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The Craving Stops Before You Feel It: Neural Correlates of Chocolate Craving During Cue Exposure with Response Prevention

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Cue reactivity and craving can be influenced by cue exposure with response prevention (CERP). This study investigated the neural correlates of CERP using functional magnetic resonance imaging, while participants smelled chocolate (17 participants) or a control object (17 participants). CERP was interrupted by 7 scanning sequences measuring the brain response to neutral and chocolate pictures. Chocolate craving was hypothesized to be mirrored by activation in brain reward regions. As expected, control group craving remained similar throughout the session. A short exposure (30 min) increased chocolate craving in the experimental group, which was mirrored by significant group differences in activation in brain reward regions. Unexpectedly, a long exposure (60 min) did not lead to craving extinction in the experimental group, although craving started to decrease at this point. On a neural level, however, activation in regions of interest in the experimental group seemed to have extinguished after the long exposure, as activation levels returned to or fell below control group levels. These results indicate that brain reward activation during CERP is linked to craving, at least for a short exposure. Regarding a longer exposure, the decline in brain reward activation in the experimental group may be a precursor of a decrease in craving.

Keywords: brain-as-predictor, cue reactivity, food craving, fMRI, interoceptive awareness, real food versus imagined taste

Introduction

Eating behavior and food cravings do not only depend on internal sensations of hunger and satiety; they are also controlled by external cues. A revealing example is a study with people suffering from amnesia who, after having had lunch, forgot about having eaten and readily continued eating when served a second and even a third lunch a short time later (Rozin et al. 1998; Higgs et al. 2008). This research showed that the simple presence of a meal induces food intake and apparently overrides any satiety signal if one cannot remember that one has recently eaten. Similarly, participants ate considerably more soup when it was served in a bottomless bowl, which concealed the amount of soup that they already had consumed, instead of a normal bowl (Wansink et al. 2005). Apart from food cues such as the presence of a meal or the lacking information about the consumed amount of soup, there are many more cues that promote food intake. These cues include environmental context (Boggiano et al. 2009), food variety (Guerrieri et al. 2008; Remick et al. 2009), advertisements (Harris et al. 2009), and intake of other people (Herman et al. 2003, 2012). These and other studies (for a review see Jansen et al. 2011) show that food cues increase the likelihood of food intake, and that cue-elicited eating easily leads to overeating and weight gain. Therefore, it is of specific interest to find ways of reducing the appetite-enhancing influence of food cues. This study will investigate the neural correlates of craving during an intervention that aims to reduce this influence: Cue exposure with response prevention (CERP).

Food cues are known to elicit reactivity. Physiological responses reflecting food cue reactivity are insulin release and increased salivation (Jansen et al. 2011). These physiological responses are supposed to be subjectively experienced as craving, which is best described as a strong desire for a given food. In its turn, this promotes consumption (Jansen 1998). This cue-elicited food craving is thought to reflect a learning history. According to the classical conditioning model of binge eating proposed by Jansen (1998), food cues function as a conditioned stimulus associated with food intake, which serves as an unconditioned stimulus. The more experience one has had with the consumption of a particular food, the stronger the reactivity to a cue associated with that food. Thus, overconsumption may contribute to greater cue reactivity, which in turn might facilitate overeating. Indeed, in overweight adults, overweight children, and binge eaters, reactivity to food cues was greater than in healthy-weight participants (Jansen et al. 2003; Sobik et al. 2005; Ferriday and Brunstrom 2011). In obese participants, neural activation in response to high-calorie food versus control pictures in regions associated with food reward was negatively correlated with success in achieving and maintaining weight loss after a weight-loss treatment (Murdaugh et al. 2012). A study with adolescent girls showed similar results in which activation in food reward regions in response to food versus neutral stimuli was positively correlated with body mass index (BMI) and, in one of these regions, was predictive of future weight gain (Yokum et al. 2011). Interestingly, formerly obese successful dieters showed decreased cue reactivity compared with currently obese unsuccessful dieters (Jansen et al. 2010). This suggests that decreased cue reactivity may aid weight-loss maintenance.

A possible way to decrease food cue reactivity is CERP. During food-related CERP, one is continuously exposed for about an hour to cues or contexts that normally predict food intake, but eating is not allowed. During this exposure, it is learned that the food cue (e.g. the sight, smell, or context of food intake) no longer predicts food intake (US). After a successful CERP treatment, which usually takes several sessions in different contexts, the cue predicts a "no eating" response and, consequently, the conditioned response (food cue reactivity and craving) will have been extinguished. In substance abuse, CERP treatment has not always been effective in achieving abstinence (Havermans and Jansen 2003), but this may have been due to the methods being largely suboptimal

