

Dietary Restraint Violations Influence Reward Responses in Nucleus Accumbens and Amygdala

Kathryn E. Demos*, William M. Kelley, and Todd F. Heatherton

Abstract

■ Numerous studies have demonstrated that consuming high-calorie food leads to subsequent overeating by chronic dieters. The present study investigates the neural correlates of such self-regulatory failures using fMRI. Chronic dieters ($n = 50$) and non-dieters ($n = 50$) consumed either a 15-oz glass of cold water or a 15-oz milkshake and were subsequently imaged while viewing pictures of animals, environmental scenes, people, and appetizing food items. Results revealed a functional dissociation in nucleus

accumbens and amygdala activity that paralleled well-established behavioral patterns of eating observed in dieters and non-dieters. Whereas non-dieters showed the greatest nucleus accumbens activity in response to food items after water consumption, dieters showed the greatest activity after consuming the milkshake. Activity in the left amygdala demonstrated the reverse interaction. Considered together with previously reported behavioral findings, the present results offer a suggested neural substrate for diet failure. ■

INTRODUCTION

Obesity is a major health problem with both physical and psychological consequences, yet treatment success remains elusive. Nationally representative samples indicate that obesity rates have increased dramatically in the United States from fewer than 15% of the population meeting criteria for obesity in 1980 (body mass index [BMI] ≥ 30 kg/m²) to more than 33% meeting criteria in 2004 (Ogden et al., 2006). Moreover, current estimates suggest that nearly 67% of the U.S. population is overweight or obese (Ogden et al., 2006). As such, there have been urgent calls for research to understand the epidemic of obesity and how it can be prevented or treated (Volkow & O'Brien, 2007). This manuscript examines the neural basis of one possible reason that obesity remains an entrenched problem, namely, maladaptive responses to dietary violations.

An interesting feature of the apparent obesity epidemic is that it is occurring even while most people are familiar with the health risks of excessive body weight and many have a strong desire to lose weight. Indeed, many are actively dieting in attempts to lose weight or at least deter weight gain. For instance, in one study, more than two thirds of women and more than half of men reported wanting to lose weight (Heatherton, Mahamedi, Striepe, Field, & Keel, 1997). Similarly, one study of a large representative sample found that 29% of men and 44% of women were currently dieting to lose weight, with an equal number controlling eating in an attempt to not gain weight (Serdula et al., 1999). Although many people diet in an attempt to lose weight, there are reasons to be pessimistic about the

extent to which they are able to maintain weight loss, regardless of the diet's nutritional emphasis (Sacks et al., 2009; Mann et al., 2007). The typical pattern is that people tend to lose weight within the first months on a diet, but within a year or two, they return to their original weight because of steady weight regain, or they even end up weighing more than when they began dieting (Aronne, Wadden, Isoldi, & Woodworth, 2009; Dansinger, Tattioni, Wong, Chung, & Balk, 2007). Thus, it is clear that dieters can lose weight over the short term, presumably by controlling food intake, yet various factors appear to sabotage their weight loss efforts over the long term. Likewise, the continuing increase in the rate of obesity implies that many people are unable to follow diets that prevent weight gain. Thus, it is of crucial importance to understand the factors that interfere with dietary success and thereby contribute to obesity. The goal of this research was to identify neural patterns of activity associated with dietary violations. Dieting is common among people who are not clinically obese, and the behavioral patterns after dietary violations are similar between the two groups (Baumeister, Heatherton, & Tice, 1994). Here we assess neural activity in chronic dieters who are not obese because we are primarily interested in the response to dietary violations rather than obesity per se.

Insight into diet failure has been obtained through behavioral research examining eating in the laboratory. In one of the first studies of its kind, Herman and Mack (1975) experimentally violated the diets of dieters by requiring them to eat a high-calorie food as part of a supposed perception study. College-aged women (dieters and non-dieters, as assessed by a self-report measure of frequent dieting) participated in a "taste test" experiment that was represented to subjects as a study of the influence of one

Dartmouth College

*Currently at Brown University.

sensory experience upon another. Subjects were told that they would have from zero to two taste experiences in the form of a milkshake before sampling flavors of ice cream and that the experimenters were interested in the taste perception of the flavors. In reality, the taste ratings were of no consequence, and the milkshake preload was intended to disrupt the dieters' diets. After the mock taste test, the total amount of ice cream consumed was covertly measured. Although non-dieters ate less after consuming the milkshakes, presumably because they were full, dieters paradoxically consumed the most ice cream after having the milkshake preload. This disinhibition of dietary restraint has been replicated numerous times (Herman & Polivy, 2004; Heatherton & Baumeister, 1991) and demonstrates that dieters often eat a great deal after they perceive their diets to be broken. Indeed, chronic dieters often oscillate between periods of restraint, marked by restricted caloric intake, and bouts of excessive caloric intake or disinhibited overeating that thwarts their dietary goals (Heatherton, Herman, & Polivy, 1991, 1992; Heatherton, Polivy, & Herman, 1989; Polivy, Heatherton, & Herman, 1988; Herman & Mack, 1975; Herman & Polivy, 1975). Thus, dietary disinhibition is likely one of the key components of why many people struggle with their weight (Heatherton & Polivy, 1992; Polivy & Herman, 1987).

To study the neural correlates of diet failure, we adopted a cue-reactivity paradigm that has been successfully implemented in studies of appetitive behaviors (Passamonti et al., 2009; Rothenmund et al., 2007). Both human and animal studies have demonstrated that exposure to drug cues increases the likelihood that the cued substance will be consumed (Jansen, 1998; Glautier & Drummond, 1994; Drummond, Cooper, & Glautier, 1990; Stewart, de Wit, & Eikelboom, 1984) and additionally increases cravings, attention, and physiological responses such as changes in heart rate (Payne, Smith, Adams, & Diefenbach, 2006; Drobles & Tiffany, 1997; Stewart et al., 1984). Recent neuroimaging research has identified a distributed network of brain regions that are active during exposure to relevant drug cues (for reviews, see Wilson, Sayette, & Fiez, 2004; Jentsch & Taylor, 1999). Across a number of studies, activity in the amygdala, hippocampus, nucleus accumbens (NAcc), and ventral tegmental area has been observed, perhaps implicating the experience of drug reinforcement and the memory of the learned association between the drug and its rewarding properties. In addition, activity in the ACC, OFC, and dorsolateral PFC (dlPFC) has also been observed in response to rewarding drug cues, and it has been suggested that these responses reflect the craving and cognitive control aspects of drug cue reactivity (Wilson et al., 2004; Franken, 2003; Goldstein & Volkow, 2002; See, 2002).

Recent neuroimaging studies assessing reactivity to food cues have also found activity in human reward circuitry, including ventral striatum and mesolimbic and mesocortical dopamine circuits (Passamonti et al., 2009; Schur et al., 2009; Stoeckel et al., 2008; DelParigi et al., 2007; Simmons, Martin, & Barsalou, 2005; Killgore et al., 2003; Small, 2002).

Some evidence suggests that this response to food cues may be more potent for images of high-calorie food (Schur et al., 2009; Stoeckel et al., 2008) and that personality traits, such as how sensitive an individual is to the sights and smells of food, relate to differences in the neural response to food cues (Passamonti et al., 2009). Importantly, obese women exhibit greater activity in reward areas including the NAcc in response to high-calorie food items than healthy weight control subjects (Stoeckel et al., 2008).

An open question, however, is whether responsivity to food cues changes as a function of whether a diet is intact or broken. In the present study, chronic dieters and non-dieters were asked to consume either a 15-oz glass of water or a 15-oz milkshake under the guise that the experimenters were interested in the effects of mouth temperature on signal quality in functional brain imaging. During scanning, subjects viewed images of animals, environmental scenes, people, and food and made simple person perception judgments (i.e., whether there were people present in the image or not). We sought to identify brain regions whose activity mirrored the behavioral patterns of eating observed in the literature and thus may underlie dietary restraint violations. Given that chronic dieters overeat when their diets are broken, we hypothesize that any event that disrupts the diet will produce heightened reward activity in response to food cues. Specifically, then, we predict that a milkshake preload, known to lead to greater eating among dieters, will produce heightened cue reactivity to food cues in brain reward regions. Conversely, satiating an appetitive state is associated with diminished reward responding. Thus, a similar milkshake given to non-dieters should suppress cue reactivity to food cues in reward regions. We used a between group factorial design with a large sample size to test these hypotheses.

