Running Head: REWARD RESPONSE IN PAST AND CURRENT DIETERS

Differential reward response to palatable food cues in past and current dieters: An fMRI study

Alice V. Ely, M.S.,[a] Anna Rose Childress, Ph.D.,[b] Kanchana Jagannathan, M.S.,[b] Michael R. Lowe, Ph.D.,[a]

[a] Department of Psychology, Drexel University,

[b] Department of Psychiatry, University of Pennsylvania

Corresponding Author: Alice V. Ely, M.S., Drexel University,

Bellet Building MS 626, 1505 Race St, Philadelphia, PA 19102.

Phone: 215-762-3679, Fax: 215-762-7441

Email: ave24@drexel.edu

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/oby.20599

What is already known about this subject?

- Obese and normal-weight individuals differ in their neurobiological response to highly palatable food.
- Recent studies suggest that restrained eaters may exhibit different patterns of brain activation in response to food reward than unrestrained eaters.
- Behavioral research shows that dieters have different patterns of eating behavior, and may be more prone to weight gain than restrained eaters.

What does this study add?

- The first fMRI study of dieters' neurobiological reward response to highly palatable food.
- Evidence that those with a history of dieting show higher levels of brain activation in response to highly palatable food after having eaten than those who have never dieted before or those currently dieting.
- Evidence demonstrating differential patterns of brain activation in current dieters as compared to historical dieters, despite similar weight history and past frequency of dieting.

Abstract

Objective: Prior neuroimaging research (1,2) has shown that restrained and unrestrained eaters demonstrate differential brain activation in response to food cues that parallels their food intake in lab studies. We extended these findings by comparing brain activation in response to food cues in normal weight Nondieters, Historical Dieters, and Current Dieters under the conditions that mimicked past lab studies.

Design & Methods: Participants (N=30) were shown pictures of highly and moderately palatable food and neutral cues while being scanned in an fMRI BOLD paradigm following an eight-hour fast and again after a liquid meal.

Results: In the Fed state, Historical Dieters showed elevated reward circuitry activation in response to highly palatable food, as compared to Nondieters and Current Dieters. In contrast, Current Dieters showed increased activation in response to moderately palatable food in the Fasted state compared to Historical Dieters, and this activation was significantly correlated with inhibition.

Conclusions: The parallels between eating behavior and regional brain activation across groups suggest that 1) a neurophysiological response which could represent a vulnerability to overeat exists in some normal weight young women that may increase susceptibility to weight gain in the long term, and 2) current dieting temporarily reverses this vulnerability.

Keywords: Dieting, brain, predisposition

Introduction

Given the magnitude of the obesity epidemic and the difficulty of treating it successfully, an emphasis on prevention is critical. Preventative interventions will be most efficient if we have empirically-based evidence of factors that predict and protect against weight gain in normal weight individuals. One of these factors is dietary restraint, a dimension measured by Herman and Polivy's Restraint Scale (3) that encompasses past unsuccessful dieting, emotional eating and weight fluctuation. In behavioral studies, this characteristic is associated with a counterintuitive increase in food intake following a preload (4). Paradoxically, it seems that eating does not reduce (and may, in fact increase) restrained eaters' desire to eat. It follows that, due to the increased desire to eat after a preload, they would be at increased risk for weight gain and potentially, obesity. In fact, a history of weight-loss dieting (historical dieting) robustly predicts future weight gain, and does so more consistently than measures of restraint (5-7). This behavioral evidence suggests that there may be a neurobiological basis for individual differences in appetitive responsiveness following a meal.

Two recent studies (1,2) examined the brain-based underpinnings of overeating and weight gain proneness in restrained eaters (8) by measuring brain activity in response to food cues before or after eating, paralleling behavioral preload studies of restraint (9). Participants with high dietary restraint, when viewing pictures of highly palatable foods after consuming a preload, showed more activity than unrestrained eaters in the orbitofrontal cortex, prefrontal cortex (PFC), insula, striatum and nucleus accumbens, brain regions related to desire for food and expectation of reward, in addition to behavioral inhibition in the case of the PFC. This post-meal activation suggests that reward value of highly palatable food is independent of hunger state in restrained eaters, and that consumption may not diminish the motivation to eat or,

potentially, elevate it. Further, *current* dieting status has been shown (10) to moderate the eating behavior of historical dieters. Current dieters significantly reduce their food intake following a preload (11), and (in contrast to historical dieters) will not work to obtain food even when little work is required (12).

Because dietary restraint can encompass both unsuccessful past dieters and those currently dieting, the aim of this study was to determine if specific types of dieting behavior affect brain activation in response to highly palatable food cues in normal weight individuals in fasted or fed states. It was hypothesized that historical dieters, i.e. those with a history of dieting who are not currently on a diet, would demonstrate elevated activity in reward-related regions when fed in comparison to 1) historical nondieters and 2) themselves when fasted.

Furthermore, assuming that neurophysiological differences between restrained and unrestrained eaters mirror their behavioral responding (1), we hypothesized that participants currently on a diet viewing highly palatable food, relative to historical dieters who are not currently dieting, would show 1) less activity in reward circuitry and greater activity in inhibitory regions when fed and 2) the opposite pattern when fasted. Nondieters were not directly compared to current dieters, as they would differ both on history of dieting and on current dieting status, thus it would be impossible to determine which of these variables underlie any differences between groups. This study is the first to examine neural correlates of historical and current dieting, which at a behavioral level have opposing influences on risk for overconsumption.

Methods and Procedures

Participants

Female participants were recruited from a large urban university. Informed consent took

place with prospective participants, including an explanation of the study purposes. Diet and weight history, demographics and psychiatric history were assessed using self-report questionnaires. In addition, participants had to be right handed, between 18 and 25 years of age, and with a BMI between 19 and 25 as determined by self-report, with weight confirmed by the researcher at the first study visit.

Participants were excluded from the study if they reported a history of a diagnosed eating disorder, as assessed by an abridged version of the Eating Disorder Examination (13), if they had begun taking any medication known to affect weight and appetite within the prior 6 months (including hormonal birth control), or currently smoked. Participants reporting no history of past dieting were excluded if they demonstrated high dietary restraint (as defined below) and historical dieters were excluded if the converse were true. Screening consent was obtained from all participants prior to determining eligibility and full informed consent was completed at the study visit prior to participation.

Comparison groups. Participants were divided into three groups based on past and current dieting status. Individuals reporting at least two intentional efforts to lose weight, but who were not currently dieting were labeled Historical Dieters (HDs, $N = 10$). Those reporting no history of weight-loss dieting were defined as Nondieters (NDs, $N = 10$). Current Dieters (CDs, $N = 10$) consisted of individuals who reported being on a diet at the time of scanning; they also had a history of at least two intentional efforts to lose weight.