in earlier studies investigating CERP in drug addiction (e.g. using only one extinction context, which reduces extinction generalizability and therefore increases relapse probability; Conklin and Tiffany 2002). A more recent study (Vollstädt-Klein et al. 2011) did successfully show that a CERP training led to a reduction in neural cue reactivity to alcohol cues in detoxified alcohol-dependent patients, compared with a control intervention. A nicotine CERP intervention using virtual reality also led to a decrease in cue reactivity to smoking cues (Choi et al. 2011). In food studies, data suggest that CERP might be an effective treatment for overeaters: In small-scale pilot studies with binge-eating patients, several sessions of CERP significantly reduced the number of eating binges (Jansen et al. 1989; Toro et al. 2003; Martinez-Mallén et al. 2007). Further, CERP treatment in patients with bulimia nervosa was more effective than a training of self-control techniques (Jansen et al. 1992) or a nonexposure-based intervention in addition to cognitive behavior therapy (Carter et al. 2006). Although this research has been limited to binge eaters and patients with bulimia nervosa, obese people might profit from CERP treatment as well, since eating binges are prevalent in a considerable number of obese people (Bruce and Agras 1992; De Zwaan and Mitchell 1992). Further evidence of the efficacy of CERP is a study, in which chocolate cravers showed a reduction in cue-induced chocolate craving during a second CERP session with chocolate, compared with the first session, whereas a control group did not show such a reduction (Van Gucht, Vansteenwegen, Beckers, Hermans, et al. 2008). As far as we know the neural correlates of craving before and after food-related CERP have not yet been investigated, which is therefore the aim of the current study.

Food cravings are accompanied by the activation of brain regions associated with reward processing. Indeed, activation in response to food cues is typically found in the amygdala, hippocampus, insula, caudate, ventral tegmental area and substantia nigra, ventral pallidum, nucleus accumbens, and related striatum, as well as in the anterior cingulate, orbitofrontal, prefrontal, and posterior fusiform cortices (Appelhans 2009; Kringelbach 2009; Small 2009; Berridge et al. 2010; Rolls 2010; Berthoud 2011; Van der Laan et al. 2011; Carnell et al. 2012; Frankort et al. 2012). Therefore, we hypothesize that food cue reactivity during a short exposure will be reflected by increased brain activation in the mentioned reward regions, in comparison with a control group exposed to a neutral stimulus. The question arises whether this activation diminishes with the extinction of food craving. To examine this question, a 65-min CERP was conducted with chocolate in healthy-weight women. The chocolate exposure was interrupted intermittently by short brain scans, measuring the response to chocolate and neutral pictures. The chocolate exposure group was compared with a control group who underwent the same procedure except that the controls were exposed to a pencil instead of chocolate.

Materials and Methods

Participants

Participants were 34 females (17 in the exposure group and 17 in the control group) of Caucasian ethnicity who were recruited among undergraduate students from Maastricht University willing to participate in research. Only right-handed, healthy-weight participants who had a low score (total score <14) on the Restraint Scale (Herman and Polivy 1980) and who were not currently on a weight-loss diet were selected. Further exclusion criteria were a self-reported history of mental disorder or family history of eating disorders. The groups did not differ regarding age, hunger, restraint, or trait chocolate craving. However, the groups did tend to differ in BMI, $P = 0.06$, with the experimental chocolate exposure group being heavier than the control pencil exposure group, while, at the same time, all participants had a healthy weight (BMI <24.9) except for one slightly overweight participant in the experimental group (BMI = 26.0). Participant characteristics are shown in Table 1. The datasets of 7 additional participants had to be discarded due to scanner problems or excessive head movement. Remuneration for participation was €30 or course credits. The study was approved by the local ethics committee.

Assessment

Momentary Chocolate Craving

Momentary chocolate craving was measured repeatedly during the scanning session on a visual analog scale (VAS) asking "how much do you crave chocolate at this moment," ranging from 0 ("not at all") to 100 ("very much").

Trait Chocolate Craving

The craving subscale of the Attitudes to Chocolate Questionnaire (Benton et al. 1998) was used to assess the trait preoccupation with chocolate and the degree of compulsive behavior that is elicited by (thinking of) chocolate. The craving score was the mean of 10 VAS items (0–100) of the subscale, containing questions about chocolate preoccupation, with the scale for each question ranging from 0 ("this does not apply to me at all") to 100 ("this very much applies to me"). The subscale was found to be valid and reliable (Cramer and Hartleib 2001; Müller et al. 2008).

Hunger

Hunger was measured on a VAS: "How hungry do you feel at this moment?," ranging from 0 ("not hungry at all") to 100 ("very hungry").

Restraint

The Restraint Scale (Herman and Polivy 1980) measures the participant's intention to restrain her food intake, her concern about body weight, and weight fluctuations. The minimum and maximum total scores are 0 and 35, respectively. Higher scores reflect more intentions to restrain and increased difficulty of controlling food intake. The scale was found to be sufficiently valid and reliable (Scagliusi et al. 2005; Van Strien et al. 2007; Williamson et al. 2007).

Table 1
Characteristics and self-report data of participants

	Experimental group ($n = 17$)		Control group ($n = 17$)		$t_{(32)}$	P-values
	M	SD	M	SD		
Age (years)	19.8	1.4	20.2	1.5	0.89	0.38
BMI	22.8	1.7	21.6	1.8	1.94	0.06
Time between lunch and scan (min)	86.5	14.4	82.6	20.9	0.62	0.54
Hunger[a]	18.6	14.5	14.9	14.1	0.74	0.46
Restraint[b]	10.6	2.6	10.8	4.7	0.18	0.86
Trait chocolate craving[c]	38.3	19.1	35.0	13.2	0.58	0.56

Note: All values represent the mean ± standard deviation (SD).
[a]Scored on 100-mm VAS scales, ranging from 0 ("not hungry at all") to 100 ("very hungry").
[b]Scored on the Restraint Scale (Herman and Polivy 1980), with a minimum total score of 0 ("no restraint") and a maximum of 35 ("high restraint").
[c]Scored on the craving subscale of the Attitudes to Chocolate Questionnaire (Benton et al. 1998), with a minimum total score of 0 ("no trait chocolate craving") and a maximum of 100 ("high trait chocolate craving").
BMI: body mass index.