METHODS

Subjects

A total of 109 native English-speaking women from the Dartmouth community between the ages of 18 and 35 years (mean age = 19 years) participated in this experiment. Participants were classified as dieters or non-dieters as a function of their scores on the Restraint Scale (Polivy, Herman, & Howard, 1988; Herman & Mack, 1975), a well-validated measure that is widely used in the eating literature (for a discussion of its psychometric features, see Heatherton, Herman, Polivy, King, & McGree, 1988). We recruited only female participants because men and women differ in how and why they gain and lose weight (Holm-Denoma, Joiner, Vohs, & Heatherton, 2008), and college-aged women are more likely to strive for an "ideal" body weight and thus more apt to exhibit restraint in their eating behaviors (Herman & Mack, 1975). No subjects reported abnormal neurological history, and all had normal or corrected-to-normal visual acuity. Each subject provided informed consent in accordance with the guidelines set

by the Committee for the Protection of Human Subjects at Dartmouth College, and each subject received either course credit or monetary compensation for participating.

Data from five subjects were excluded because of excessive artifact and noise in imaging data, and four subjects were excluded because of obesity ($BMI \geq 30 \text{ kg/m}^2$). Obese participants were excluded because of potential neuroanatomical differences that vary as a function of BMI (Gunstad et al., 2008). Although height and weight was initially reported in a prescreen interview, these four subjects weighed more than they self-reported when actually weighed on a medical scale after the scan session (which was done because weight feedback may lead to negative affect and subsequent disinhibition; see Stice, Maxfield, & Wells, 2003; McFarlane, Polivy, & Herman, 1998). Analyses reported herein are therefore derived from a total of 100 participants, which included 50 dieters (25 in the water condition and 25 in the preload condition) and 50 non-dieters (25 in the water condition and 25 in the preload condition).

Apparatus

Imaging was performed on a Philips Intera Achieva 3-T scanner (Phillips Medical Systems, Bothell, WA) with a SENSE (SENSEitivity Encoding) head coil. During scanning, visual stimuli were generated with an Apple MacBook Pro laptop computer running SuperLab 4.0 software (Cedrus Corporation, San Pedro, CA). An Epson (model ELP-7000) LCD projector was used to display stimuli on a screen positioned at the head end of the scanner bore, which subjects viewed through a mirror mounted on top of the head coil. A fiber-optic, light-sensitive keypress interfacing with the Cedrus Lumina Box recorded subjects' responses. Cushions were placed around the head to minimize movement during scanning and increase comfort. After scanning, subjects were tested behaviorally using Apple iMacs running SuperLab software.

Imaging

Anatomic images were acquired using a high-resolution 3-D magnetization-prepared rapid gradient-echo sequence (MPRAGE; 60 sagittal slices, echo time = 4.6 msec, repetition time = 9.9 msec, flip angle = 8° , voxel size = $1 \times 1 \times 1 \text{ mm}$). Functional images were collected using T2* fast field echo, functional EPis sensitive to BOLD contrast (repetition time = 2500 msec, echo time = 35 msec, flip angle = 90° , $3 \times 3 \text{ mm}$ in-plane resolution, sense factor of 2). During each of the four functional runs, 160 axial images (36 slices, 3.5 mm slice thickness, 0.5 mm skip between slices) were acquired allowing complete brain coverage.

Procedure

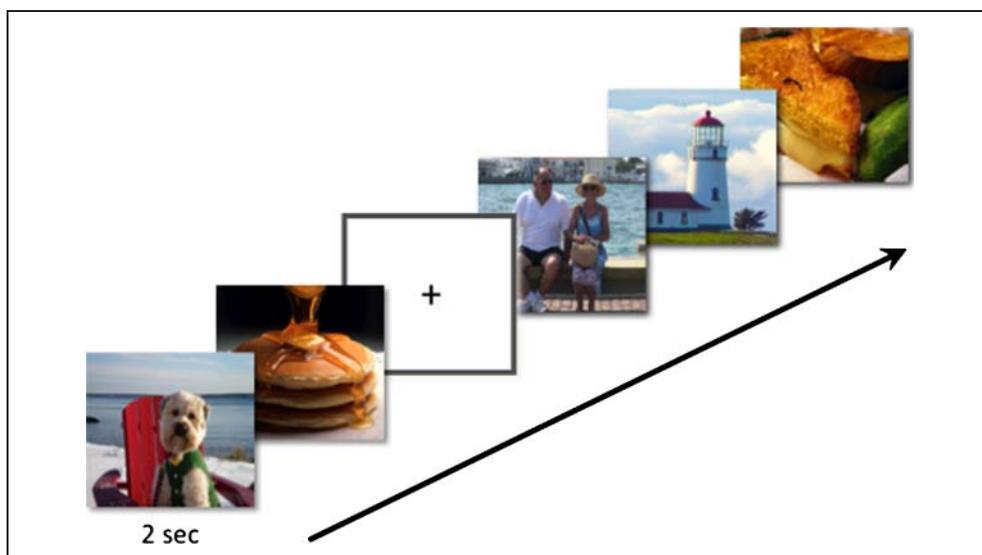
Subjects took part in a mass testing in which their scores on the Restraint Scale and self-reported height and weight

were obtained. This mass testing included numerous unrelated questionnaires, and when individuals were contacted to participate in the present study, they were simply informed they were eligible on the basis of their responses to the questionnaires in general and were therefore not aware they were recruited on the basis of dieting status. Consistent with past research (e.g., Heatherton et al., 1991), participants were eligible to participate if they scored more than 15 on the Restraint Scale (dieters) or less than 12 (non-dieters). To reduce potential differences in hunger level and time since the participants' last meal, each participant was asked to refrain from eating, from consuming alcohol or caffeine, and from smoking for 2 hours before the fMRI session. To measure participants' compliance with these instructions and to assess their current hunger level, immediately before scanning, each subject provided responses to questions regarding their current state wherein they listed food and drink consumption, activity level, and current hunger level on a scale of 1 to 5.

After completion of this "current state" questionnaire, each participant was given a cover story in which she was told that the aim of the present study was to investigate social perception and to test technical methods for increasing fMRI signal in the frontal cortex, an area of the brain that is often implicated in such tasks but is near the sinus cavity and thus highly susceptible to signal loss. Subjects were shown an fMRI image in which there was apparent signal loss in the frontal cortex and were led to believe that, among other things (e.g., biting on a graphite bar), significantly cooling the roof of the mouth (and thus 'lowering the temperature of the air in nearby sinus space') may produce better signal recovery in this brain area and that the purpose of the study was to test this possibility. All participants were informed that they were in this "cold mouth condition," and this portion of the cover story did not differ across participants. Critically, however, half of the participants ($n = 50$; 25 dieters, 25 non-dieters) were then given a 15-oz (425-g) chocolate milkshake (approximate calories = 885) to "cool their mouths," whereas the other half of participants ($n = 50$; 25 dieters, 25 non-dieters) were given a 15-oz (425-g) glass of water to "cool their mouths."

Subjects were then scanned while viewing images of animals (100), appetizing food (100), people (100), and environmental scenes (100) in an event-related design (Figure 1). These images were compiled from the Internet and scaled in size using Adobe Photoshop 7.0 (San Jose, CA) to be 480×360 pixels. During scanning, subjects were asked to simply determine whether each image contained a person and to use keypresses to make their responses (left-handed response for "nonperson"; right-handed response for "person"). This was done both to disguise the primary goals of the study and to ensure that participants were attending to the images. Images were presented for 2000 msec followed by a fixation crosshair (500 msec) and were randomly intermixed with jittered periods of fixation (jittered fixation = 0–15000 msec; mean intertrial

Figure 1. The event-related fMRI paradigm is depicted. Images of animals, food, people, and scenes were displayed for 2 sec each and interspersed with jittered periods of fixation baseline. In total, participants viewed 100 images of animals, 100 images of food, 100 images of people, and 100 images of environmental scenes.



interval = 3825 msec). Of interest was the neural response to viewing food images in each group of individuals.

