

salient stimuli, both of which conspire to induce self-regulatory collapse (for a review, see Heatherton & Wagner, 2011).

A large body of electrophysiological and neuroimaging research has shown that the reward value of food is represented in the OFC and striatum. In animal studies, the OFC increases its firing rate during the presentation of visual or olfactory food cues (for a review, see Rolls, 2000), which in turn is modulated by the animal's relative satiety (Critchley & Rolls, 1996). In humans, functional neuroimaging research has demonstrated that activity in the OFC is increased when tasting, smelling, or viewing food images (Demos, Kelley, & Heatherton, 2011; Yokum, Ng, & Stice, 2011; Schienle, Schäfer, Hermann, & Vaitl, 2009; Wang et al., 2004, 2009; Stoeckel et al., 2008; Rothemund et al., 2007; Beaver et al., 2006; Killgore & Yurgelun-Todd, 2006; Porubská, Veit, Preissl, Fritsche, & Birbaumer, 2006; Simmons, Martin, & Barsalou, 2005; Gottfried, O'Doherty, & Dolan, 2003; Kringelbach, O'Doherty, Rolls, & Andrews, 2003; Morris & Dolan, 2001; O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001; O'Doherty et al., 2000). Moreover, when viewing food images, activity in the OFC is correlated with individual differences in hunger (Morris & Dolan, 2001) and reward sensitivity (Beaver et al., 2006) and also predicts future weight gain (Yokum et al., 2011).

If emotional distress leads to sensitization of the human brain's reward system to food and drugs, then it follows that brain regions involved in representing the reward value of appetitive stimuli, such as the OFC and striatum (O'Doherty, 2004), would show an exaggerated response to food cues following emotional distress. To test this hypothesis, we used functional neuroimaging to measure food-cue-related activity in 30 chronic dieters. We used a validated mood manipulation procedure based on interpersonal distress to induce negative mood in half the chronic dieting sample and neutral mood in the other half. Immediately after, participants in both conditions were exposed to appetizing food images. Before and after the experiment, participants were asked to complete a self-esteem measure to index the degree to which they were affected by the experimental manipulations. We predicted that, compared with chronic dieters in a neutral mood, those who experienced negative emotional distress would subsequently show an exaggerated neural response in brain regions involved in representing the reward value of appetizing food cues.

METHODS

Participants

Thirty healthy right-handed female dieters (mean age = 19.7 years, range = 18–22 years) with normal or corrected-to-normal visual acuity and no history of neurological problems participated in this study. Chronic dieters were

recruited from a larger sample of college students who completed the Restraint Scale, a validated measure of chronic dieting tendencies (Heatherton, Herman, Polivy, King, & McGree, 1988; Herman & Mack, 1975) as part of a mass testing session. Participants with restraint scores greater than 16 were considered chronic dieters (see Heatherton, Polivy, & Herman, 1991) and were invited to participate in the current study (mean restraint = 18.8, range = 16–26). All participants remained unaware of these selection criteria until debriefing. Participant selection was limited to young women, because young women show a higher incidence of dieting (e.g., Herman & Mack, 1975) and are at increased risk for weight gain (Holm-Denoma, Joiner, Vohs, & Heatherton, 2008) and because of the known gender differences in reasons for dieting (e.g., Pingitore, Spring, & Garfield, 1997). Before scanning, participants were randomly assigned to receive either a negative mood induction ($n = 15$) or a neutral mood induction ($n = 15$). Negative and neutral mood induction groups did not differ in terms of weight, estimated body mass index (BMI), self-esteem or scores on the Restraint Scale (all $p > .34$; Table 1). All participants gave informed consent in accordance with the guidelines set by the Committee for the Protection of Human Subjects at Dartmouth College.