Bogus Chocolate Taste Test

A bogus chocolate taste test, in which the actual consumption of chocolate was measured, was conducted after the scanning session. Data of this test will be published in a forthcoming paper.

Experimental Design

The experimental design was a mixed design comparing an experimental group (exposure to chocolate) with a control group (exposure to a control stimulus), with repeated measures of the brain response to chocolate pictures (when compared with neutral control pictures) and of the momentary craving for chocolate.

Stimuli

Stimuli were 56 pictures of chocolate and chocolate products and 56 neutral pictures of office supplies and utensils not related to food. Chocolate pictures did not have any festive associations (such as Valentine, Easter, and birthday). The majority of stimuli were purchased online (www.istockphoto.com). Stimuli were presented as pop-out figures on a light gray background in the center of the screen, covering a visual angle of approximately 12°. For statistical power reasons and to reduce habituation effects, the stimuli were assigned to 2 separate picture pools. The first picture pool contained 24 chocolate and 24 neutral pictures that were shown in the most crucial runs at the beginning, the peak, and the end of the scanning session (runs 1, 5, and 7, respectively). These runs were used for between-group comparisons. Thus, within each of the mentioned 3 runs, some pictures of this pool were shown twice, but in the course of the whole scanning session, each picture from this pool was shown 4 times. The second picture pool, intended to measure the time course of neural craving correlates in the chocolate exposure group, contained 32 chocolate and 32 neutral pictures and was used in the remaining runs 2, 3, 4, and 6, respectively. In this pool also, each picture was shown 4 times in the course of each scanning session.

Stimulation Protocol

Using E-Prime version 2.0.8.90 (PST 1996), the stimuli were presented in a blocked design with a block duration of approximately 15 s (some blocks in the first 2 runs were presented up to 15.1 s, probably due to the time it took E-Prime to retrieve the pictures from the local hard disk for the first time and write them to the cache. Blocks always started with the reception of a trigger pulse indicating the MRI scanner's radiofrequency pulse to synchronize with image acquisition). Blocks contained either 8 chocolate or 8 neutral pictures, with each picture being presented during 1850 ms and chosen randomly without replacement from the relevant picture pools. To maintain the participants' attention, half of the stimulus blocks were followed by a question block with a duration of 3 s (Fig. 1). In this block, the participant was asked to indicate whether the depicted picture was presented in the preceding stimulus block. The response was given by means of a button press. All blocks were preceded by a black fixation cross on a light gray background with a duration of 12 s (before stimulus blocks) or 6 s (before question blocks). Additionally, after the last block, a fixation cross was shown for 12 s to allow for the recording of the remainder of the blood oxygen level-dependent response.

One run consisted of 4 chocolate blocks, 4 neutral blocks, and 4 question blocks. For each of 7 runs, the order of stimulus blocks was randomized with the constraint that no more than 2 stimulus blocks of the same category occurred subsequently. Then the question blocks were inserted randomly with the constraint that they had to follow a chocolate block twice and a neutral block twice. Thus, 7 run orders were determined, fixed for all participants. The presentation order of these 7 run orders was randomized separately for each participant. The duration of a run was on average 270 s (this was longer than the anticipated 264 s because some of the trigger pulses were missed, leading to prolongation of fixation times between blocks, as waiting times for trigger pulses between blocks were filled with fixation). Between runs, the participant remained in the scanner and was instructed to hold and smell the object (a piece of chocolate or a pencil) that was handed to her for the exposure duration. This exposure duration increased over time and amounted to 1 min after runs 1 and 2, 2 min after run 3, 3 min after runs 4 and 5, and 20 min after run 6 (Fig. 1).

Session Protocol

The length of the session was 65 min, during which CERP was conducted with real chocolate (experimental group) or with a control stimulus (control group) in healthy-weight women, while the olfactory exposure was interrupted intermittently by 6 of in total 7 short brain scans (Fig. 1). During the brain scans, there was no exposure to real chocolate; only the response to both chocolate and neutral pictures was measured. The session duration of approximately 1 h was chosen due to results of CERP treatment studies (Jansen et al. 1989; Toro et al. 2003), in which the subjective ratings of cue reactivity as measured in the first session increased directly after the start of the exposure, peaked after 10–30 min, decreased thereafter, and finally extinguished. The session started with a functional run and was then followed by exposures and functional runs in an alternating order. Exposure durations were initially short and increased with increasing time, amounting to 1, 1, 2, 3, 3, and 20 min respectively. The final prolonged exposure duration was long to attain an extinction of craving.