Measures

Demographic information. A questionnaire was created to identify general demographic information. Participants were asked about age, ethnicity, weight, height, smoking status, and current medications.

Dieting and Weight History Questionnaire. The Dieting and Weight History Questionnaire, which has been used in multiple studies of dieting (4), asked participants to respond to questions concerning weight suppression, history of weight loss dieting, current dieting status, and whether or not the participant has ever had an eating disorder.

Hunger Questionnaire. The Hunger Questionnaire is a widely used measure of hunger and appetite for laboratory studies of eating-related behaviors (1, 14). This served as a manipulation check and to confirm compliance with instructions regarding food intake prior to the study visit.

Dietary Restraint Scale. Scores on the restraint subscale of the Three-Factor Eating Questionnaire (15) were of primary interest, with higher scores indicating greater cognitive restraint. It has been shown to have a robust factor structure and to be both valid and reliable measure of these three eating constructs (16).

Procedure

Study visit timeline is depicted in Figure 1. Participants who met inclusion criteria were invited to participate, and were instructed not to eat or drink for 8 hours prior to their study visit, apart from water. Resource limitations restricted the use of counterbalancing hunger status. Upon arrival at the scanning room, participants completed informed consent, took a urine pregnancy test, and were weighed using a digital scale wearing light clothing. Ratings of hunger and fullness were assessed using the Hunger Questionnaire. Following completion of the first scanning session, lasting approximately 10 minutes, they then consumed 500 kcal of a chocolate-flavored liquid meal (12g of fat, 80g carbohydrate, 18g protein). Participants then read or did homework for 20 minutes. Prior to the second scanning session, they completed hunger and fullness ratings again. The full study visit lasted approximately one hour.

The design was modeled on the Coletta et al study (1), but using a "fast", randomized event-related design that offers improved statistical power (fMRI) (17-19). Jittered stimuli were presented for 500 milliseconds, with an inter-stimulus interval (ISI) of 1.5 seconds. Though this is briefer than the 2-second presentation length by Coletta et al (1), research suggests that evocative cues as short as 33 milliseconds can activate reward-related limbic regions (20). The order of the pictures was quasi-randomized, with no more than three of the same cue categories in a row. Each of the sixteen cues (four from each stimuli category) was presented a total of twelve times in both the fasted and fed scanning blocks.

Stimuli. Cues were based on those used in Coletta et al (1), and were color photographs on a white background obtained through Google Image. Though our focus will be the food-related contrasts, we also included four romantic cues as a reference condition; these results are the topic of a separate manuscript. Cues were displayed on a rear-projection screen and viewed using a mirror mounted on the head coil. Highly palatable cues were french fries, pizza, chocolate cake, and ice cream. Moderately palatable cues were an apple, a slice of white bread, carrots, and a plain baked potato. Food was determined to be moderately or highly palatable based on informal normative data among women of the same age group. Neutral cues were a car, stapler, tree and bowling ball and were the same cues used in Coletta et al (1). All pictures were matched for hue and luminance, and a fixation cross was included between each cue. This manuscript will focus on brain activation unique to highly as compared to moderately palatable food to determine whether there is differential brain activation to highly palatable foods per se. Information regarding methods of MRI data acquisition and image processing is included in the Supplementary Material in the interest of space considerations.

A Priori Regions of Interest

Extant neuroimaging research in obesity implicates several regions related to reward or inhibitory processing in general and of food in particular, and from these, regions of interest (ROIs) were chosen. ROIs were anatomically defined using Harvard-Oxford Structural Atlas and then the ROI masks were thresholded for maximal probability at 25%. ROIs included amgydala, insula, striato-pallidal complex, medial orbitofrontal cortex, anterior cingulate cortex and prefrontal cortex. The amygdala is well-known to process hedonic value of stimuli and desirability (20, 22). The insula has been shown to be associated with food craving, as well as with affective valence of drug or sexual cues (19). Both the amygdala and insula are known to activate differently in obese individuals (23, 24). Research suggests that activation in the medial orbital frontal cortex (OFC) is related to reward value, palatability and desire for food (1, 22, 24). The striato-pallidal complex, made up of the caudate, putamen, nucleus accumbens, and globus pallidus, are identified as dopaminergic pathways related to hunger, craving and the rewarding properties of highly palatable food (25, 26). Anterior cingulate cortex and prefrontal cortex were included ROIs as these regions have been shown to relate to both self-control and to reward response. Anterior cingulate activation is linked to the ingestion of a meal (28) and to behavioral inhibition (29 for review), as well as anticipated food reward (30). Similarly, prefrontal activation is associated with hunger and palatability (31) in addition to resisting motivation to eat (27, 32). Left-sided prefrontal activity has been linked to approach behavior generally (33) as well as appetitive responsivity and disinhibition in obese individuals (31).

For the within-group analyses, Monte Carlo simulation was performed using 3dClustSim (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html), to control for type I error. Parameters used with the region of interest mask were an individual voxel $p = 0.003$ with 10,000 iterations, 2-sided and full width at half maximum (estimated from SPM). The

simulations demonstrated that a cluster extent of at least 32 contiguous voxels, exceeding a height threshold of $p<0.003$ corresponds to a cluster corrected threshold $p<0.05$. Because of its small size, we report clusters in the amygdala larger than 10 voxels uncorrected at $p < 0.003$.

Results

Descriptive variables

Descriptive data for all groups are reported in Table 1 and were calculated using SPSS version 19 software (IBM, Armonk, NY). The average age of participants was 20.27 years, with no significant differences between the three groups ($F(2,27)=2.15$, $p=0.136$). The current sample (N =30) was 26.7% Asian American, 6.7% African American, 3.3% Hispanic, 60% Caucasian and 3.3% Other. This ethnic breakdown is consistent with the population of the university at which the study took place. There were no significant differences between groups on BMI ($F(2,27)=1.34$, $p=0.279$). Each comparison was made up of 10 participants.

TFEQ restraint subscale scores differed significantly between groups ($F(2,27)=35.14$, $p<0.001$). Post-hoc Scheffe comparisons demonstrated that the HD and CD groups were significantly greater than the ND group ($p<0.001$), and CDs scored significantly higher than HDs ($p=0.027$). Weight suppression also differed significantly between groups ($F(2,27)=4.23$, $p = 0.025$). Post-hoc Scheffe comparisons showed a trend toward NDs being lower in weight suppression than the other two groups (ND vs. HD $p=0.061$; ND vs. CD $p=0.055$). HDs and CDs did not differ significantly on frequency of past dieting ($p = 0.399$).