Mood Induction Procedures

The negative and neutral mood induction procedures used in this study were adapted from the widely used Velten (1968) mood induction procedure (VMIP) in which participants read a series of 60 increasingly negative self-referential statements designed to induce feelings of inadequacy and dysphoria (e.g., "I've doubted that I'm a worthwhile person"). Female dieters frequently report greater body dissatisfaction, lower self-esteem, and greater social anxiety than their nondieting peers (Johnson & Wardle, 2005; Heatherton, 1993). Accordingly, for the negative mood induction, we implemented a social distress version of the original VMIP using statements

Table 1. Characteristics of Dieters in the Negative and Neutral Mood Induction Groups

	<i>Negative Mood Induction (n = 15)</i>	<i>Neutral Mood Induction (n = 15)</i>
Age (years)	19.1	19.3
Weight (lbs)	127.3	131.3
BMI (kg/m ²)	20.9	21.9
Self-esteem	117	119.4
Restraint score	19	18.7

There were no between-group differences in age, BMI, self-esteem, or restraint scores (all $p > .34$).

designed to induce increasing feelings of social rejection and isolation (e.g., “I’m convinced that no one likes me”).

A pilot study was conducted to ensure that the social distress VMIP had measurable effects on mood and self-esteem. Twenty-nine participants performed the neutral VMIP (Velten, 1968), followed by the State Self-Esteem Scale (Heatherton & Polivy, 1991) and a 24-item mood scale (Heatherton & Vohs, 2000). Participants then completed the social distress VMIP, and once again state self-esteem and mood were assessed. Results of this pilot indicated that the social distress VMIP led to reduced positive mood, $t(28) = 3.27, p = .003$, increased negative mood, $t(28) = 2.24, p = .03$, and a reduction in social state self-esteem, $t(28) = 2.46, p = .02$.

Food Cue Reactivity Task

The food cue reactivity task was adapted from prior research on neural cue reactivity to appetizing foods (e.g., Demos, Heatherton, & Kelley, 2012; Demos et al., 2011) and consisted of 150 images from one of three categories: 50 images of appetizing, high-calorie foods (e.g., desserts, fast food, snacks); 50 images involving people; and 50 natural scenes, such as landscapes. Participants were asked to indicate via a button press whether an image took place indoors or outdoors. This *incidental* task was chosen so as to disguise the purpose of the study and also to ensure that participants were attending to the images. All images conformed to an image dimension of 480×360 pixels at 72 dpi.

Task and Experimental Design

Before scanning, participants were randomly assigned to receive either the negative ($n = 15$) or neutral ($n = 15$) mood induction procedures. Participants were instructed that they would be completing two tasks: a reading task (i.e., the mood induction task) and a simple categoriza-

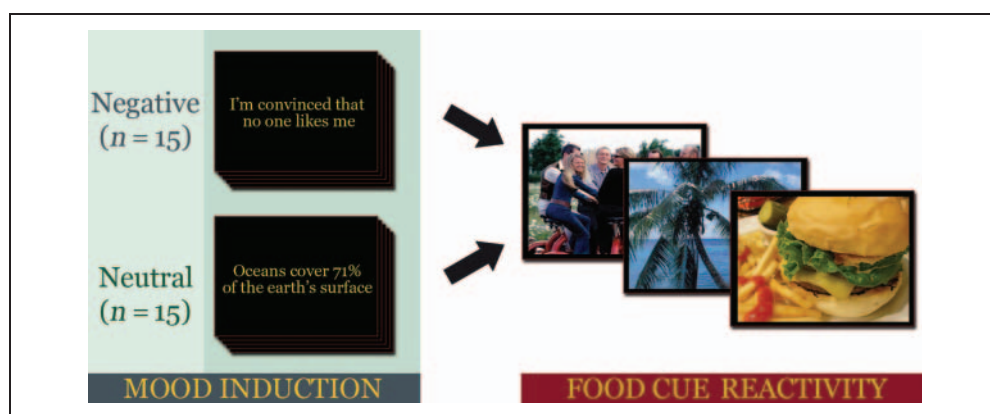
tion task (i.e., the cue reactivity task). At no time was it mentioned that the tasks were designed to manipulate mood or measure responses to appetizing foods. For the mood induction procedure, participants were instructed to read each statement and to recall moments in their lives where they have experienced the feelings described. For the image categorization task, participants were instructed to categorize, via button press, each image according to whether it took place indoors or outdoors. After scanning, participants completed a self-esteem assessment (Fleming & Courtney, 1984) and were debriefed regarding the purposes of the experiment and the nature of the mood induction. If they had received the negative mood induction, they were offered a list of statements to read from the positive version of the VMIP to return their mood to baseline (Figure 1).