For participants in the experimental group, the exposure was done with a real chocolate. Chocolate was chosen as a cue to perform CERP in healthy participants, because it is the food most frequently craved by Western women (Pelchat 1997). During each exposure cycle, the participant held a piece of chocolate (approximately 4 cm × 2 cm × 1 cm), the lower part of which was wrapped in an odorless tissue, under her nose. This was handed to her by the experimenter at the beginning of each exposure and was given back to the experimenter at the end of each exposure. Therefore, during functional runs, there was no exposure to real chocolate. As there were several

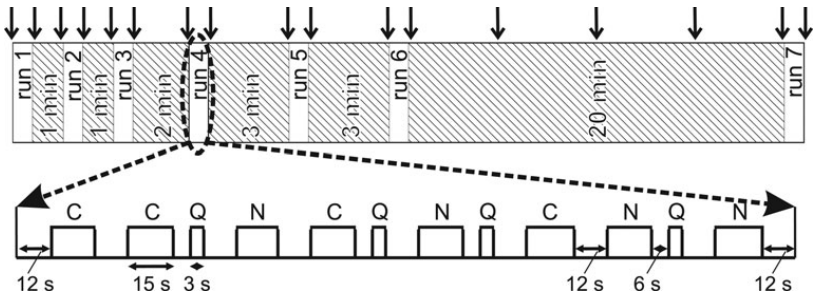

Figure 1. Session protocol with 7 scanning runs (white bars), exposure (hatched pattern), and measurements of current chocolate craving (downward arrows). Two different picture pools were used for runs 1, 5, and 7 and for runs 2, 3, 4, and 6. In the enlargement, an example of a stimulation protocol of one run is shown, consisting of 4 chocolate blocks (C), 4 neutral blocks (N), and 4 question blocks (Q). Stimulus blocks had a duration of approximately 15 s and were preceded by fixation times of 12 s. Question blocks had a duration of 3 s and were preceded by fixation times of 6 s.

types of chocolate available (8 different brands of milk and dark chocolate), the participant was instructed to ask for a new piece of chocolate as soon as she had become habituated to the smell of the current one. In practice, this resulted in a replacement of chocolate at least every few minutes. At the beginning and at the end of every functional run, the participant rated momentary chocolate craving on a VAS by means of a joystick placed on her abdomen. Additionally, in the final prolonged exposure cycle of 20 min duration, momentary chocolate craving was assessed every 5 min. The control group procedure was the same as for the experimental group, the only difference being that the participant had to sniff at 1 of the 8 available pencils instead of chocolate. After the last functional run, there was one anatomical measurement.

Procedure

There was one afternoon scanning session per participant. Participants were requested to refrain from eating chocolate products and from drinking coffee or tea on the scanning day, as the brain response is influenced by caffeine (Koppelstaetter et al. 2010). In addition, they had to consume a regular lunch 1–1.5 h before the start of the scanning session. Upon arrival, the participant's subjective hunger ratings, together with restraint and trait craving for chocolate, were assessed. Additionally, her weight and height were measured. Then the participant entered the scanner and the scanning session started. After the scanning session, the bogus chocolate taste test was done in an adjacent room. After filling in an exit form with questions about what she mainly had been thinking about while viewing chocolate and neutral pictures, the participant was thanked and compensated for participation. Debriefing was done by email at the end of the study.

Functional Magnetic Resonance Imaging Data Acquisition

All images were acquired with a 3-T Siemens Magnetom Allegra Head-only scanner. The head coil encompassed a small mirror, through which participants could see the stimuli that were projected on a screen at the head end of the scanner. Gradient-echo planar imaging parameters were optimized (Deichmann et al. 2003; Weiskopf et al. 2007) to acquire functional volumes (50 slices, repetition time [TR] = 3000 ms) with reduced susceptibility and distortion artifacts in the orbitofrontal cortex. These settings included an echo time (TE) of 25 ms, oblique axial slices acquired in an interleaved order with a negative (i.e. backward) tilt angle of 30°, a voxel size of 2 mm × 2 mm × 2.5 mm, a field of view (FoV) of 256 × 192 mm^2, an imaging bandwidth of 2790 Hz over FoV, an echo spacing of 0.42 ms, and flip angle 90°, resulting in T_2*-weighted images. There were 88 volumes per functional run. After the last functional run, an optimized magnetization-prepared rapid gradient-echo sequence was used (Mugler and Brookeman 1990; Deichmann et al. 2000) with the following settings: TR = 2250 ms, TE = 2.6 ms, flip angle = 9°, voxel size of 1 mm × 1 mm × 1 mm, echo spacing of 6.9 ms, resulting in a high-resolution, T_1-weighted anatomical scan for coregistration.

Functional Magnetic Resonance Imaging Data Preprocessing

BrainVoyager QX version 2.4.1.2052 (BrainInnovation 2001) was used for analysis. Due to T_1 saturation effects, the first 2 volumes of each functional run were excluded. Preprocessing consisted of slice scan time correction with cubic spline interpolation, removal of low-frequency noise using high-pass temporal filtering (0.0075 Hz cut-off), and 3-dimensional motion correction using trilinear interpolation for alignment and sinc interpolation for final resampling. Subsequently, preprocessed data were coregistered with the anatomical scan, resulting in coregistered 3-dimensional space data over the course of time for each run, with a functional voxel resolution of 2 mm × 2 mm × 2 mm. All data were spatially normalized using Talairach transformation procedures (Talairach and Tournoux 1988) and finally spatially smoothed with a 6-mm full-width at half-maximum isotropic Gaussian kernel. For group-level analyses, Talairach-standardized anatomical data sets of participants were averaged, based on which a whole-brain mask was generated.