Overall, participants rated moderate levels of hunger in the fasted state. Hunger ratings significantly decreased and fullness ratings significantly increased from fasted to fed (Table 2). Omnibus group differences on the second of the hunger ratings (“How strong is your desire to

eat right now?") approached significance ($F(2,29)=3.29$, $p=0.053$), however, post hoc tests revealed no significant differences between individual groups.

Imaging results

Proof of probe: Though our highly palatable food cues had been tested in a prior imaging study (1), they had not been tested for their ability to trigger reward circuitry at the shorter duration (500 msec presentations). Whole-brain analyses were conducted to ensure that highly palatable food cues would be evocative if used in the current paradigm. As shown in Supplementary Figure 1, our highly palatable food (High) cues indeed produced a robust activation of brain reward circuitry (including the ventral tegmental area/brainstem) in all three experimental groups, as compared to the brain response to Neutral cues. Comparisons of NDs and HDs and of HDs and CDs in both fasted and fed states are described in Supplemental Table 1.

A priori comparisons. We have intentionally constrained our statistical analyses to between-group comparisons within a state (Fasted or Fed) due to concerns about a change in baseline responding; see Technical Note in Supplementary Material. Below, we report 1) comparisons of NDs and HDs, 2) comparisons of HDs and CDs, in each of the Fasted and Fed conditions for the High v. Moderate cues (see Table 3). Figure 2 depicts the contrast maps of HDs v. CDs and HDs v. NDs when viewing High v. Moderate cues in a fed state.

In a fasted state, there were no significant differences in ROIs between HDs and NDs. When Fed, the only significant difference was that HDs demonstrated greater activation than NDs in the right anterior cingulate and the left middle frontal gyrus of the PFC.

Comparing CDs versus HDs in the Fasted condition, again there were no significant differences in ROIs between HDs and CDs. However, HDs showed significantly greater

activation than CDs in the Fed condition in the right middle frontal gyrus of the prefrontal cortex and bilaterally in the dorsal ACC, insula, caudate and pallidum.

Post-hoc comparisons. In order to elucidate whether differences in activation when comparing High v. Moderately palatable food cues are due to changes in response to the highly palatable food cues or to the moderately palatable food cues, between-groups comparisons were made for moderately palatable food versus neutral cues in each hunger state. Below we describe results for 1) comparisons of NDs and HDs, 2) comparisons of HDs and CDs, in each of the Fasted and Fed conditions for the Moderate v. Neutral cues.

In a Fasted state, the only significant difference was that NDs demonstrated significantly greater activation than HDs bilaterally in the prefrontal cortex. In the Fed state, however, neither group showed significantly greater activation than the other. When comparing HDs and CDs, neither group showed greater activation than the other in either state.

Discussion

Although past research has viewed frequent dieting as a cause of eating dysregulation and weight gain (34), we have argued that dieting in normal weight women is in fact a consequence of a pre-existing vulnerability toward over-consumption of palatable foods in an obesogenic environment (35, 36). Chronic dieting is a robust predictor of future weight gain (e.g., 6), and though acute dieting may temporarily delay weight gain, most dieters will eventually gain (or regain) weight (37). We therefore view the pattern of brain activation of HDs in this study as suggestive of a neurophysiological predisposition toward maintained desire for palatable food despite caloric repletion. Though the results are cross-sectional, the findings that CDs show less brain activation in response to food after having eaten than HDs (despite a similar level of past dieting) may reflect current weight control motivation and behaviors. Because both dieting

groups showed somewhat elevated weight suppression levels for college students (Lowe et la., 2006), and because weight suppression has itself consistently predicted future weight gain in past research, it is also possible that CDs are actively suppressing an effect of weight suppression on food intake, while HDs are not, and that this an acquired, rather than a predisposing, factor. However, our state-based interpretation is based on the assumption that CDs' diets will eventually end and their neurophysiological profile, and susceptibility to weight gain, will revert to that of HDs. Though there are of course other possible interpretations of these findings, the present findings, combined with past research (Lowe and Levine, 2005; Lowe and Thomas, 2009) leads us to favor the view that dieting in young women is a proxy of and reaction to susceptibility to weight gain, not a cause of such weight gain. Also, dieting may temporarily slow but rarely prevents eventual weight gain in the long term.

Overall, the findings of the current study replicated and expanded on the results found in restrained eaters (1, 2). Behaviorally, NDs, HDs and CDs exhibit different patterns of eating behavior, depending on hunger status (4). This study supports a neurobiological basis for these differences. Individuals reporting frequent past dieting differed from those who had no history of dieting when viewing highly palatable food cues in a fed state, as was hypothesized. Both when fasted and fed, NDs demonstrated no suprathreshold activation in response to highly palatable food cues as compared to HDs. HDs showed no significant difference in activation compared with NDs or CDs in ROIs when fasted, however, when fed, they demonstrated greater activity in a number of brain regions associated with hedonic value, anticipated food reward, desirability of food, and craving, as well as those linked to satiety and inhibition when contrasted with the comparison groups. The counterregulatory eating behavior of HDs (similar to classically-defined restrained eaters - 3) may be driven by an elevated reward response to highly palatable food

independent of hunger state, rather than by a "diet-breaking" effect of the preload (38), as in the latter case we would expect greater activation in inhibitory regions in the fasted state.

Furthermore, CDs (whose frequency of past dieting and weight suppression were similar to HDs) had differential activation relative to historical dieters across hunger conditions. Despite shared dieting and weight history, the pattern of brain activation seen in CDs appears to be markedly different from that of HDs. The attempt to actively inhibit highly palatable food intake is manifest in CDs neurobiological response to it, though it is unclear whether this reduction in reward activation is automatic or volitional. One recent study suggests that self-reported food intake does not differ between CDs, HDs and NDs, suggesting that CDs are eating less than wanted but not less than needed (39), and that it is not a state of negative energy balance that leads to a dampening of response. Because we did not see corresponding activation in the PFC or OFC regions linked to cognitive control, we can speculate that the reduced activation in a fed state may be due to a reduction in the rewarding value of food, whether through the conditioned association of highly palatable food with threat or simply prohibition. These results are consistent with literature noting marked differences in the eating behavior of current dieters compared to historical dieters or restrained eaters (4, 38).