The cue reactivity task used a rapid event-related design with trials consisting of a single image (food, people or nature images) displayed for 2000 msec. The order of trial types and the duration of the ISI (between 500 and 8000 msec, mean duration = 3200 msec) were pseudo-randomized. During the ISI, null event trials consisting of a white fixation cross against a black background were shown for 2500 msec and were used to introduce jitter into the fMRI time series to increase the estimation efficiency of task effects.

Image Acquisition

MRI was conducted with a Philips Achieva 3.0-T scanner using an eight-channel phased array coil. Structural images were acquired using a T1-weighted magnetization-prepared rapid gradient echo protocol (160 sagittal slices; repetition time = 9.9 msec, echo time = 4.6 msec, flip angle = 8° , $1 \times 1 \times 1$ mm voxels). Functional images were acquired using a T2*-weighted echo-planar sequence (repetition time = 2500 msec, echo time = 35 msec, flip angle = 90° , field of view = 24 cm). For each participant, a single functional run of 520 whole-brain volumes (36 axial slices per whole-brain volume, 3.5-mm

Figure 1. Schematic of the study design. Restrained eaters were randomly assigned to receive either a negative or neutral mood induction (see Methods). After this, participants performed a food cue reactivity task while undergoing fMRI. The task involved making indoor or outdoor judgments on images containing high caloric appetizing foods or natural scenes.



thickness, 0.5-mm gap; 3 × 3 mm in-plane resolution) was collected.

Image Preprocessing and Analysis

fMRI data were analyzed using the general linear model (GLM) for event-related designs in SPM8 (Wellcome Department of Cognitive Neurology, London, UK). For each functional run, data were preprocessed to remove sources of noise and artifact. Images were corrected for differences in acquisition time between slices and realigned within and across runs via a rigid body transformation to correct for head movement. Images were then unwrapped to reduce residual movement-related image distortions not corrected by realignment. Functional data were normalized into a standard stereotaxic space (3-mm isotropic voxels) based on the SPM8 EPI template that conforms to the ICBM 152 brain template space (Montreal Neurological Institute [MNI]) and approximates the Talairach and Tournoux atlas space. Finally, normalized images were spatially smoothed (6-mm FWHM) using a Gaussian kernel.

For each participant, a GLM was constructed to investigate food-cue-specific brain activity. This GLM, incorporating task effects and covariates of no interest (a box-car regressor modeling the period of VMIP, a linear trend to account for low-frequency drift, and six movement parameters derived from realignment corrections), was convolved with a canonical hemodynamic response function and used to compute parameter estimates (β) and contrast images (containing weighted parameter estimates) for each visual scene category at each voxel. Contrast images for each subject, comparing food versus natural scenes were entered into a second-level random effects analysis with the participant treated as the random effect. Monte Carlo simulations using AFNI's AlphaSim were used to calculate the minimum cluster size at an uncorrected threshold of $p < .001$ required for a whole-brain correction of $p < .05$. Simulations (10,000 iterations) were performed on the volume of our study-wide whole-brain mask using smoothness estimated from the residuals obtained from the GLM and resulting in a minimum cluster size of 56 contiguous voxels. Between-group comparisons were conducted in a priori ROIs (i.e., the OFC, defined functionally, and the nucleus accumbens, defined anatomically). The OFC region was defined from the statistical comparisons of food versus scenes across both groups using a spherical ROI (6 mm) centered on the peak voxel of clusters demonstrating an effect of food versus natural scenes. As both groups contributed equally to the ROI-defining statistical map, this ROI is statistically unbiased with regards to between-group effects. Finally, a priori anatomical ROIs of the left and right nucleus accumbens were defined using labels provided with the Harvard–Oxford probabilistic atlas of cortical and sub-cortical structures (Desikan et al., 2006). Additional exploratory between-group comparisons were conducted in

regions derived from the main effect for food versus natural scenes and were corrected for multiple comparisons across all 10 ROIs.