Data Analysis

Momentary chocolate craving scores were analyzed in a 2 (group: Exposure vs. control) × 3 (time of measurement: Prior to run 1 vs. prior to run 5 vs. prior to run 7) analysis of variance (ANOVA). Only these 3 runs were entered into the ANOVA, to keep the analyses of craving scores and brain data similar. For functional magnetic resonance imaging (fMRI) data, boxcar predictors were set for chocolate, neutral, and question blocks. Question block predictors were regarded as of no interest (confounds). All predictors were convolved with a standard hemodynamic response function (Friston et al. 1998). To optimize detection power, only runs 1, 5, and 7 were entered into the general linear model (GLM). These runs, which contained pictures of the first picture pool and were intended for between-group comparisons, were considered crucial as they captured the beginning and the end of the session as well as the expected peak of craving in the experimental group. Z-transformed motion correction parameters were added, resulting in the GLM design matrix. In this modeling approach, the response to fixation times between blocks can be considered as the baseline.

Brain responses in run 5 to chocolate and neutral pictures were analyzed in a 2 (group: Exposure vs. control) × 2 (picture type: Chocolate vs. neutral) random-effects ANOVA. Because we were interested in brain regions specifically reacting to cue exposure, we looked for an interaction between group and picture type in run 5 (the middle of the session), as the peak of the craving curve in the exposure group was expected to occur in this run, whereas no such peak was expected in the control group. Therefore, a whole-brain statistical *F*-map was created containing voxels with a significant interaction in run 5 between group and picture type. Voxel clusters consisting of at least 27 contiguous voxels, each with a *P*-value of interaction <0.01 (uncorrected), were considered a functional region of interest (fROI). This minimal cluster size was determined with a tool in BrainVoyager QX that performs a cluster-level correction of multiple comparisons at $P = 0.05$ by using a Monte Carlo simulation-based approach (Forman et al. 1995; Goebel et al. 2006) with 1000 iterations and a voxel size of 2 mm × 2 mm × 2 mm. The Talairach-standardized whole-brain mask contained 191 443 voxels of this size. Thus, at the uncorrected level of 0.01, only clusters >216 mm^3 were considered as fROIs. An anatomical localization indication of the fROIs was obtained with the Talairach Client (www.talairach.org) (Lancaster et al. 2000).

A stricter test of our hypothesis would be the identification of brain regions with a 3-way interaction of brain activation over time, in response to both picture categories and in both groups. Therefore, brain responses to chocolate and neutral pictures were additionally analyzed in a 2 (group: Exposure vs. control) × 3 (time of measurement: Run 1 vs. run 5 vs. run 7) × 2 (picture type: Chocolate vs. neutral) 3-way random-effects ANOVA. This analysis yielded a whole-brain statistical *F*-map consisting of voxels with a significant interaction ($P < 0.01$; uncorrected) of the factors group, time of measurement, and picture type. The minimal cluster size for this analysis, as determined by the BrainVoyager QX tool mentioned before, was found to be 37 functional voxels (296 mm^3).

For the second-level analysis in SPSS version 18, average β values were extracted for each fROI, run, picture type, and participant. With these β values, independent samples *t*-tests of the response to chocolate minus neutral pictures were performed for the 3 runs that were designed for between-group comparisons (runs 1, 5, and 7). Additionally, the significance of activation changes per group over the course of time was calculated with paired samples *t*-tests.

Results

Momentary Chocolate Craving

As expected, a short (30 min) chocolate exposure led to increased craving compared with the baseline, more so than exposure to a control stimulus (Fig. 2). This was indicated by a significant group × time effect in a 2 (group: Exposure vs. control) × 3 (time of measurement: Prior to run 1 vs. prior to

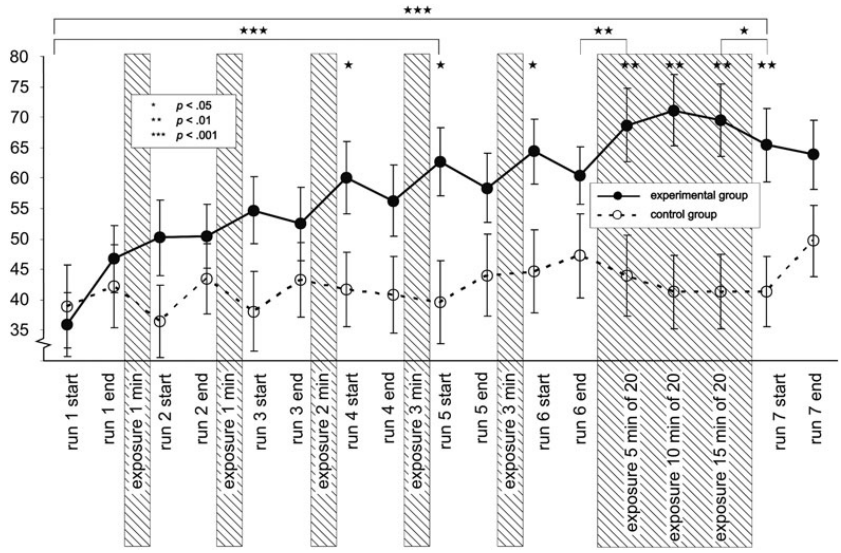

Figure 2. Momentary chocolate craving, as indicated by self-report on a 100-mm VAS scale asking "how much do you crave chocolate at this moment," ranging from 0 ("not at all") to 100 ("very much"), averaged over groups. Significance brackets correspond to within-group differences in the chocolate exposure group. Asterisks without brackets indicate significant between-group differences. Paired *t*-tests were performed only over craving levels prior to runs 1, 5, and 7 as well as over subsequent measurement time points of the final long exposure. Reported *t*-tests are uncorrected. *X*-axis is not to scale in regard to time passed.