Postscanning Behavioral Testing

One day after the scanning session, each subject returned to the lab for behavioral testing, including (1) likeability ratings for all previously viewed stimuli (rated 1–7), (2) detailed journalizing of their day after the scanning session, and (3) body measurement (height and weight). The final sample consisted of 100 participants (dieters $n = 50$, mean restraint score = 19.6; non-dieters $n = 50$; mean restraint score = 8.7).

fMRI Data Analyses

fMRI data were analyzed using Statistical Parametric Mapping software (SPM2; Wellcome Department of Cognitive Neurology, London, UK; Friston et al., 1995). For each functional run, data were preprocessed to remove sources of noise and artifact. Functional data were realigned within and across runs to correct for head movement, coregistered with each participant's anatomic data, and transformed into a standard anatomic space (3-mm isotropic voxels) on the basis of the ICBM 152 brain template (Montreal Neurological Institute), which closely approximates the Talairach and Tournoux (1988) atlas space. Normalized data were then spatially smoothed (6-mm FWHM) using a Gaussian kernel and globally scaled to permit between-group comparisons. Analyses of fMRI data took place at two levels for this experiment: formation of statistical images via a whole-brain voxelwise 2×2 ANOVA and regional analysis of hemodynamic responses.

For each participant, a general linear model incorporating task effects (modeled as an event-related function convolved with the canonical hemodynamic response

function), a mean, and a linear trend were used to compute t -contrast images (weighted parameter estimates) for each trial type at each voxel. Individual contrast images comparing each condition to the baseline control (fixation) were then used to compute a whole-brain voxelwise ANOVA (with between-subjects factors of dietary status [dieters, non-dieters] and preload [milkshake, water]) that yielded F statistical maps for both the main effects and the interaction (thresholded at $p < .05$, corrected for false discovery rate, minimum extent threshold: $k = 5$ contiguous voxels). Functionally defined ROIs (6-mm spheres centered on the peak of activation) were acquired by using an automated peak-search algorithm within these whole-brain F statistical maps.

Given that the F statistical maps are unidirectional (i.e., there is no information regarding the direction of main effects or interactions) and thus unbiased, parameter estimates were extracted for each subject and each condition and submitted to off-line ANOVAs in SPSS to determine the direction, but not magnitude, of such effects.

RESULTS

Participant Information

As per the design of the study, there was a significant difference in restraint score between chronic dieters ($M = 19.6$, $SD = 2.8$) and non-dieters ($M = 8.7$, $SD = 2.8$; $t(98) = 19.5$, $p < .0001$), although scores within subject group did not differ by condition (all p values $> .10$). At the beginning of the study, participants indicated their current hunger level and the number of hours since they last consumed food. There were no significant differences between dieters and non-dieters on either measure (see Table 1, all F values < 1). As is typical in the eating literature, the chronic dieters ($BMI = 23.5 \text{ kg/m}^2$, $SD = 2.7 \text{ kg/m}^2$) were slightly

Table 1. Summary of Participant Information for Each Condition

Condition	Mean Weight (lb)	Mean Height (in.)	Mean BMI (kg/m ²)	Mean Restraint Score	Reported Weight – Actual Weight (lb)	Mean Hunger	Mean Hours Since Meal
Diet water	141.8	64.67	23.84	18.6	4.78	2.7	2.74
Nondiet water	130.1	63.74	22.50	8.88	2.5	2.90	3.20
Diet shake	143.8	65.48	23.07	20.56	3.39	2.82	3.04
Nondiet shake	134.8	64.72	22.64	8.44	2.24	2.5	3.42

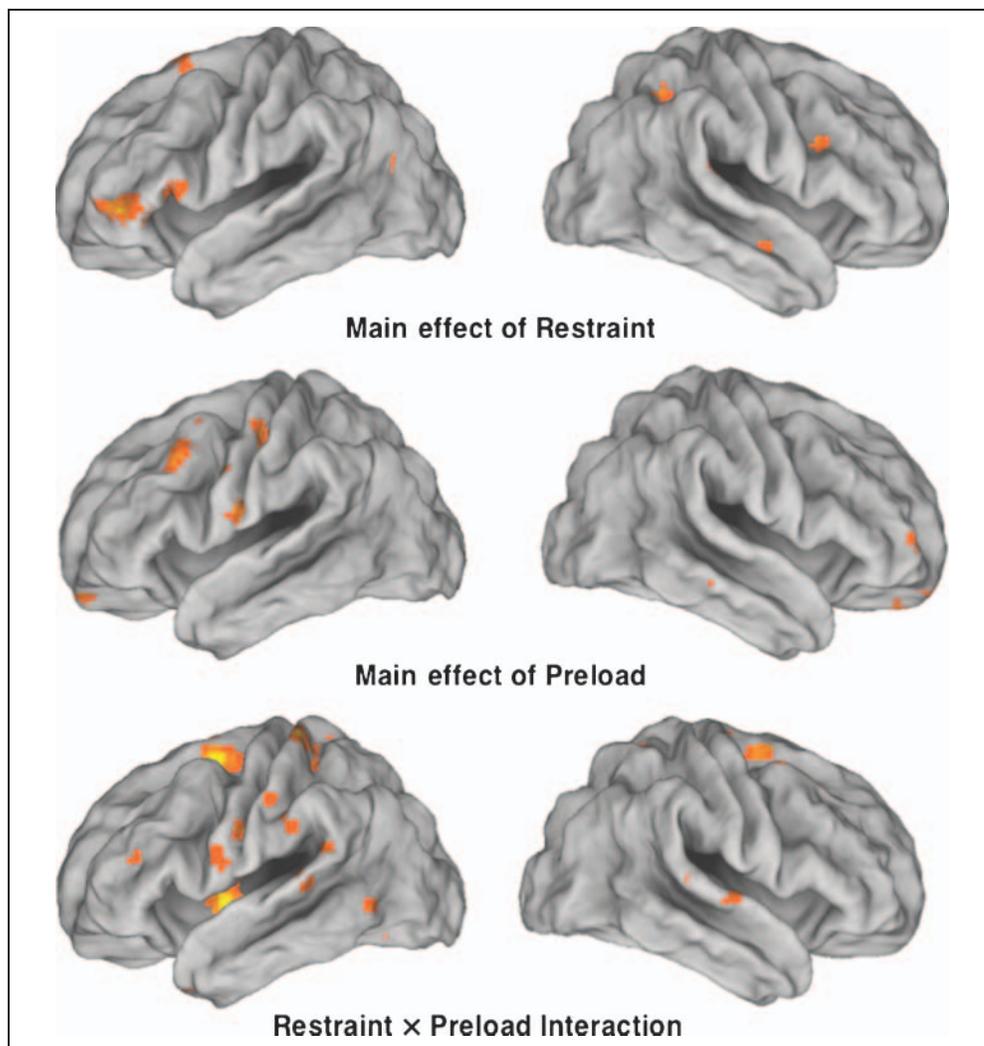
heavier than the non-dieters (BMI = 22.6 kg/m², *SD* = 2.4 kg/m²), $F(3, 96) = 3.0$, $p = .086$), although there were no differences as a function of preload condition, $F < 1$.

RTs and Ratings

Although the classification task participants performed during scanning (“are there people present in the image or not?”) was intended to simply hold participants’ attention and to bolster the idea that the study was concerned with social perception, it is possible that RTs to the food images

could differ as a function of dietary status or preload condition. Importantly, RTs to the food items did not differ across groups (Figure 2): main effect of restraint, $F < 1$; main effect of preload, $F(3, 96) = 1.77$, $p = .19$; restraint by preload interaction, $F < 1$. Thus, any differences between these groups observed in the brain imaging data cannot be attributed to a time-on-task effect. Similarly, post-scan likeability ratings for food items did not differ across the four groups: main effect of restraint, $F < 1$; main effect of preload, $F < 1$; restraint by preload interaction, $F(3, 96) = 1.62$, $p = .21$.