RESULTS

Behavioral Results

After the mood induction procedure, participants in the negative group showed a reduction in self-esteem compared with their previously assessed baseline, $t(14) = 2.73$, $p = .016$ (Mean Pre = 117, Mean Post = 102.3), whereas participants in the neutral group did not, $t(14) = 0.13$, $p = .9$ (Mean Pre = 119.4, Mean Post = 120.3). There was also a trend toward reduced self-esteem in the negative compared with the neutral mood induction groups, $t(28) = 1.98$, $p = .058$.

fMRI Results

When contrasting the BOLD response to appetizing food images to neutral natural scenes across both groups of dieters, a number of brain regions were found to exhibit food-cue-related activity (Table 2; Figure 2A). These regions were subsequently interrogated for an effect of mood manipulation condition. ROI analysis showed that participants who underwent the negative mood induction exhibited greater food-cue-related activity in the left OFC (MNI coordinates: $-27,36,-12$) than did participants in the neutral mood induction procedure, $t(28) = 2.20$,

Table 2. Brain Regions Demonstrating Greater Food-cue-related Activity (Food versus Nature Scenes) across Both Negative and Neutral Mood Induction Groups

Brain Region	Side	BA	<i>t</i>	Coordinates of Peak Activation		
				<i>x</i>	<i>y</i>	<i>z</i>
OFC	L	11	5.50	-27	36	-12
Dorsolateral pFC	L	46	5.94	-54	36	18
Dorsolateral pFC	R	46	5.57	48	39	12
Fusiform gyrus	L	18	5.78	-54	-45	-21
Fusiform gyrus	R	37	4.80	51	-57	-15
Superior parietal lobule	R	7	4.05	30	-72	33
Inferior occipital gyrus	L	19	4.34	-39	-72	-9
Middle occipital gyrus	R	18	5.43	42	-90	-3
Inferior occipital gyrus	L	19	4.34	-39	-72	-9
Calcarine sulcus	L	18	6.47	-12	-99	-12

Regions showing greater activity to food versus nature scenes across both negative and neutral mood groups ($p < .05$, corrected) are listed along with the best estimate of their location. Coordinates are in MNI stereotaxic space. BA = approximate Brodmann's area.

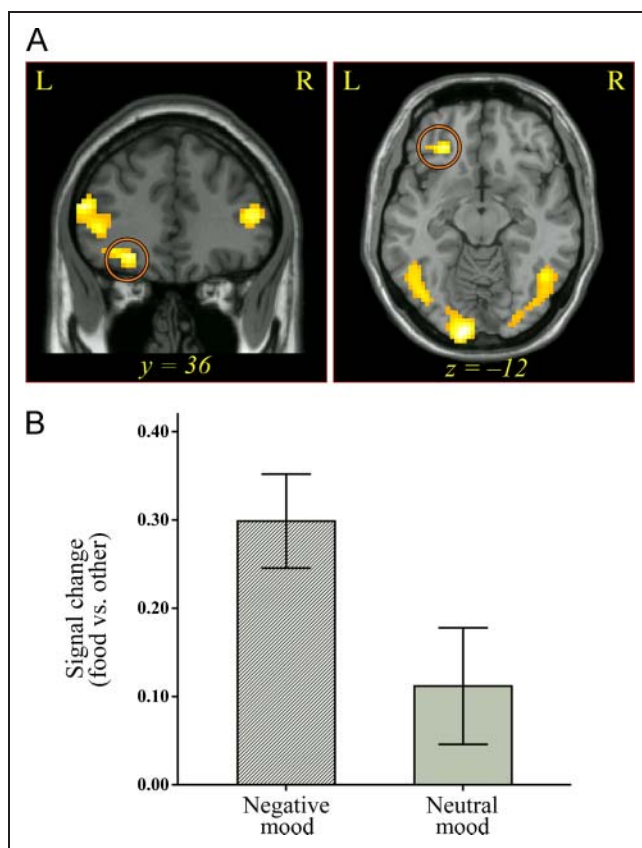


Figure 2. (A) The left OFC (MNI coordinates: $-27, 36, -12$) demonstrated greater activity to appetizing food images compared with neutral scenes across both groups ($p < .05$, corrected). (B) Within this region, dieters in the negative mood condition exhibited a larger response to appetizing food cues. Error bars indicate *SEM*. Coordinates are in MNI stereotaxic space.

$p = .036$ (Figure 2B). No other region differentiated between negative and neutral mood induction groups, both at a corrected threshold for multiple comparisons across all ROIs, but also uncorrected (all $p > .17$). Analysis of the nucleus accumbens, using a priori anatomical ROIs, revealed no between-group differences in food-cue-related activity (left NAc., $t(28) = 1.17, p = .25$; right NAc., $t(28) = 0.92, p = .37$).