run 5 vs. prior to run 7) ANOVA, $F_{2,\ 31} = 7.10$, $P = 0.003$. This interaction effect qualified a significant main effect of time, $F_{2,\ 31} = 8.19$, $P = 0.001$. Craving scores did not differ between groups at baseline, $t_{(32)} = 0.35$, $P = 0.73$, but did differ in the middle of the session (prior to run 5), $t_{(32)} = 2.62$, $P = 0.01$, and at the end of the session (prior to run 7), $t_{(32)} = 2.90$, $P = 0.007$. Looking at the chocolate craving ratings of all 6 exposure durations, significant group differences were found prior to runs 4, 5, 6, and 7, as well as during the final prolonged exposure. Interesting is the progress of craving before and after run 7: The highly significant ($P < 0.01$) group difference prior to this run disappeared ($P = 0.09$) after the brain scan.

Within the chocolate exposure group, craving levels prior to runs 5 and 7 were significantly different from the baseline, $t_{(16)} = 6.03$, $P < 0.001$ and $t_{(16)} = 4.99$, $P < 0.001$, respectively (Fig. 2). No difference was found between craving in the middle of the session (prior to run 5) and at the end of the session (prior to run 7), $t_{(16)} = 0.84$, $P = 0.42$. This demonstrates that the short (30 min) chocolate exposure was successful in increasing craving in the exposure group, but that, contrary to our hypothesis, the long (60 min) exposure did not lead to the extinction of craving. In the control group, no significant differences in momentary chocolate craving prior to runs 1, 5, and 7 were found, which confirmed our expectations.

The 6 individual chocolate exposures were each successful in increasing craving in the exposure group, as the average of the 6 postexposure craving ratings in this group was significantly higher than that of the 6 pre-exposure craving ratings, $t_{(16)} = 3.57$, $P = 0.003$. In the control group, the opposite was found: The average of the 6 post-pencil-exposure ratings of momentary chocolate craving was significantly lower in this group than that of the 6 pre-pencil-exposure craving ratings, $t_{(16)} = 2.27$, $P = 0.04$.

Brain Response

The less restrictive 2-way analysis in which fROIs were based on the brain activation of the peak run yielded 9 significantly large fROIs with a significant interaction between group and picture type (see Table 2 and Fig. 3, locations and bar plots in orange): Both amygdalae, posterior fusiform gyri in both hemispheres, medial posterior cingulate cortex, a region in right parahippocampal and lingual gyrus, and regions in the left somatosensory cortex, left frontal eye fields (FEFs), and left supplementary motor area (SMA). The first 7 of these fROIs are considered to be involved in reward processing (Killgore et al. 2003; Van der Laan et al. 2011) and the last 2 in inhibitory control and control of attention (Fox et al. 2005). The second-level analysis with β values of these fROIs showed 2 response patterns, coinciding with the presumed function of the respective region: In the regions associated with reward, the activation in run 5 was significantly higher in the chocolate exposure than in the control group (all Ps < 0.01), indicating a higher reward in the experimental group during the presentation of chocolate pictures versus neutral pictures. In the regions associated with control, this activation was lower in the experimental than in the control group (all Ps < 0.01), indicating a lower effort of controlling chocolate craving in the former group. In both response patterns, the activations in run 1 (before the first exposure) and run 7 (the last run) did not differ between groups.

The 3-way analysis of group, time of measurement, and picture type resulted in 6 fROIs larger than the respective minimal cluster size, each with a significant 3-way interaction (see Table 3 and Fig. 3, locations and bar plots in green). These fROIs were located in the left and right caudate, left striate, and bilateral extrastriate cortex, and on the border of the right parahippocampal gyrus with the lingual and posterior cingulate gyrus. Between-group *t*-tests of the β values of these fROIs showed that, during the last run, the chocolate

Table 2
fROIs resulting from the 2-way interaction of group (exposure vs. control) and picture type (chocolate vs. neutral) in run 5 (the middle of the session as well as the expected peak of craving in the exposure group)