Figure 2. A voxel-by-voxel whole-brain ANOVA was used to compute *F* statistical maps for main effect of restraint (top panel), the main effect of preload (middle panel), and the restraint by preload interaction (bottom panel). Statistical images thresholded at $p < .05$, corrected for false discovery rate with a minimum extent threshold (k) = 5 contiguous voxels, were superimposed on a fiducial cortical rendering of the left and right cortical surfaces (Van Essen et al., 2001).



fMRI Results

Two analyses were performed to investigate the neural response to food items. The first analysis examined neural signatures associated with dietary restraint, preloading, and the interaction between them. Contrast images comparing the response to food items to baseline fixation for each subject were examined using a voxelwise whole-brain ANOVA (2×2 between-subjects design with the factors of dietary status [dieters vs. non-dieters] and preload [water vs. shake]). Figure 2 and Table 2 summarize brain regions that revealed a main effect of dietary status, a main effect of preload, and an interaction between dietary status and preload in response to food items. To explore the directionality of each effect, regions identified in the statistical *F*-maps were examined further using ROI analyses.

Brain Regions Preferentially Sensitive to Dietary Status

Several regions exhibited differential activity in response to food items for dieters compared with non-dieters, including two regions of the ventral lateral PFC (vlPFC) along the left inferior frontal gyrus (BA 47; $-48\ 41\ -2$) and BA 44 extending into BA 45 ($-54\ 19\ 7$). Similar effects were observed in a region of the left superior frontal gyrus (BA 6; $-15\ 18\ 60$), left middle temporal gyrus (BA 39; $-54\ -72\ 23$), right lingual gyrus (BA 7; $36\ -50\ 49$), and a region within the right insular cortex ($36\ 4\ 14$). Each region showed greater activity for dieters compared with non-dieters (see Table 2). There were no differences as a function of preload or the interaction between preload and dietary status in any of these regions.

Non-dieters showed increased activity (compared with their dieting counterparts) in the right middle frontal gyrus (BA 9; $36\ 19\ 27$) and the right inferior occipital gyrus (BA 18; $29\ -86\ -7$).

Brain Regions Preferentially Sensitive to Preload

A number of brain regions exhibited differential responses to food items as a function of preloading, with subjects given the milkshakes showing greater activity in the right ventral anterior cingulate ($15\ 26\ -9$), the right OFC ($15\ 60\ -21$), and the right cuneus (BA 17; $9\ -96\ 2$) (Table 2).

Regions demonstrating selective increased responses to food items in subjects given the water preload include two regions of the left precentral gyrus (BA 4: $-42\ -18\ 45$ and $-24\ -15\ 48$), left lateral OFC (BA 10: $42\ 58\ -5$), right middle temporal gyrus (BA 21: $74\ -41\ -6$), and a region of the dorsal ACC (BA 32/8: $6\ 34\ 34$).

Brain Regions Exhibiting an Interaction of Dietary Status and Preload

Two regions within the ventral striatum, including the right NAcc ($12\ 9\ -3$) and the left NAcc extending into the putamen ($-15\ 3\ -8$), demonstrated a cross-over interaction

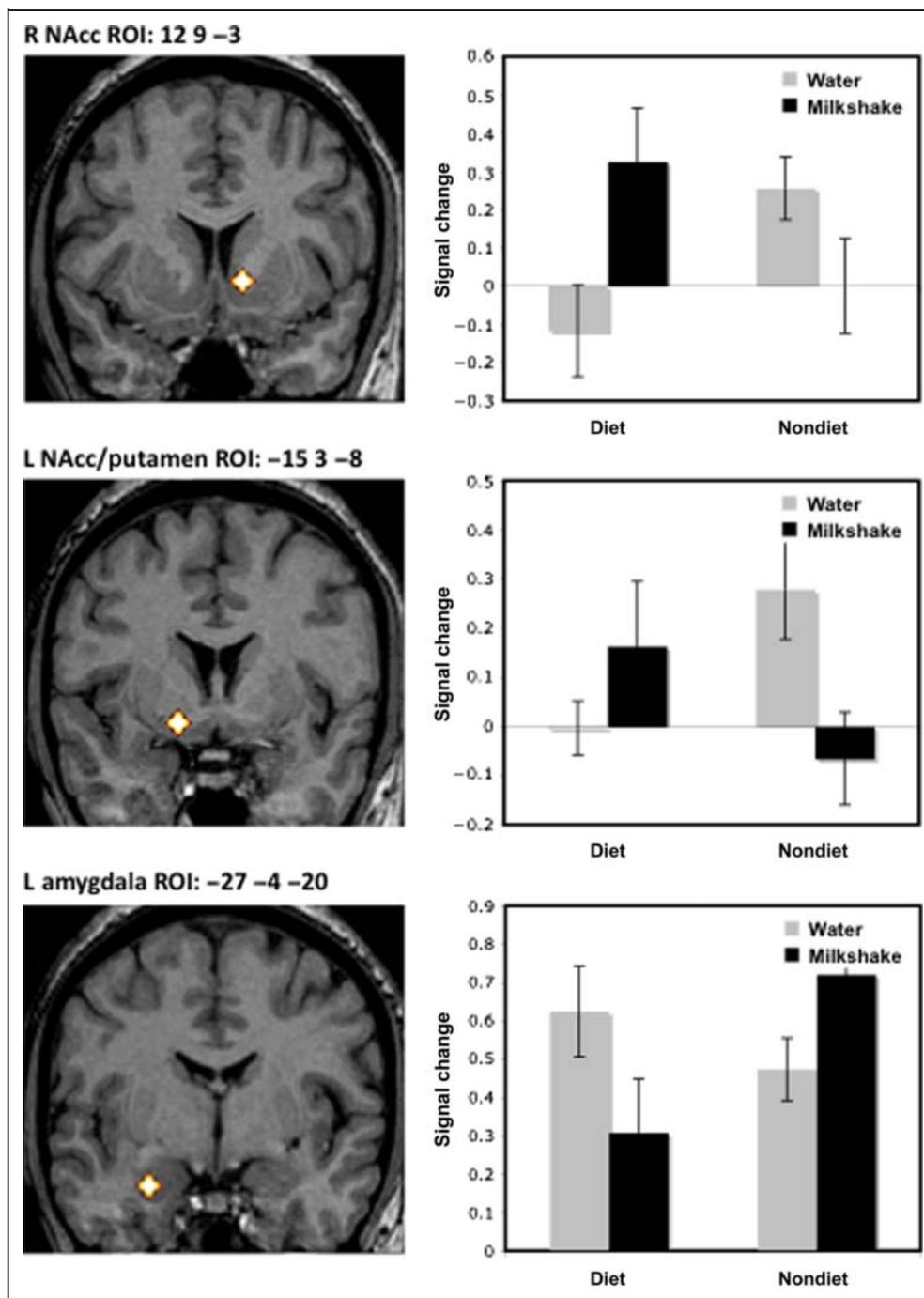
such that responses to food images in these regions were greatest for dieters that received a milkshake preload and non-dieters that received a water preload (see Figure 3). As can be observed in Figure 3, non-dieters in the water condition showed a robust NAcc response to food cues,

Table 2. Identification of BOLD Signal Changes in Response to Food Items Associated with the Main Effects of Restraint, Preload, and the Restraint by Preload Interaction