Correlation with Post-scan Change in Self-esteem

Next, we examined the relationship between food-cue-related activity and individual differences in the degree to which participants were affected by the negative mood induction (using changes in self-esteem scores as a proxy) and correlated these with the BOLD response from the OFC and anatomically derived ROIs in the nucleus accumbens. This analysis revealed a significant relationship between reductions in self-esteem and food-cue-related activity in the OFC ($r = 0.52, p = .047$) and bilaterally in the nucleus accumbens (left: $r = 0.54, p = .040$; right: $r = 0.53, p = .042$), indicating that participants who exhibited

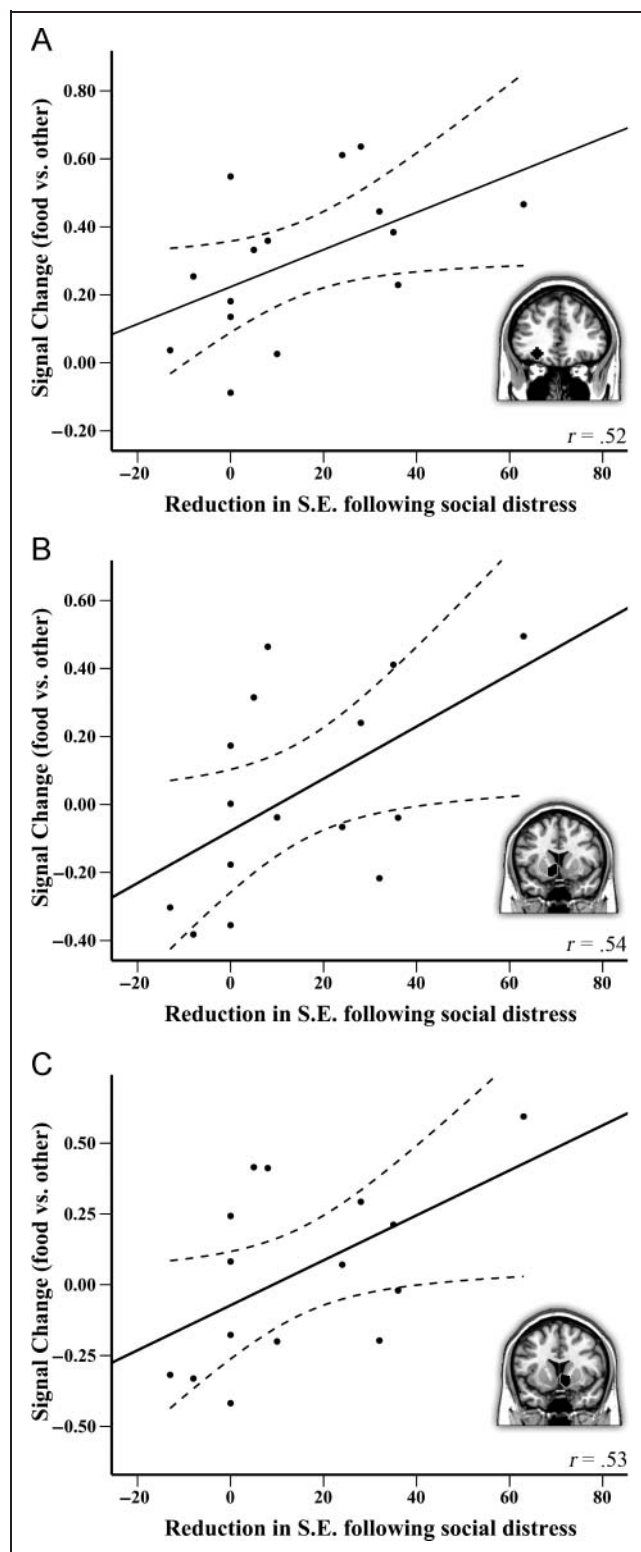


Figure 3. ROI analysis of the left OFC (A) and the left and right nucleus accumbens (B and C) demonstrated that individual differences in the degree to which the negative mood induction affected dieters' self-esteem was correlated with food-cue-related activity. Dashed lines indicate 95% confidence intervals. The OFC was defined functionally in an unbiased manner from the contrast of food versus other scenes across both groups. The left and right nucleus accumbens were defined anatomically based on the Harvard-Oxford probabilistic cortical and subcortical atlas (Desikan et al., 2006).

a greater decrease in self-esteem after the negative mood induction subsequently demonstrated a greater increase in food-cue-related activity in the OFC and nucleus accumbens (Figure 3).