Cluster	Size (mm^3)	Anatomical label	Peak voxel values[a]					
			Estimated BA[b]	*x*	*y*	*z*	*F*	*P*-value
A	1024	Peak 1 : amygdala R	–	20	−4	−14	20.04	0.00009
		Peak 2 : parahippocampal gyrus R	–	24	−12	−15	13.61	0.00080
B	262	Peak 1: uncus L	28	−19	0	−22	14.44	0.00061
		Peak 2: amygdala L	–	−18	−4	−16	10.78	0.00248
C	388	Fusiform gyrus R	37	49	−54	−13	17.39	0.00020
D	489	Fusiform gyrus L	37	−43	−41	−17	13.06	0.00100
E	314	Frontal eye fields L	8	−26	17	49	16.92	0.00025
F	306	Posterior cingulate (medial)	29	−4	−48	13	16.06	0.00034
G	364	Parahippocampal gyrus R	30	13	−38	−1	14.88	0.00052
H	265	Pre-supplementary motor area L	6	−44	6	42	13.91	0.00074
I	226	Somatosensory cortex L	3	−32	−31	59	12.78	0.00114

[a]Voxel coordinates are reported in Talairach space.
[b]Identified with the "nearest gray matter" option in the Talairach Client (www.talairach.org) (Lancaster et al. 2000).
BA: Brodmann area; R: right hemisphere; L: left hemisphere.

exposure group's activation was significantly lower than that of the control group, whereas, in the first run or in the middle of the session, this pattern was reversed. While Figure 3 shows the β values of the crucial runs 1, 5, and 7 only, Supplementary Figure S1 shows the β values of all 7 runs of the mentioned fROIs. Because of the quick and direct succession of runs 2, 3, and 4 with the same stimuli, it is likely that habituation has occurred in these runs, which can be seen from decreasing activation from run 2 to 4 in most of the fROIs.

Discussion

The current study investigated the neural correlates of craving during CERP, which is an intervention to reduce the appetite-enhancing influence of contextual or food cues on food intake, provided the exposure is long enough (approximately 1 h). Note that a short exposure leads to an increase in craving. In participants, smelling chocolate or smelling a control stimulus (a pencil), chocolate craving, as well as brain activation in response to neutral and chocolate pictures were measured intermittently during the exposure session. In the chocolate exposure group, craving was expected to rise after the start of the exposure session, to peak after approximately 30 min (the middle of the session, considered a short exposure), and then to decline and extinguish by the end of the session (65 min, considered a long exposure). In the control group, craving was expected to only slightly increase over the course of the procedure, due to the presentation of chocolate pictures during the 7 scans. Brain reward activation, which is activation in response to chocolate pictures minus the response to neutral pictures in regions associated with reward, was expected to be concomitant with chocolate craving ratings, that is, to be equal in both groups at the beginning and at the end of the exposure session, and to be higher in the chocolate exposure group than in the control group at the expected peak of the exposure session.

In the chocolate exposure group, craving did rise as expected after the start of the exposure session, but did not decline toward the end of the session. In this group, only a small (but significant) decrease in craving was found at the end of the final prolonged exposure. In the control group, craving did not significantly change over the course of the session. Between-group comparisons revealed that there were no group differences at the start of the session (prior to run 1), but that there were significant differences at the expected peak of craving (prior to run 5), which continued to exist until after the final prolonged exposure (prior to run 7). Thus, craving of the chocolate exposure group cannot be considered to have extinguished at the end of the session. Given that the largest between-group difference in craving ratings between the first and the last exposure occurred just prior to run 5, brain activation analyses were conducted as planned with run 1 (start of the session), run 5 (short exposure, middle of the session), and run 7 (long exposure, end of the session).

Further analyses of craving ratings revealed that the smell of real chocolate (during exposures) was more effective in increasing chocolate craving than the sight of chocolate pictures (during brain scans), as indicated by a higher average of the 6 craving ratings "after" when compared with "before" each exposure in the chocolate exposure group. The opposite pattern in the control group, which is lower average postexposure craving ratings when compared with pre-exposure ratings, indicated that the sight of chocolate pictures during the scan runs was more effective in increasing chocolate craving than the smell of a pencil. These findings are in line with previous literature, in that perception of a real food cue and mental imagery of that cue overlap with regard to elicited craving (Kavanagh et al. 2005; Tiggemann and Kemps 2005) and habituation to the (imagined) food (Morewedge et al. 2010). Our findings in the chocolate exposure group add to this literature by indicating that the perception of the real food is a stronger cue than the image of that food with its accompanying imagined smell and taste.

Regarding brain reward activation, fROIs were first determined by a whole-brain 2-way interaction between group and picture type in the middle of the session. This resulted in 9 fROIs, all of which have been associated with reward processing in previous studies. In 7 fROIs, brain reward activation in the middle of the session was higher in the chocolate exposure group than in the control group, whereas this group difference was absent both at the start and at the end of the exposure session. These 7 fROIs have been implicated