<i>Brain Region</i>		<i>F</i>	<i>x</i>	<i>y</i>	<i>z</i>
<i>Main Effect of Dietary Status—Dieters > Non-dieters</i>					
BA 39	L middle temporal gyrus	11.9	-54	-72	23
BA 47	L inferior frontal gyrus	11.3	-48	41	-2
BA 7	R lateral parietal sulcus	10.1	36	-50	49
BA 6	L superior frontal gyrus	9.4	-15	18	60
BA 44/45	L inferior frontal gyrus	8.3	-54	19	7
Insula	R insula	7.1	36	4	14
<i>Main Effect of Dietary Status—Non-dieters > Dieters</i>					
BA 18	R inferior occipital gyrus	7.8	29	-86	-7
BA 9	R middle frontal gyrus	7.7	36	19	27
<i>Main Effect of Preload—Milkshake > Water</i>					
BA 10	R OFC	8.2	15	60	21
BA 17	R cuneus	7.1	9	-96	2
BA 32	R ventral anterior cingulate	6.9	15	26	-9
<i>Main Effect of Preload—Water > Milkshake</i>					
BA 4	L precentral gyrus	11.5	-42	-18	45
BA 21	R middle temporal gyrus	9.9	74	-41	-6
BA 10	L lateral OFC	9.8	42	58	-5
BA 4	L precentral gyrus	9.2	-24	-15	48
BA 32/8	Dorsal anterior cingulate	5.9	6	34	34
<i>Restraint × Preload Interaction</i>					
Striatum	R NAcc	8.2	12	9	-3
Striatum	L putamen	7.2	-18	6	8
Striatum	L NAcc/putamen	6.5	-15	3	-8
Striatum	L caudate	6.2	-12	15	16
Amygdala	L amygdala	5.6	-27	-4	-20

Activations determined to be significant (thresholded at $p < .05$, corrected for false discovery rate, minimum extent threshold: $k = 5$ contiguous voxels) are listed along with the best estimate of their location. BA = Brodmann's area location. Coordinates are from the Talairach and Tournoux (1988) atlas. Locations of the activations are determined on the basis of the functional responses superimposed on averaged anatomical MRI images and are referenced to the Talairach atlas.

Figure 3. Coronal sections display right NAcc (top), left NAcc/putamen (middle), and left amygdala (bottom) spherical ROIs superimposed on a normalized anatomic image. Graphs to the right of each image display signal change (parameter estimates) across the four conditions relative to baseline fixation. Error bars indicate *SEM*. Activity in each region exhibits an interaction of restraint by preload.



whereas non-dieters showed minimal activity after the milkshake preload. Conversely, dieters in the water condition showed minimal NAcc activity, but dieters in the milkshake preload condition showed robust NAcc activity. Other regions of the striatum, including the left putamen (-18 6 8) and the left caudate (-12 15 16), demonstrated a similar restraint by preload interaction.

Interestingly, the left amygdala (-27 -4 -20) showed a Restraint \times Preload interaction that was opposite those observed in the ventral striatum. Specifically, amygdala response to food images was greatest for dieters receiving the water preload and non-dieters receiving the milkshake

preload (Figure 3). Thus, as with the NAcc findings, dieters and non-dieters responded differentially to the water and milkshake preloads.

Importantly, the interaction observed in each of these regions was specific to food images. None of these regions demonstrated differential responses to the nonfood images (all *F* values < 1).

DISCUSSION

Consistent with the hypothesis that dietary violations are associated with increased reactivity to food cues in brain

reward regions, dieters who consumed a milkshake showed greater ventral striatal activity when viewing pictures of appetizing food than did dieters who consumed only water. Also as expected, non-dieters showed the reverse pattern of greater striatal activity to appetizing food images when they consumed water compared with when they consumed the milkshake preload. Prior imaging studies of food cue reactivity have generally not focused on dieters or challenged dietary standards. Hence, these findings provide new insights into the neural basis of dietary failure.

The results for the non-dieters are consistent with past research demonstrating robust ventral striatal activity associated with viewing images of appetizing food (Passamonti et al., 2009; Schur et al., 2009; Stoeckel et al., 2008; DelParigi et al., 2007; Killgore et al., 2003; Small, 2002). This is not surprising; food is a primary reward and an inherent source of pleasure, and thus food and food-related cues are powerful motivation cues, the neural basis of which has been shown to rely on dopaminergic pathways (see reviews by Wilson et al., 2004; Jentsch & Taylor, 1999). These findings support the general proposition that mesolimbic and mesocortical systems are generally involved in reward. For instance, activity in reward regions has been observed when people view attractive faces (Cloutier, Heatherton, Whalen, & Kelley, 2008) and erotic images (Hamann, Herman, Nolan, & Wallen, 2004) and anticipate monetary reward (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Knutson, Adams, Fong, & Hommer, 2001; Knutson, Fong, Adams, Varner, & Hommer, 2001). It has long been known that food is less rewarding when one is full (Cabanac, 1971). Thus, the absence of NAcc activity in non-dieters after the large milkshake preload likely reflects the normal reduction in palatability associated with satiety, at least for non-dieters.

The findings also implicate dopaminergic systems in maladaptive behaviors (such as overeating) after dietary violation, as dieters showed increased NAcc activity to food cues after they were required to drink a large chocolate milkshake. Likewise, prior work has shown that obese women generally exhibit heightened activity NAcc in response to high-calorie food items (Stoeckel et al., 2008), collectively suggesting that NAcc activity is associated with overeating. This notion is also consistent with recent work by Stice, Spoor, Bohon, and Small (2008) and Stice, Spoor, Bohon, Veldhuizen, and Small (2008), who identified a region of the dorsal striatum that was negatively correlated with weight change in individuals who possess the Taq1A A1 gene allele, a genotype that has been linked to obesity. In their study, participants received food rewards during scanning. A growing body of research suggests that the dorsal striatum may be more involved in the direct consummatory response to rewards (e.g., eating; Stice, Spoor, Bohon, & Small, 2008; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001), whereas the ventral striatum is more often recruited during the anticipation of reward (e.g., cue reactivity; Stice, Spoor, Bohon, Veldhuizen, et al., 2008; Gottfried, O'Doherty, & Dolan, 2003; Small, 2002). These

results converge nicely with the data herein, further suggesting a role for motivation and reward circuitry in dieting and dietary restraint failure.

Interestingly, the amygdala followed an opposite pattern of activation from the striatum such that activity in the amygdala was greatest when NAcc was weak (i.e., for dieters who received water and non-dieters who received the milkshake). Such activity may reflect an avoidance response to the food images because both non-dieters who are sated and dieters with unbroken diets avoid rich, indulgent foods. Research by LaBar et al. (2001) suggests a hunger/motivational state-dependent response to food items in the amygdala. In their study, participants were food deprived for 8 hours before scanning and viewed food and nonfood images (tools) during scanning. Subjects then consumed a satiating meal and were scanned again. Participants showed an increased amygdala response to food images during the hungry state compared with the sated state, and the authors interpret these results to suggest a role for the amygdala in mediating the real-time significance of food stimuli. In the current study, the amygdala response of dieters after a water preload is consistent with this finding and may reflect a dieter's overall state of hunger. However, non-dieters who were sated by a milkshake preload show a similarly high level of amygdala activation in response to food images. It is difficult to reconcile the somewhat disparate findings, in part because the prior work enrolled both male and female participants and without regard to their dietary status. One possible alternative explanation for the differential amygdala response to food images is that it reflects a general arousal response to the food. For the dieters, it is a potentially aversive response because dieters are actively trying to avoid such foods. For the non-dieters, amygdala activity may also index a similar arousal response to food items because the rich milkshake may satiate non-dieters to a point of making additional food aversive (as evidenced by the finding that non-dieters eat very little when they are full). On-line ratings of food items were not taken during scanning, but it is possible that amygdala activity is indicative of the motivational appraisal afforded to food items at the present moment, whereas activity in the NAcc is more indicative of future behavior (i.e., desire to eat the pictured food). A second possibility is that the amygdala plays a more direct role in the self-regulation of eating behavior, as high amygdala activity is accompanied by reduced NAcc activity. However, given the well-established linkage between amygdala responsivity and arousal, a more parsimonious account is that the amygdala is not directly involved in self-regulation per se but is instead indirectly engaged via an interplay between subcortical regions like amygdala and NAcc with cortical regions of frontal cortex.

