances such as anxiety experienced during periods of decreased food intake (e.g., dieting) are akin to withdrawal symptoms from drug addiction (Volkow and Wise, 2005). Nevertheless, the importance of these studies is in providing the much needed knowledge on mechanisms that could aid in the development of prevention and intervention strategies for disordered eating. In this light, the determination of shared mechanisms between problems with obesity and problems with addiction could facilitate effective treatment for addiction (e.g., those that target craving mechanisms) that could potentially also benefit compulsive overeating.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2012.08.073.

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