DISCUSSION

Negative affect has long been associated with lapses in self-control (Heatherton, 2011; Heatherton & Wagner, 2011; Schachter, Goldman, & Gordon, 1968). This study investigated the hypothesis, derived from animal models of drug addiction, that emotional distress sensitizes the brain's reward system to appetitive stimuli (e.g., Sinha, 2001; Piazza & Le Moal, 1996, 1998) and their cues (e.g., Peciña et al., 2006). Compared with nondistressed dieters, those who underwent a negative mood induction showed greater food-cue-related activity in the OFC. Moreover, additional analyses showed that food-cue-related activity in the OFC and ventral striatum was correlated with individual differences in the amount of distress produced by the negative mood induction.

In both animals and humans, the OFC and ventral striatum are involved in representing the reward value and motivational salience of appetitive stimuli such as food (Demos et al., 2011; Killgore & Yurgelun-Todd, 2006; Simmons et al., 2005; Wang et al., 2004; Gottfried et al., 2003; Morris & Dolan, 2001; O'Doherty et al., 2001; Rolls, 2000), but also drugs of abuse (Wagner, Dal Cin, Sargent, Kelley, & Heatherton, 2011; David et al., 2005; Wilson, Sayette, & Fiez, 2004; Brody et al., 2002). Moreover, previous research has shown that activity in the OFC indexes satiety and the subjective pleasantness of food during consumption (Kringelbach et al., 2003; Small et al., 2001; O'Doherty et al., 2000). For example, when consuming appetizing foods, activity in the OFC decreases as satiety increases, suggesting that the OFC represents moment-by-moment changes in the subjective reward value of foods (O'Doherty et al., 2000). Finally, the results reported here are consistent with a recent meta-analysis of food cue exposure research (van der Laan, de Ridder, Viergever, & Smeets, 2011), showing that the left OFC is the most commonly recruited region in comparisons of food and non-food items (e.g., tools, scenery).

Numerous laboratory studies have shown that when dieters experience negative emotional distress they subsequently eat more than nondieters or dieters in a neutral mood (e.g., Heatherton et al., 1992, 1998; Heatherton, Polivy, Herman, & Baumeister, 1993; Heatherton, Herman, et al., 1991; Frost et al., 1982). Particularly relevant is a study by Frost and colleagues (1982) in which dieters who underwent the negative VMIP subsequently ate more food than both depressed nondieters and a control group of dieters in a neutral mood (Frost et al., 1982). Using the same type of mood induction procedure, we found that when dieters experience negative affect, neural activity in regions associated with the hedonic value of appetizing food show increased activity relative

to dieters in a neutral mood. Additional research shows that negative mood increases women's attentional bias toward appetizing food cues as well as their subjective hunger (Hepworth, Mogg, Brignell, & Bradley, 2010). These behavioral results, in conjunction with our neuroimaging findings, suggest that negative affect sensitizes the reward system to the hedonic value of appetizing foods, thereby precipitating self-regulatory failure and, in turn, overeating. One limitation of this study is that we recruited only dieters; however, given the behavioral research outlined above, it is likely that nondieters are unlikely to show an effect of mood on neural responses to food cues. Future research should seek to confirm this conjecture.

The propensity for negative moods to cause a breakdown in self-control is true not only of dieting but also of many other regulated behaviors, such as drug addiction (e.g., Heatherton, 2011; Sinha, 2009; Marlatt & Gordon, 1985), alcoholism (Witkiewitz & Villarreal, 2009), and smoking (Magid, Colder, Stroud, Nichter, & Nichter, 2009; Kassel, Stroud, & Paronis, 2003). For example, inducing negative mood in smokers increases both cigarette craving (Perkins et al., 2008; Willner & Jones, 1996; Tiffany & Drobes, 1990) and smoking intensity (McKee et al., 2011). Similar effects of negative mood induction on craving have been found in alcoholics (Sinha et al., 2009; Fox, Bergquist, Hong, & Sinha, 2007; Cooney, Litt, Morse, Bauer, & Gaupp, 1997) and drug addicts (Childress et al., 1994). More broadly, research has shown that experiencing emotionally negative life events is a potent trigger for drug relapse (Witkiewitz & Villarreal, 2009; Sinha, 2007). Even outside the domain of drug addiction, experiencing negative mood is associated with failures of self-control, such as excessive television viewing (Dittmar, 1994) or internet usage (LaRose, Lin, & Eastin, 2003). Hence, negative affect may act, in a general way, to enhance reward signals associated with desired behaviors, thereby making it harder to inhibit engaging in those behaviors (Heatherton & Wagner, 2011).