Dietary Violations and Self-regulation Failure

One interesting finding in the current research is that chronic dieters did not show increased activity in brain

reward regions in response to food cues in the control condition where they consumed only water. This stands in contrast to non-dieters who show robust activity in NAcc to attractive food cues, as has also been found repeatedly in the cue reactivity literature. How is it that chronic dieters were able to ignore the rewarding properties of food cues? Metcalfe and Mischel (1999), in their hot/cool systems analysis of delay of gratification, proposed that “hot” processing is emotional and impulsive and occurs when focus is placed on the stimulus, whereas “cool” processing is more cognitive and emotionally neutral (Metcalfe & Mischel, 1999). Similarly, Bechara (2005) proposes interacting impulsive and reflective systems that, when imbalanced, lead to addiction. One potential reason why diets fail may be that circumstances promote a focus on the rewarding properties of food, such as taste and emotional comfort. In this way, diet success may be rooted in either a shift to more functional “cool” processing of food or overcoming attention to the strong rewarding aspects of food. Thus, dieters with intact diets may somehow process appetitive cues in a way that removes their reward value.

Similar mechanisms of suppressing reward responses have been recently demonstrated. For example, Delgado, Gillis, and Phelps (2008) observed an attenuation of neural activity in the striatum when participants actively practiced emotion regulation. This may suggest a potential strategy for weight control—by regulating “hot” processing of food stimuli, dieters may be able to diminish reward activity from the NAcc, which may lead to more effective self-regulation. Recent evidence suggests that frontal regions of the brain often implicated in inhibitory control and self-regulation play a role in promoting food-related control. A recent study by Hare, Camerer, and Rangel (2009) required self-reported dieters to choose between “healthy” and “tasty” foods compared with neutrally rated foods, revealing that activity in the vmPFC tracked the value of a food (i.e., how tasty it was) regardless of the decision outcome, whereas the dlPFC was more active only when participants exerted self-control, making decisions on the basis of health rather than taste. Relatedly, successful weight loss maintainers, individuals who have lost a significant amount of weight and have managed to keep it off for at least 10 years, demonstrate consistent restraint without disinhibition, and when viewing high-calorie food items show increased activity in frontal regions of the brain relative to both obese and normal weight counterparts (McCaffery et al., 2009).

The notion of a reciprocal relation between cortical and subcortical brain regions has been observed across a number of domains (Drevets & Raichle, 1998). That is, under normal circumstances, increased activity in frontal regions is associated with decreased activity in subcortical regions, such as the amygdala (Kim, Somerville, Johnstone, Alexander, & Whalen, 2003). However, as situational cues lead to activity in subcortical regions, such as NAcc and amygdala, there appears to be a concomitant reduction in frontal activity. As such, a sufficiently strong appetitive sig-

nal may, at times, overwhelm executive control functions of the PFC. In the present work, regions of the left inferior frontal gyrus/vlPFC (BA 47 and BA 44/45) were more active in dieters compared with non-dieters in response to food images, irrespective of the preload manipulation. One interpretation of these results is that dieters attempt to exert self-control whether their diet is intact or not, with dietary failure driven by more basic, reward-related mechanisms. That is, once a diet is broken by the milkshake, self-regulation breaks down as subcortical reward regions take precedence over cortical regions associated with executive functions that support inhibition. The left inferior frontal cortex/vlPFC has been implicated in emotional control (Ochsner, Bunge, Gross, & Gabrieli, 2002; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001) and more generally in cognitive control and decision making (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004) through inhibition of emotional, physical, and social influences. In the present study, activity observed in this area may reflect automatic efforts to exert restraint in response to food items. An open question, however, is why activation in these or other frontal control regions (e.g., dlPFC) did not differ between preloaded and nonpreloaded dieters (i.e., LIFG/vlPFC activity was not diminished for “disinhibited” dieters that received the milkshake as might have been expected). Given that participants were not making explicit decisions about the food items and no demand characteristics were involved, one possibility is that in the case of the cue reactivity paradigm, these control regions are involved in attempts at self-regulatory control at a more sustained, tonic level.

Unfortunately, such effects cannot be readily explored in event-related fMRI paradigms. Whereas responses in the NAcc and amygdala are transient, activating to brief presentations of food cues, regions whose function are to maintain a state of inhibition, will likely remain either tonically active or inactive for the duration of that condition (Visscher et al., 2003). Recent neuroimaging work has highlighted an elegant method for capturing such sustained state effects while simultaneously measuring the transient responses to individual items in mixed state-item fMRI designs (Burgund, Lugar, Miezin, Schlaggar, & Petersen, 2006; Wenger, Visscher, Miezin, Petersen, & Schlaggar, 2004; Burgund, Lugar, Miezin, & Petersen, 2003; Velanova et al., 2003; Visscher et al., 2003; Donaldson, Petersen, & Buckner, 2001; Donaldson, Petersen, Ollinger, & Buckner, 2001). Future research will likely need to capitalize on such designs to better disentangle sustained and transient signals, as it will be important to understand how and when self-regulation breaks down and how subcortical reward regions interact with cortical executive regions to result in differences in inhibition.

Consistent with this notion, in addition to the notable difficulty of accurately imaging the hypothalamus given its size and location using standard imaging parameters, it is possible that the inability of event-related designs to detect sustained responses also accounts for the absence of

hypothalamic activity in the present report. Given the role of the hypothalamus in hunger and satiety, differences across dietary and preload conditions may have been expected. However, such differences may not manifest as transient responses to food cues but rather as more general states of either heightened or reduced satiety levels. Indeed, changes in hypothalamic activity occur relatively slowly (approximately 5–10 min after intake) and have been shown to persist over relatively long periods (i.e., 30 min) (Smeets, de Graaf, Stafleu, van Osch, & van der Grond, 2005a, 2005b). Given that participants in the present study were scanned immediately after ingesting either water or high-calorie milkshakes, it is probable that differences in the hypothalamic activity had not yet been fully realized.

One potential limitation to the current study is that our dieters were normal to overweight rather than obese, and it is possible that the truly obese might respond differently than our dieters. For instance, it is possible that obese dieters would fail to show the reduced NAcc activity to food images after water preload that we observed here. Studies of adolescents with Prader–Willi syndrome (Holsen et al., 2006) indicate strong reward responses to food images. However, it is notable that such individuals are obese because of chronic overeating. Similarly, obese women exhibit greater activity in reward areas including the NAcc in response to high-calorie food items compared to healthy weight control subjects (Stoeckel et al., 2008). Future studies that examine cue reactivity across the range of disordered eating (e.g., anorexia, binge eating disorder) may be particularly informative. Additionally, diets are broken not only by ingesting high-calorie food but also by emotional distress and self-regulatory depletion (Vohs & Heatherton, 2000; Heatherton et al., 1991). The findings presented here would be particularly compelling if such manipulations produced similar patterns of activity in response to food cues as a diet-breaking food preload.

Obesity is a growing problem in the western world, and many dieters struggle to achieve and maintain long-term weight loss. The present study, along with the extant neuroimaging literature on eating, suggests a neural underpinning for diet failure and perhaps self-regulatory failures, such as addiction, more generally. The results of the current study provide initial evidence that self-regulatory failure associated with breaking a diet may be mediated by hyperactive reward and motivational responses to food. At the same time, we uncovered a particularly intriguing finding that dieters somehow manage to observe tempting foods, at least when their diets are intact, without activating reward regions. At the most general level, these data suggest that attempts to regulate behavior, such as trying to overcome addictions, control anger, or avoid other temptations, may rely on a common mechanism centered around brain reward regions. The use of a dieting analogue provides a novel and important way to assess the breakdown of restraints. Given the enormous societal costs of self-regulation failures, drug addiction, obesity, and so forth, understanding the neural mechanisms involved in successful

self-regulation and its breakdowns should be a high scientific priority (Delgado et al., 2008; Bechara, 2005).

Acknowledgments

We thank Cary Savage, Paul Whalen, Tammy Moran, Courtney Rogers, Leah Somerville, Kristina Caudle, and Dylan Wagner for their assistance on this project. This work was supported by the National Institute of Drug Abuse (DA022582).

Reprint requests should be sent to Kathryn E. Demos, Department of Psychiatry & Human Behavior, Weight Control & Diabetes Research Center, Brown University, 196 Richmond, St., Providence, RI 02906, or via e-mail: kathryn_demos@brown.edu.