There were some notable differences between the results of the Coletta et al (1) study comparing high v. moderately palatable food and the ones reported here. Though their results focused on restrained versus unrestrained eaters rather than dieting per se, current dieters and those high in weight suppression were excluded, so the sample used was arguably analogous to this one. When fasted, unrestrained eaters in Coletta et al (1) demonstrated activation in brain regions associated with hunger and food reward in response to highly palatable food cues that was not seen in NDs in the current study. Further, HDs showed activity in the prefrontal cortex

and anterior cingulate in a fed state, whereas Coletta et al found activation in orbitofrontal, insular, and dorsolateral prefrontal cortex, in restrained eaters. These differences might be due to sample characteristics, length of stimulus presentation (2 seconds in Coletta et al. versus 500 ms here) or stimulus characteristics. Generally, however, these findings provide confirmation of the results obtained by Coletta et al.

There are a few limitations with the current study. We included only college-aged females; older dieters and men across the age spectrum might show different brain responses under these conditions. In addition, palatability of food cues was not confirmed in the current sample, however given the marked difference in activation in response to highly versus moderately palatable food, we can conclude that these cues were regarded as provocative in dissimilar ways. Though the current study has a relatively small *N*, the statistical significance of the results and their consistency with the Coletta et al. study suggests that the demonstrated effects are robust. Further, the order effects of having participants undergo scans fasted and then fed may have had an influence on the results. However, given the habituation seen within-block, order effects might have more likely produced a reduction in activation than the pattern seen. For future similar studies, measurement of the baseline state with a quantitative perfusion technique such as Arterial Spin-Labeled Perfusion fMRI (40) would enable statistical management of differences in baseline state associated with hunger vs. satiety.

Stage of menstrual cycle was not controlled for in this study. Recent research by Alonso-Alonso and colleagues (41) shows that follicular phase impacted changes in brain activation in from fasting to fed states. However, lack of control over phase of menstruation would, if anything, increase error variance, theoretically reducing the ability to detect differences. In addition, results cannot be attributed to restraint as measured by TFEQ. Though restraint varied

significantly between groups, when controlling for restraint scores the patterns of activation of the three groups remained equivalent (results not reported here). Furthermore, CDs reported significantly higher restraint than HDs while demonstrating a different pattern of activation, suggesting that actively dieting qualitatively changes the impact of shared dieting history or restraint on appetitive neurobiological processes.

In sum, the main hypothesis was supported: individuals who had frequently dieted in the past showed reward-related activation after a meal when viewing highly palatable food cues as compared to individuals who had never dieted. In addition, a state of attempting to currently limit food intake to lose weight is related to brain activation patterns in ways consistent with extant behavioral research in current dieters. These results support the characterization of dieters, both historical and current, as prone to overeating (albeit under different conditions) and future weight gain (40). The evidence of susceptibility to overeating in normal weight individuals has implications for obesity prevention.

7. Conflict of interest

The authors declare no conflict of interest.

8. Acknowledgements

AVE, ARC and MRL conceived and designed the experiment, AVE and KJ analyzed data. AVE carried out the experiment. All authors were involved in writing the paper and had final approval of the submitted and published versions. The authors acknowledge the technical and general support of Yin Li and Charles Corbitt, respectively. Competing interests: the authors have no competing interests

9. References

1. Coletta M, Platek S, Mohamed F & Lowe, MR (2009) Brain Activation in Restrained and Unrestrained Eaters: An fMRI Study. *J Abnorm Psychol, 118,* 598-609
2. Demos KE, Kelley WM, Heatherton TF (2011) Dietary restraint violations influence reward responses in nucleus accumbens and amygdala. *J Cognitive Neurosci, 23,* 1952-1963
3. Heatherton TF, Herman CP, Polivy J, King GA, McGree ST (1988) The (mis)measurement of restraint: an analysis of conceptual and psychometric issues. *J Abnorm Psychol, 97,* 19-28
4. Lowe MR (1993). The effects of dieting on eating behavior: A three-factor model. *Psychol Bull, 114-1,* 100-121.
5. Lowe MR, Annunziato, R.A., Markowitz, J.T., Didie, E., Bellace, D.L., Riddell, L., et al. (2006). Multiple types of dieting prospectively predict weight gain during the freshman year of college. *Appetite, 47,* 83-90.
6. Neumark-Sztainer D, Wall M, Guo J, Story M, Haines J, Eisenberg M (2006) Obesity, disordered eating, and eating disorders in a longitudinal study of adolescents: how do dieters fare 5 years later? *J Am Diet Assoc, 106*, 559-68
7. Field AE, Austin SB, Taylor CB, Malspeis S, Rosner B, Rockett HR, Gillman MW, Colditz GA (2003) Relation between dieting and weight change among preadolescents and adolescents. *Pediatrics, 112,* 900-6.
8. Polivy J, & Herman CP. (1985). Dieting and binging: A causal analysis. *Am Psychol, 40,* 193-201.
9. Herman CP & Polivy J. (1980). Restrained eating. In A.J. Stunkard (Ed.), Obesity, 208-

255; Philadelphia: Saunders.

10. Lowe, M.R., & Thomas, J.G. (2009). Measures of restrained eating: Conceptual evolution and psychometric update. In Allison, D. & Baskin, M.L. (eds.), Handbook of assessment methods for obesity and eating behaviors (pp. 137-185). New York: Sage.
11. Lowe MR (1995) Restrained eating and dieting: replication of their divergent effects on eating regulation. *Appetite, 25,* 115-8
12. Giesen JC, Havermans RC, Nederkoorn C, Strafaci S, Jansen A (2009) Working harder to obtain more snack foods when wanting to eat less. *Behav Res & Ther, 47,* 13-7
13. Fairburn, C., Cooper, Z., & O'Connor, M. (2008). Eating Disorders Examination (EDE 16.0). In C. G. Fairburn (Ed.), Cognitive behavior therapy and eating disorders (pp. 265–308). New York: Guilford Press.
14. Friedman, M. I., Ulrich, P., & Mattes, R. D. (1999). A figurative measure of subjective hunger sensations. *Appetite*, 32(3), 395-404.
15. Stunkard AJ, Messick S (1985) The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger, *J Psychosom Res, 29,* 71-83.
16. Cappelleri JC, Bushmakin AG, Gerber RA, Leidy NK, Sexton CC, Karlsson J, Lowe MR (2009) Evaluating the Power of Food Scale in obese subjects and a general sample of individuals: development and measurement properties. *Int J Obesity, 33,* 913-22.
17. Buckner RL and Logan JM (2001) Functional neuroimaging methods: PET and fMRI. In Cabeza, R. and Kingstone, A. (Eds.) Handbook of Functional Neuroimaging of Cognition. Cambridge: MIT Press. pp. 27-48.
18. Brett M, Penny WD, & Kiebel, SJ (2003). Introduction to Random field theory. In R. S. J. Frackowiak, K. J. Friston, C. Frith, R. Dolan, K. J. Friston, C. J. Price, S. Zeki, J.