Limitations

A limitation of this study is the lack of subjective ratings on participants' desire for the appetizing food cues. Although the use of an incidental task allowed us to mitigate experimenter demand we cannot, however, confirm that the negative mood induction increased participants' food cravings or likability ratings for the food items. However, as reviewed above, a large body of behavioral research strongly suggests that experimental inductions of negative affect increase food cravings and consumption in dieters (e.g., Hepworth et al., 2010; Heatherton et al., 1992, 1998; Heatherton, Herman, et al., 1991; Frost et al., 1982). A related issue is whether the between-group difference in food-cue-related activity found in the left OFC, and the correlation with decrements in self-esteem found in the left OFC and the nucleus accumbens necessarily

indicate increased reward-related processing. A large number of prior imaging studies have related both of these regions to subjective reports of food craving (Morris & Dolan, 2001), desirability (Goldstone et al., 2009), pleasantness (Kringelbach et al., 2003; Small et al., 2001), reward sensitivity (Schienle et al., 2009; Beaver et al., 2006), and satiety (O'Doherty et al., 2000). The findings of these studies, along with the previously reviewed behavioral evidence in which negative affect increases craving and overeating, argue that the differences we see in dieters who experienced negative affect reflect changes in the reward value of appetizing foods. Furthermore, although our task defined food-cue-related activity as the difference between highly appetizing foods and non-food scenes, other research shows that, in cases where high- versus low-calorie food cues are compared, activity in both the OFC and nucleus accumbens is largest for high-calorie foods (i.e., Goldstone et al., 2009). Moreover, recent research has shown that food-cue-related activity in the nucleus accumbens, assessed using the same task and stimuli as used in this study, is predictive of future weight gain assessed 6 months later (e.g., Demos et al., 2012), strongly suggesting that activity in this region (when viewing appetizing food cues) reflects differential reward sensitivity.

Conclusions

Although the causes of self-regulatory failure are many (see Heatherton & Wagner, 2011), a frequent catalyst is negative affect (Heatherton, 2011). In humans, inducing negative emotional distress has been shown to increase eating in dieters (Heatherton et al., 1998), smoking in smokers (Tiffany & Drobles, 1990), and drug use in drug addicts (Childress et al., 1994). Research in non-human animals suggests a possible mechanism whereby distress impairs the self-regulatory functions of the pFC (Arnsten, 2009) while simultaneously sensitizing the reward system to food and drugs (Adam & Epel, 2007; Piazza & Le Moal, 1996). The current findings are consistent with this research by demonstrating that, in humans, inducing negative mood increases the neural response to appetizing food cues in the OFC and ventral striatum—both key regions involved in representing the reward value of food (O'Doherty, 2004). This interpretation is supported both by research in animals (e.g., Peciña et al., 2006; Miczek & Mutschler, 1996; Ramsey & Van Ree, 1993), but also by human research, showing that stress-induced increases in salivary cortisol in dieters is directly related to subsequent overeating (Epel, Lapidus, McEwen, & Brownell, 2001). Moreover, the artificial administration of glucocorticoids in humans increases eating without any concomitant increase in physical exertion (Tataranni et al., 1996).

As mentioned earlier, prior work shows that the reward system's response to appetizing food cues predicts weight gain 6 months later (Demos et al., 2012), which suggests that the response profile of these regions to appetitive stimuli can be used to index real-world sensitivity to

food. Thus, we propose that the oft-observed relationship between negative affect and dieters' self-regulatory failures may be due to difficulty in inhibiting overwhelming food cravings driven by a reward system rendered hyperresponsive to food cues and that this in turn puts dieters at risk of breaking their diets and binge eating.

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