REFERENCES

- Adcock, R. A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., & Gabrieli, J. D. (2006). Reward-motivated learning: Mesolimbic activation precedes memory formation. *Neuron*, *50*, 507–517.
- Aronne, L. J., Wadden, T., Isoldi, K. K., & Woodworth, K. A. (2009). When prevention fails: Obesity treatment strategies. *American Journal of Medicine*, *122*(4 Suppl. 1), S24–S32.
- Baumeister, R. F., Heatherton, T. F., & Tice, D. (1994). *Losing control: How and why people fail at self-regulation*. San Diego: Academic Press.
- Bechara, A. (2005). Decision making, impulse control and loss of willpower: A neurocognitive perspective. *Nature Neuroscience*, *8*, 1458–1463.
- Bunge, S. A., Ochsner, K. N., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (2001). Prefrontal regions involved in keeping information in and out of mind. *Brain*, *124*, 2074–2086.
- Burgund, E. D., Lugar, H. M., Miezin, F. M., & Petersen, S. E. (2003). Sustained and transient activity during an object-naming task: A mixed blocked and event-related fMRI study. *Neuroimage*, *19*, 29–41.
- Burgund, E. D., Lugar, H. M., Miezin, F. M., Schlaggar, B. L., & Petersen, S. E. (2006). The development of sustained and transient neural activity. *Neuroimage*, *29*, 812–821.
- Cabanac, M. (1971). Physiological role of pleasure. *Science*, *173*, 1103–1107.
- Cloutier, J., Heatherton, T. F., Whalen, P. J., & Kelley, W. M. (2008). Are attractive people rewarding? Sex differences in the neural substrates of facial attractiveness. *Journal of Cognitive Neuroscience*, *20*, 941–951.
- Dansinger, M. L., Tatsioni, A., Wong, J. B., Chung, M., & Balk, E. M. (2007). Meta-analysis: The effect of dietary counseling for weight loss. *Annals of Internal Medicine*, *147*, 41–50.
- Delgado, M. R., Gillis, M. M., & Phelps, E. A. (2008). Regulating the expectation of reward via cognitive strategies. *Nature Neuroscience*, *11*, 880–881.
- DelParigi, A., Chen, K., Salbe, A. D., Hill, J. O., Wing, R. R., Reiman, E. M., et al. (2007). Successful dieters have increased neural activity in cortical areas involved in the control of behavior. *International Journal of Obesity (London)*, *31*, 440–448.
- Donaldson, D. I., Petersen, S. E., & Buckner, R. L. (2001). Dissociating memory retrieval processes using fMRI: Evidence that priming does not support recognition memory. *Neuron*, *31*, 1047–1059.
- Donaldson, D. I., Petersen, S. E., Ollinger, J. M., & Buckner, R. L. (2001). Dissociating state and item components of recognition memory using fMRI. *Neuroimage*, *13*, 129–142.

- Drevets, W. C., & Raichle, M. E. (1998). Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: Implications for interactions between emotion and cognition. *Cognition and Emotion*, *12*, 353–385.
- Drobes, D. J., & Tiffany, S. T. (1997). Induction of smoking urge through imaginal and in vivo procedures: Physiological and self-report manifestations. *Journal of Abnormal Psychology*, *106*, 15–25.
- Drummond, D. C., Cooper, T., & Glautier, S. P. (1990). Conditioned learning in alcohol dependence: Implications for cue exposure treatment. *British Journal of Addiction*, *85*, 725–743.
- Franken, I. H. (2003). Drug craving and addiction: Integrating psychological and neuropsychopharmacological approaches. *Progress in Neuro-psychopharmacology & Biological Psychiatry*, *27*, 563–579.
- Friston, K., Holmes, A., Worsley, K., Poline, J., Frith, C., & Frackowiak, R. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, *2*, 189–210.
- Glautier, S., & Drummond, D. C. (1994). Alcohol dependence and cue reactivity. *Journal of Studies on Alcohol*, *55*, 224–229.
- Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*, *159*, 1642–1652.
- Gottfried, J. A., O'Doherty, J., & Dolan, R. J. (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science*, *301*, 1104–1107.
- Gunstad, J., Paul, R. H., Cohen, R. A., Tate, D. F., Spitznagel, M. B., Grieve, S., et al. (2008). Relationship between body mass index and brain volume in healthy adults. *International Journal of Neuroscience*, *118*, 1582–1593.
- Hamann, S., Herman, R. A., Nolan, C. L., & Wallen, K. (2004). Men and women differ in amygdala response to visual sexual stimuli. *Nature Neuroscience*, *7*, 411–416.
- Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. *Science*, *324*, 646–648.
- Heatherton, T. F., & Baumeister, R. F. (1991). Binge eating as escape from self-awareness. *Psychological Bulletin*, *110*, 86–108.
- Heatherton, T. F., Herman, C. P., & Polivy, J. (1991). Effects of physical threat and ego threat on eating behavior. *Journal of Personality and Social Psychology*, *60*, 138–143.
- Heatherton, T. F., Herman, C. P., & Polivy, J. (1992). Effects of distress on eating: The importance of ego-involvement. *Journal of Personality and Social Psychology*, *62*, 801–803.
- Heatherton, T. F., Herman, C. P., Polivy, J., King, G. A., & McGree, S. T. (1988). The (mis)measurement of restraint: An analysis of conceptual and psychometric issues. *Journal of Abnormal Psychology*, *97*, 19–28.
- Heatherton, T. F., Mahamedi, F., Strieppe, M., Field, A. E., & Keel, P. (1997). A 10-year longitudinal study of body weight, dieting, and eating disorder symptoms. *Journal of Abnormal Psychology*, *106*, 117–125.
- Heatherton, T. F., & Polivy, J. (1992). Chronic dieting and eating disorders: A spiral model. In J. H. Crowther, S. E. Hobfall, M. A. P. Stephens, & D. L. Tennenbaum (Eds.), *The etiology of bulimia nervosa: The individual and familial context* (pp. 133–155). Washington, DC: Hemisphere Publishers.
- Heatherton, T. F., Polivy, J., & Herman, C. P. (1989). Restraint and internal responsiveness: Effects of placebo manipulations of hunger state on eating. *Journal of Abnormal Psychology*, *98*, 89–92.
- Herman, C. P., & Mack, D. (1975). Restrained and unrestrained eating. *Journal of Personality*, *43*, 647–660.
- Herman, C. P., & Polivy, J. (1975). Anxiety, restraint, and eating behavior. *Journal of Abnormal Psychology*, *84*, 66–72.
- Herman, C. P., & Polivy, J. (2004). The self-regulation of eating: Theoretical and practical problems. In R. F. Baumeister & K. D. Vohs (Eds.), *Handbook of self-regulation* (pp. 492–508). New York: Guilford.
- Holm-Denoma, J. M., Joiner, T. E., Vohs, K. D., & Heatherton, T. F. (2008). The “freshman fifteen” (the “freshman five” actually): Predictors and possible explanations. *Health Psychology*, *27*(1 Suppl.), S3–S9.
- Holsen, L. M., Zarcone, J. R., Brooks, W. M., Butler, M. G., Thompson, T. I., Ahluwalia, J. S., et al. (2006). Neural mechanisms underlying hyperphagia in Prader-Willi syndrome. *Obesity (Silver Spring)*, *14*, 1028–1037.
- Jansen, A. (1998). A learning model of binge eating: Cue reactivity and cue exposure. *Behaviour Research and Therapy*, *36*, 257–272.
- Jentsch, J. D., & Taylor, J. R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behavior by reward-related stimuli. *Psychopharmacology*, *146*, 373–390.
- Killgore, W. D., Young, A. D., Femia, L. A., Bogorodzki, P., Rogowska, J., & Yurgelun-Todd, D. A. (2003). Cortical and limbic activation during viewing of high- versus low-calorie foods. *Neuroimage*, *19*, 1381–1394.
- Kim, H., Somerville, L. H., Johnstone, T., Alexander, A. L., & Whalen, P. J. (2003). Inverse amygdala and medial prefrontal cortex responses to surprised faces. *NeuroReport*, *14*, 2317–2322.
- Knutson, B., Adams, C. M., Fong, G. W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *Journal of Neuroscience*, *21*, RC159.
- Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *NeuroReport*, *12*, 3683–3687.
- LaBar, K. S., Gitelman, D. R., Parrish, T. B., Kim, Y. H., Nobre, A. C., & Mesulam, M. M. (2001). Hunger selectively modulates corticolimbic activation to food stimuli in humans. *Behavioral Neuroscience*, *115*, 493–500.
- Mann, J., Cummings, J. H., Englyst, H. N., Key, T., Liu, S., Riccardi, G., et al. (2007). FAO/WHO scientific update on carbohydrates in human nutrition: Conclusions. *European Journal of Clinical Nutrition*, *61*(Suppl. 1), S132–S137.
- McCaffery, J. M., Haley, A. P., Sweet, L. H., Phelan, S., Raynor, H. A., Del Parigi, A., et al. (2009). Differential functional magnetic resonance imaging response to food pictures in successful weight-loss maintainers relative to normal-weight and obese controls. *The American Journal of Clinical Nutrition*, *90*, 928–934.
- McFarlane, T., Polivy, J., & Herman, C. P. (1998). Effects of false weight feedback on mood, self-evaluation, and food intake in restrained and unrestrained eaters. *Journal of Abnormal Psychology*, *107*, 312–318.
- Metcalfe, J., & Mischel, W. (1999). A hot/cool-system analysis of delay of gratification: Dynamics of willpower. *Psychological Review*, *106*, 3–19.
- Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. (2002). Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, *14*, 1215–1229.
- Ogden, C. L., Carroll, M. D., Curtin, L. R., McDowell, M. A., Tabak, C. J., & Flegal, K. M. (2006). Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA*, *295*, 1549–1555.