Ashburner, & W.D. Penny (Eds.), Human Brain Function (2nd ed.) London: Academic Press.

19. Burock MA, Buckner RL, Woldorff MG, Rosen BR, Dale AM (1998) Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI. *Neuroreport, 9,* 3735-3738.
20. Arana FS, Parkinson JA, Hinton E, Holland AJ, Owen AM, Roberts AC (2003) Dissociable contributions of the human amygdala and orbitofrontal cortex to incentive motivation and goal selection. *J Neurosci, 23,* 9632-9638
21. Stice E, Spoor S, Ng J, Zald DH (2009) Relation of obesity to consummatory and anticipatory food reward. *Physiol & Behav, 97,* 551-560
22. Stoeckel LE, Weller RE, Cook EW, Tweig DB, Knowlton RC, Cox JE (2008) Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage, 41,* 636-647
23. Killgore WDS, Young AD, Femia LA, Bogorodzki P, Rogowska J, & Yurgelun-Todd, DA (2003). Cortical and limbic activation during viewing of high- versus low-calorie foods. *Neuroimage, 19*, 1381–1394.
24. Volkow ND, Wang GJ, Fowler JS, Logan J, Jayne M, Franceschi D, Wong C, Gatley SJ, Gifford AN, Ding YS, Pappas N (2002) Nonhedonic food motivation in humans involves dopamine in the dorsal striaum and methylphenidate amplifies this effect. *Synapse, 44,* 175-180
25. Volkow ND, Wise RA (2005) How can drug addiction help us understand obesity? *Nat Neurosci, 8,* 555-560
26. Tataranni PA, DelParigi A (2003) Functional neuroimaging: a new generation of human

brain studies in obesity research. *Obes Rev, 4,* 229 – 238

27. Chambers CD, Garavan H, Bellgrove MA (2009) Insights into the neural basis of response inhibition from cognitive and clinical neuroscience, *Neurosci and Biobehav R, 33,* 631-46
28. Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM (2008) Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. *J Abnorm Psychol, 117,* 924-935
29. Karhunen LJ, Vanninen EJ, Kuikka JT, Lappalainen RI, Tiihonen J, Uusitupa MI. (2000) Regional cerebral blood flow during exposure to food in obese binge eating women. *Psychiat Res, 99,* 29–42.
30. Wang GJ, Volkow ND, Telang F, Jayne M, Ma J, Rao M, Zhu W, Wong T, Pappas NR, Geliebter A, Fowler JS (2004). Exposure to appetitive food stimuli markedly activates the human brain. *NeuroImage, 21,* 1790–1797.
31. Harmon-Jones E, Gable PA, Peterson CK (2010) The role of asymmetric frontal cortical activity in emotion-related phenomena: a review and update. *Biol Psychol, 84,* 451-62
32. Polivy, J & Herman CP (1985) Dieting and binging: A causal analysis. *American Psychologist, 40,* 193-201
33. Lowe MR & Levine AS (2005). Eating motives and the controversy over dieting: Eating less than needed versus less than wanted. *Obes Res, 13,* 797 – 806
34. Herman CP & Polivy J (1983) A boundary model for the regulation of eating. *Psychiatric Annals, 13,* 918-927
35. Lowe MR & Butryn ML (2007). Hedonic hunger: A new dimension of appetite? *Physiol & Behav, 91*, 432-439

36. Wadden TA, Butryn ML, Byrne KJ (2004) Efficacy of lifestyle modification for long-term weight control. *Obes Res, 12,* Suppl:151S-62S

37. Goldstein SP, Katterman SN & Lowe ML (2013) Relationship of dieting and restrained eating to self-reported caloric intake in female college freshmen. *Eating Behaviors, 14*, 237-240

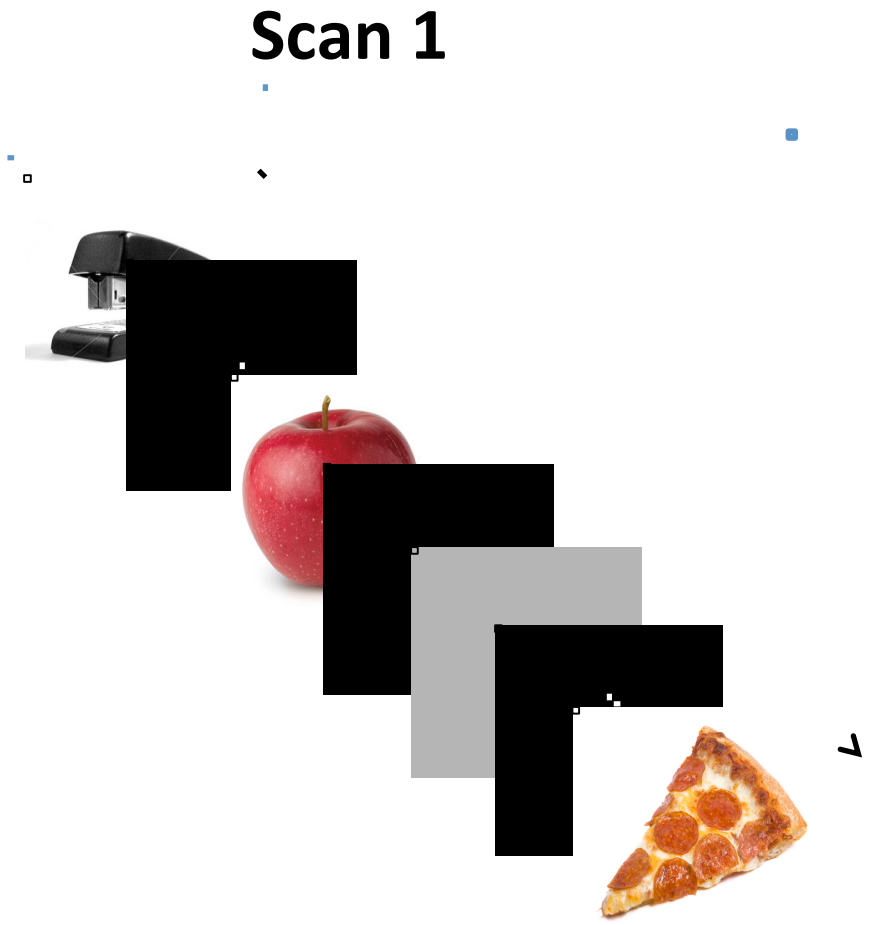
38. Detre JA, Wang J (2002) Technical aspects and utility of fMRI using BOLD and ASL. *Clinical Neurophysiology, 113,* 621-634

39. Alonso-Alonso M, Ziemke F, Magkos F, Barrios FA, Brinkoetter M, Boyd I, Rifkin-Graboi A, Yannakoulia M, Rojas R, Pascual-Leone A, Mantzoros CS (2011) Brain responses to food images during the early and late follicular phase of the menstrual cycle in healthy young women: relation to fasting and feeding. *Am J of Clin Nutr, 94,* 377-84.

Informed Consent
Pregnancy Test
Weight measurement
Hunger/Fullness

Liquid Meal

Hunger/Fullness



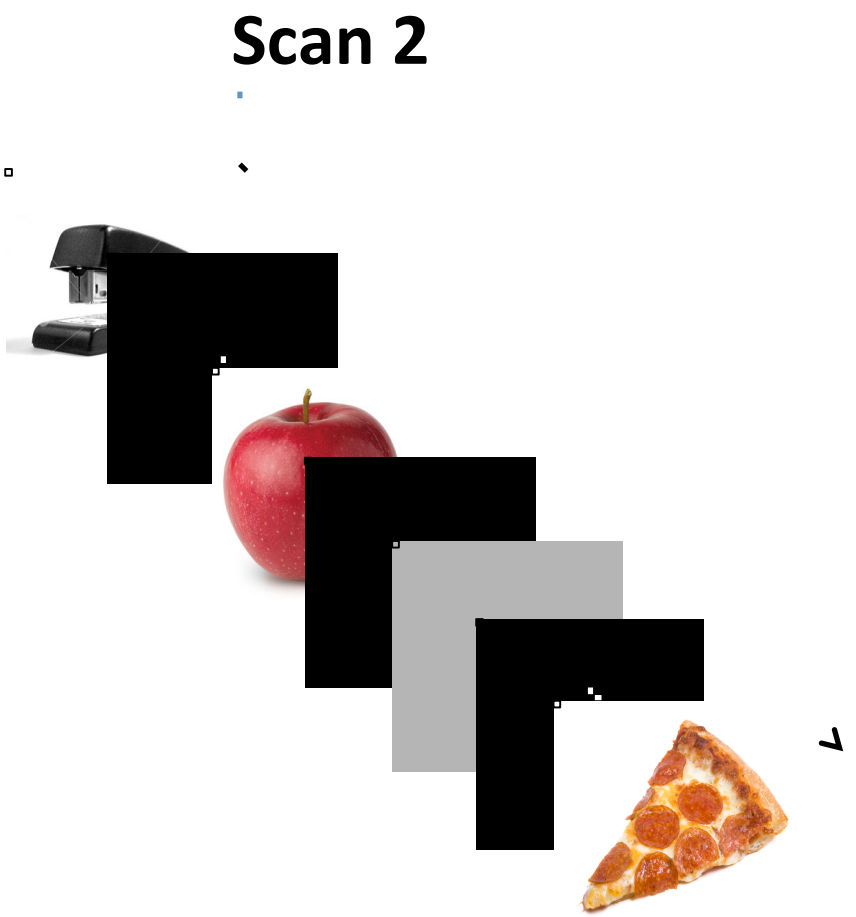


Figure 1. Following consent and initial assessments, participants underwent the MRI scan, lasting ~10 minutes. Images shown above are similar to those used as experimental stimuli. After the scan, participants drank 500 calories of chocolate flavored liquid meal and read for ~20 minutes. They then completed the Hunger Questionnaire again and the scanning procedure was repeated.

Figure 2. Contrast maps comparing Historical Dieters' response to highly versus moderately palatable food with that of Nondieters and of Current Dieters'