- Passamonti, L., Rowe, J. B., Schwarzbauer, C., Ewbank, M. P., von dem Hagen, E., & Calder, A. J. (2009). Personality predicts the brain's response to viewing appetizing foods: The neural basis of a risk factor for overeating. *Journal of Neuroscience*, *29*, 43–51.
- Payne, T. J., Smith, P. O., Adams, S. G., & Diefenbach, L. (2006). Pretreatment cue reactivity predicts end-of-treatment smoking. *Addictive Behaviors*, *31*, 702–710.
- Polivy, J., Heatherton, T. F., & Herman, C. P. (1988). Self-esteem, restraint, and eating behavior. *Journal of Abnormal Psychology*, *97*, 354–356.
- Polivy, J., & Herman, C. E. (1987). Diagnosis and treatment of normal eating. *Journal of Consulting and Clinical Psychology*, *55*, 635–644.
- Polivy, J., Herman, C. P., & Howard, K. (1988). The restraint scale: Assessment of dieting. In M. Herson & A. S. Bellack (Eds.), *Dictionary of behavioral assessment techniques* (pp. 377–380). New York: Pergamon.
- Ridderinkhof, K. R., van den Wildenberg, W. P. M., Segalowitz, S. J., & Carter, C. S. (2004). Neurocognitive mechanisms of cognitive control: The role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and Cognition*, *56*, 129–140.
- Rothmund, Y., Preuschhof, C., Bohner, G., Bauknecht, H. C., Klingebiel, R., Flor, H., et al. (2007). Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage*, *37*, 410–421.
- Sacks, F. M., Bray, G. A., Carey, V. J., Smith, S. R., Ryan, D. H., Anton, S. D., et al. (2009). Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *New England Journal of Medicine*, *360*, 859–873.
- Schur, E. A., Kleinhans, N. M., Goldberg, J., Buchwald, D., Schwartz, M. W., & Maravilla, K. (2009). Activation in brain energy regulation and reward centers by food cues varies with choice of visual stimulus. *International Journal of Obesity (London)*, *33*, 653–661.
- See, R. E. (2002). Neural substrates of conditioned-cued relapse to drug-seeking behavior. *Pharmacology, Biochemistry and Behavior*, *71*, 517–529.
- Serdula, M. K., Mokdad, A. H., Williamson, D. F., Galuska, D. A., Mendlein, J. M., & Heath, G. W. (1999). Prevalence of attempting weight loss and strategies for controlling weight. *JAMA*, *282*, 1353–1358.
- Simmons, W. K., Martin, A., & Barsalou, L. W. (2005). Pictures of appetizing foods activate gustatory cortices for taste and reward. *Cerebral Cortex*, *15*, 1602–1608.
- Small, D. M. (2002). Toward an understanding of the brain substrates of reward in humans. *Neuron*, *33*, 668–671.
- Small, D. M., Zatorre, R. J., Dagher, A., Evans, A. C., & Jones-Gotman, M. (2001). Changes in brain activity related to eating chocolate: From pleasure to aversion. *Brain*, *124*, 1720–1733.
- Smeets, P. A., de Graaf, C., Stafleu, A., van Osch, M. J., & van der Grond, J. (2005a). Functional magnetic resonance imaging of human hypothalamic responses to sweet taste and calories. *American Journal of Clinical Nutrition*, *82*, 1011–1016.
- Smeets, P. A., de Graaf, C., Stafleu, A., van Osch, M. J., & van der Grond, J. (2005b). Functional MRI of human hypothalamic responses following glucose ingestion. *Neuroimage*, *24*, 363–368.
- Stewart, J., de Wit, H., & Eikelboom, R. (1984). Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychological Review*, *91*, 251–268.
- Stice, E., Maxfield, J., & Wells, T. (2003). Adverse effects of social pressure to be thin on young women: An experimental investigation of the effects of “fat talk.” *International Journal of Eating Disorders*, *34*, 108–117.
- Stice, E., Spoor, S., Bohon, C., & Small, D. M. (2008). Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. *Science*, *322*, 449–452.
- Stice, E., Spoor, S., Bohon, C., Veldhuizen, M. G., & Small, D. M. (2008). Relation of reward from food intake and anticipated food intake to obesity: A functional magnetic resonance imaging study. *Journal of Abnormal Psychology*, *117*, 924–935.
- Stoeckel, L. E., Weller, R. E., Cook, E. W., III, Twieg, D. B., Knowlton, R. C., & Cox, J. E. (2008). Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage*, *41*, 636–647.
- Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: An approach to cerebral imaging*. New York: Thieme Medical Publishers.
- Van Essen, D. C., Dickson, J., Harwell, J., Hanlon, D., Anderson, C. H., & Drury, H. A. (2001). An integrated software system for surface-based analyses of cerebral cortex. *Journal of American Medical Informatics Association*, *8*, 443–459.
- Velanova, K., Jacoby, L. L., Wheeler, M. E., McAvoy, M. P., Petersen, S. E., & Buckner, R. L. (2003). Functional-anatomic correlates of sustained and transient processing components engaged during controlled retrieval. *Journal of Neuroscience*, *23*, 8460–8470.
- Visscher, K. M., Miezin, F. M., Kelly, J. E., Buckner, R. L., Donaldson, D. I., McAvoy, M. P., et al. (2003). Mixed blocked/event-related designs separate transient and sustained activity in fMRI. *Neuroimage*, *19*, 1694–1708.
- Vohs, K. D., & Heatherton, T. F. (2000). Self-regulatory failure: A resource-depletion approach. *Psychological Science*, *11*, 249–254.
- Volkow, N. D., & O'Brien, C. P. (2007). Issues for DSM-V: Should obesity be included as a brain disorder? *American Journal of Psychiatry*, *164*, 708–710.
- Wenger, K. K., Visscher, K. M., Miezin, F. M., Petersen, S. E., & Schlaggar, B. L. (2004). Comparison of sustained and transient activity in children and adults using a mixed blocked/event-related fMRI design. *Neuroimage*, *22*, 975–985.
- Wilson, S. J., Sayette, M. A., & Fiez, J. A. (2004). Prefrontal responses to drug cues: A neurocognitive analysis. *Nature Neuroscience*, *7*, 211–214.