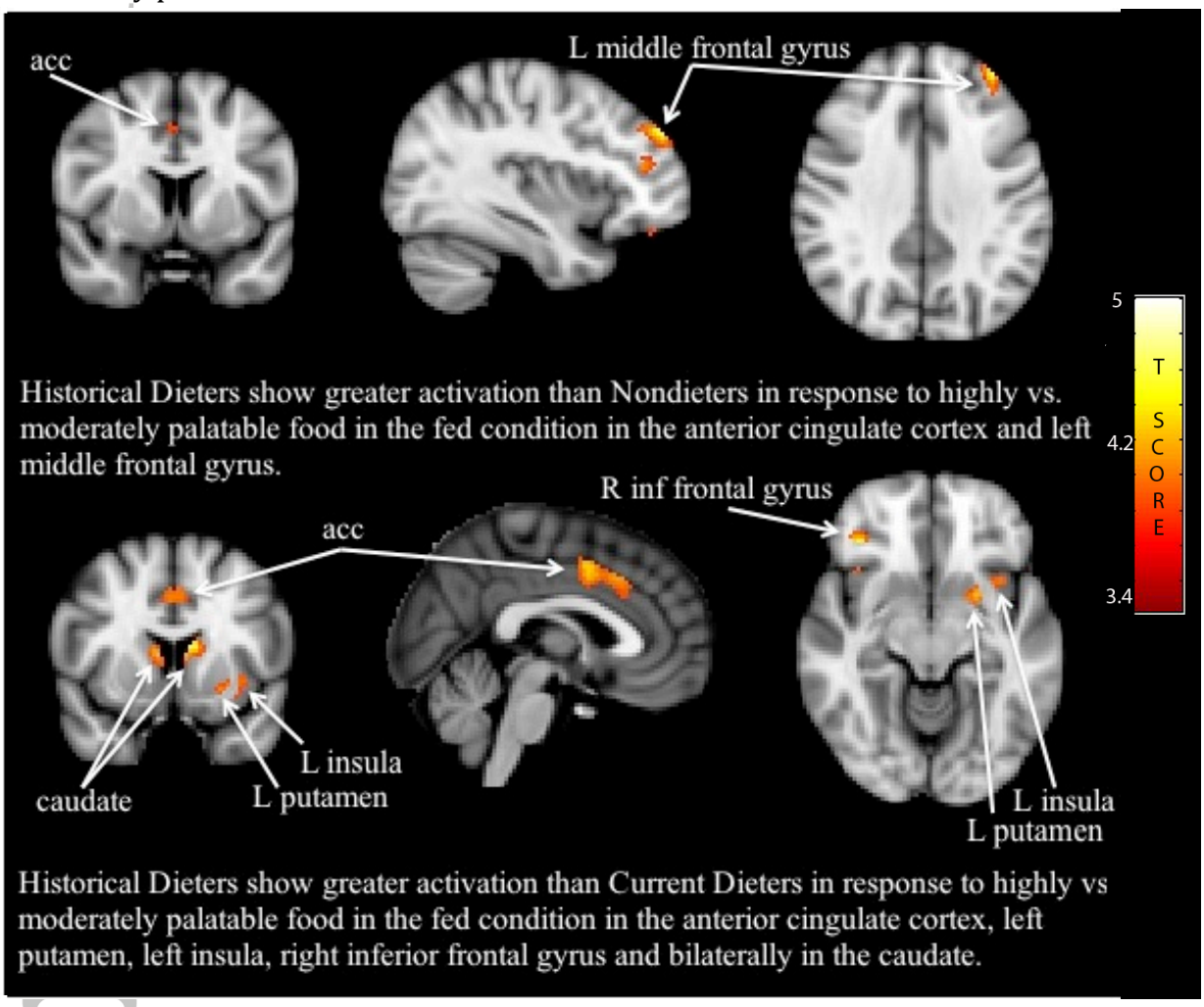


Table 1. Descriptive Variables

	Nondieters	*Historical Dieters*	*Current Dieters*
N	10	10	10
Age (years)	21.1 (±2.08)	19.3 (±1.16)	20.4 (±2.41)
BMI (kg/m^2)	22.04 (±1.60)	21.11 (±0.66)	21.96 (±1.73)
Weight Supression (lbs)	0.65 (±3.38)	6.0 (±5.10)*	6.1 (±5.61)*
Number of past diets	0	5 (±2.0)*	3.5 (±2.6)*
TFEQ - Restraint score	3.1 (±1.1)	6.1 (±1.2)*	7.7 (±1.4)*

* $p < .05$

Table 2. Mean Hunger/Fullness Ratings by Group

Question	ND	HD
Fasted		
How hungry do you feel right now?	4.5 (±1.35)	5.0 (±1.56)
How strong is your desire to eat right now?	4.0 (±1.33)	5.6 (±1.58)
How much food do you think you could eat right now?	4.4 (±1.07)	5.3 (±1.34)
How full does your stomach feel right now?	2.9 (±0.99)	2.4 (±0.84)
Fed		
How hungry do you feel right now?	1.9 (±0.57)	2.6 (±1.78)
How strong is your desire to eat right now?	1.8 (±0.63)	2.9 (±1.91)
How much food do you think you could eat right now?	2.3 (±0.48)	3.4 (±1.90)
How full does your stomach feel right now?	6.4 (±1.58)	5.6 (±2.07)

ND: Nondieters, HD: Historical Dieters, CD: Current Dieters

CD
5.4 (±1.71)
5.8 (±2.15)
5.4 (±1.84)
2.3 (±0.95)
2.2 (±0.92)
2.3 (±0.67)
3.0 (±1.25)
5.8 (±1.93)

Table 3

Brain regions that differed by group in Fasted and Fed states when viewing Highly v. Moderately palatable food cues

Fasted							Fed						
	Peak voxel							Peak voxel					
Region of Interest	x	y	z	Cluster size	t	p	Region of Interest	x	y	z	Cluster size	t	p
HD > ND							**HD > ND**						
NS							Anterior Cingulate	4	2	46	36	3.5	0.001
							Middle Frontal Gyrus	-36	46	34	115	4.4	<0.001
								-32	40	14	51	4.3	<0.001
ND > HD							**ND > HD**						
NS							NS						
HD > CD							**HD > CD**						
NS							Dorsal Anterior Cingulate	0	4	42	385	3.4	<0.001
							Amygdala	-22	4	-12	10	3.4	0.002
							Insula	-34	12	-6	57	3.5	0.001
								30	26	-2	49	3.3	0.002
							Middle Frontal Gyrus	38	34	-12	53	4.3	<0.001
							Caudate	-8	8	14	83	4.3	<0.001
								10	8	12	39	3.8	0.001
							Pallidum	-24	6	-10	61	3.6	0.001
CD > HD							**CD > HD**						
NS							NS						

ND: Nondieters, HD: Historical Dieters, CD: Current Dieters

NS: Nonsignificant at the $p = 0.003$ level

MRI data acquisition

Data was acquired on a 3 Tesla Trio MR Scanner (Siemens, Erlangen, Germany) at Hospital of the University of Pennsylvania using Siemens Trio 3T scanner. Functional images were collected with T2*-weighted with single shot gradient echo (GRE) echo planar imaging (EPI) sequence to BOLD contrast (field of view (FOV) = 192mm; matrix = 64×64; TR = 2sec; TE = 30msec; flip angle = 90°; voxel size =3.4x3.4x4.5mm with a 1mm slice gap). A 5-minute T1 weighted high-resolution scan were acquired for normalization and anatomical coregistration of the images. Acquisition parameters for the 3-dimensional high resolution MPRAGE structural scan in the axial plane were (repetition time (TR)=1510ms; echo time (TE)= 3.71ms; field of view (FOV) = 250mm matrix;=192x256. Flip Angle = 9).

Image Processing and Analysis.

SPM5 (www.fil.ion.ucl.ac.uk/spm) standard routines were used for the analysis of the functional images. Images were realigned, coregistered to the anatomical T1 image, normalized to the MNI standard space and smoothed with a Gaussian kernel of FWHM 9mm^3. Motion parameters of all subjects were in an acceptable range not exceeding 3mm for each single subject.

For each subject, experimental condition (fixation cross, moderately palatable food items, highly palatable food items) was modeled using a canonical hemodynamic response function as the basis function. Past research suggests that brain activity to evocative stimuli (such as emotional stimuli and cues for drugs of abuse) can "carry over" to neutral stimuli in the same scanning block, thereby progessively undermining

the contrast in activation between control cues and experimental cues (1, 2). In the current study, activation contrasts were thus constrained to the first half of each scanning block, helping to avoid the possible "carry-over" effects, and/or habituation. First-level contrast maps were used for statistical testing of group or condition effects at the second level (e.g. HDs vs. NDs). The contrast maps were entered to into a random effects analysis to test for a significant activation unique to highly palatable food versus moderately palatable food.

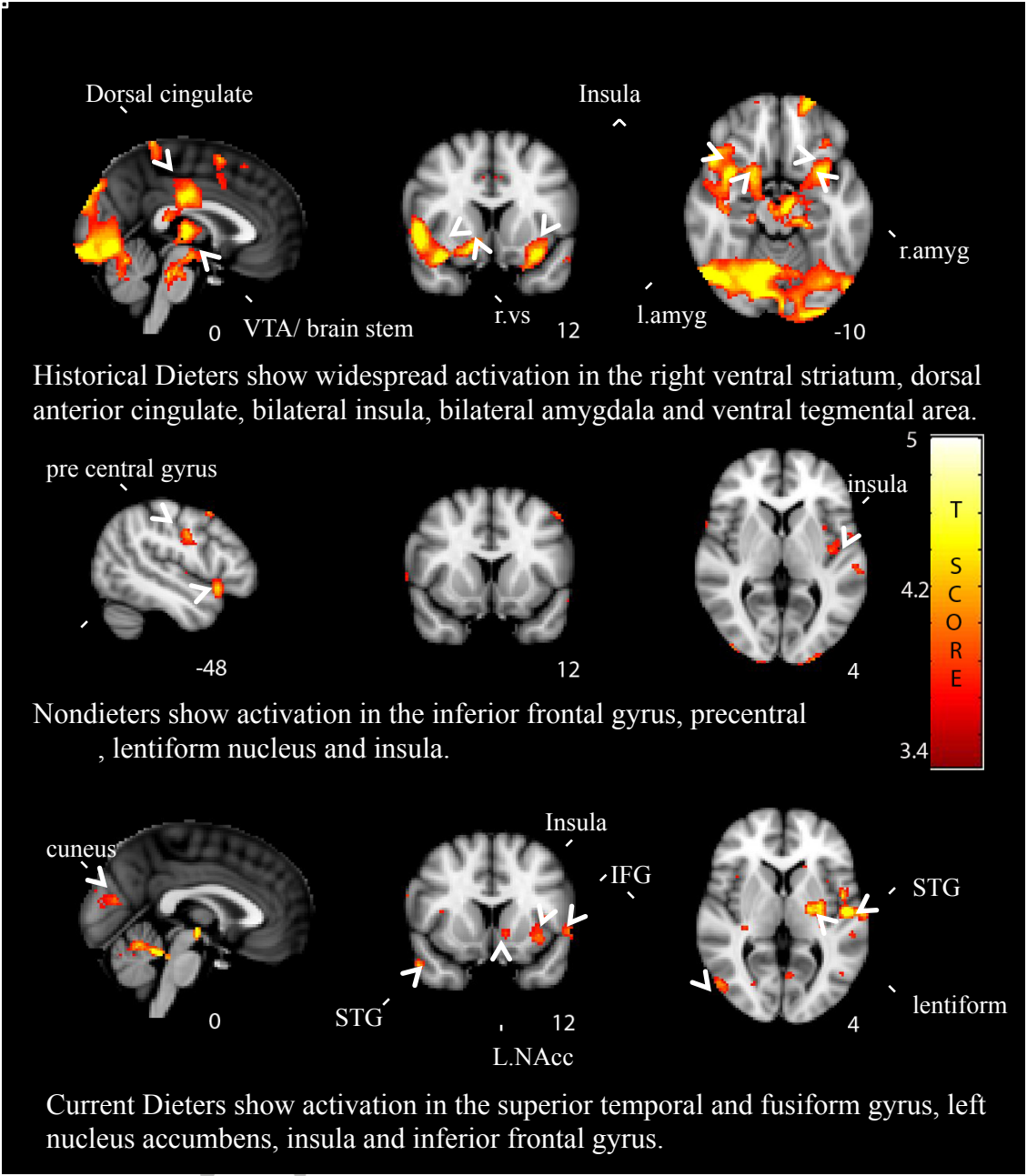
Technical Note

This constraint reflects our awareness that second-level comparisons across the Fasted v. Fed conditions could be impacted by a change in 'baseline' brain activity (global or/and regional) resulting from the experimental manipulation (feeding). Though designs attempting to compare BOLD measures at two separate time points are common in the imaging literature, these "longitudinal" paradigms are vulnerable to baseline differences (whatever the source, e.g., a change in physiologic state due to illness, medication, or even changes in the tuning of the MR scanner) that may confound the comparisons. Statistical approaches to BOLD acknowledge these potential baseline confounds but it is only possible to detect them indirectly. We examined for the impact of baseline by comparing the brain response to a reference cue category (e.g., Neutral) against the implicit baseline (the time period during which the participant passively viewed the fixation screen) for both the Fasted and Fed states (3), for the three study groups. This approach revealed large differences in the brain response to the Neutral cues vs. the implicit baseline in the Fasted and the Fed states, for the three groups. These differences in the response to Neutral cues point to differences in baseline across states,

and encouraged our constraint of analyses to "between-groups, within-state". NDs demonstrated high levels of activation in ROIs in response to Neutral (and food cues) when fasted, but no significant activation when fed. Conversely, HDs and CDs showed a widespread response across Neutral (and food) cues when fasted and maintained this activation in response to highly palatable food when fed.

References

1. Childress AR, Ehrman RN, Wang Z ,Li Y, Sciortino N, Hakun J, Jens W, Suh J, Listerud J, Marquez K, Franklin T, Langleben D, Detre J, O'Brien CP (2008) Prelude to Passion: Limbic activation by "unseen" drug and sexual cues. PLoS One 1: e1506
2. Sharma D, Money S (2010) Carryover effects to addiction-associated stimuli in a group of marijuana and cocaine users. *J Psychopharmacol, 24*, 1309-16
3. Smith SM (2004) Overview of fMRI analysis. *Brit J of Radiol, 77,* S167 – S175



Supplementary Figure 1. In the Fed condition, activation in response to highly palatable food cues as compared to neutral items (High v. Neutral), in each experimental group independently.

Supplementary Table 1

Brain regions that differed by group in Fasted and Fed states when viewing Highly palatable food v. Neutral cues

	Fasted							Fed						
	Peak voxel							Peak voxel						
Region of Interest	x	y	z	Cluster size	t	p		Region of Interest	x	y	z	Cluster size	t	p
HD > ND								**HD > ND**						
NS								NS						
ND > HD														
Medial OFC	0	46	-18	69	3.5	0.001								
Medial Frontal Gyrus	4	54	4	50	3.8	0.001								
Middle Frontal Gyrus	-20	64	16	54	3.7	0.001		**ND > HD**						
Superior Frontal Gyrus	-12	54	36	33	3.2	0.003		NS						
HD > CD								**HD > CD**						
NS								Middle Frontal Gyrus	-32	64	14	50	4.27	<0.001
								Superior Frontal Gyrus	24	56	30	73	3.85	0.001
								Superior Frontal Gyrus	30	68	-4	22	3.31	0.002
CD > HD								**CD > HD**						
Medial OFC	-2	40	-30	72	3.3	0.002		NS						

ND: Nondieters, HD: Historical Dieters, CD: Current Dieters

NS: Nonsignificant at the $p = 0.003$ level