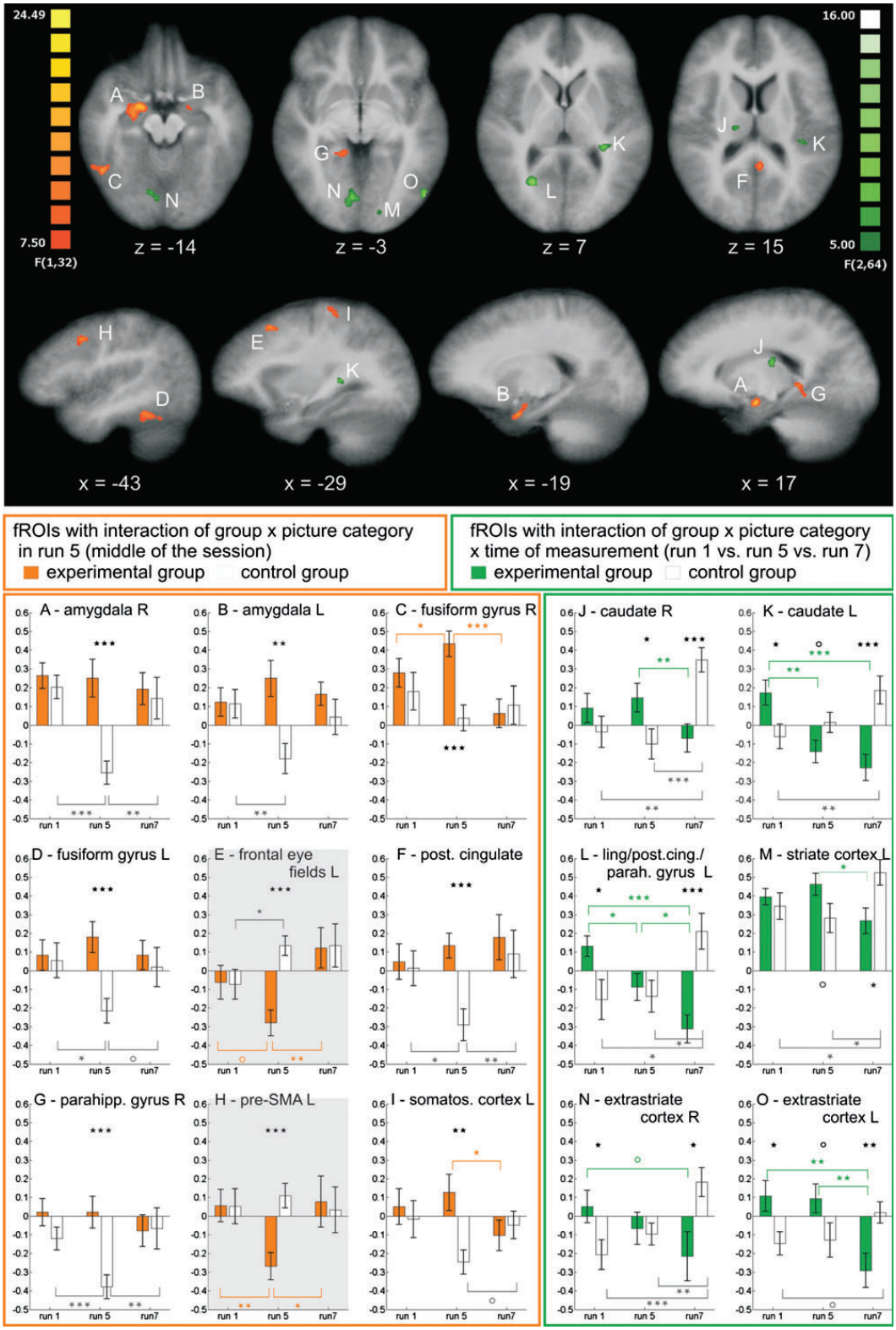

Figure 3. Upper part: in orange: *F*-map of clusters >216 mm^3 with a significant group × picture type interaction in run 5 (the expected peak of craving in the experimental group). In green: *F*-map of clusters >296 mm^3 with a significant time of measurement × group × picture type interaction. *F*-maps were overlayed on a brain averaged over all participants, shown in radiological convention. Lower part: Bar plots of β values of clusters shown above, indicating group responses to chocolate pictures minus neutral pictures (*z*-scores ± standard error of the mean). Bar plots of 2 inhibition regions, shown with a gray background, have the opposite response of reward regions. Significance indications: $^{\circ}P < 0.09$; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. Significance brackets correspond to within-group differences. Asterisks without brackets indicate significant between-group differences. Reported *t*-tests are uncorrected.

Table 3
fROIs resulting from the 3-way interaction of group (exposure vs. control), picture type (chocolate vs. neutral), and time of measurement (run 1 vs. run 5 vs. run 7)

Cluster	Size (mm^3)	Anatomical label	Peak voxel values[a]					
			Estimated BA[b]	*x*	*y*	*z*	*F*	*P*-value
J	414	Caudate body R (spreading into claustrum and thalamus)	—	20	−19	21	11.02	0.00008
K	306	Peak 1: caudate tail L	—	−30	−34	7	8.77	0.00043
		Peak 2: posterior insula L	13	−37	−28	13	7.36	0.00132
L	639	Lingual, posterior cingulate, and parahippocampal gyrus R	30	25	−62	5	11.58	0.00005
M	305	Striate cortex L	17	−13	−93	−8	8.44	0.00055
N	1334	Peak 1: declive (cerebellum) R	—	6	−75	−11	9.14	0.00030
		Peak 2: extrastriate cortex R	18	7	−75	−5	8.68	0.00046
O	309	Extrastriate cortex L	19	−50	−72	−3	10.19	0.00014

[a]Voxel coordinates are reported in Talairach space.
[b]Identified with the "nearest gray matter" option in the Talairach Client (www.talairach.org) (Lancaster et al. 2000).
BA: Brodmann area; R: right hemisphere; L: left hemisphere.

in encoding the motivational value of food stimuli: Bilateral amygdalae (Arana et al. 2003; Killgore et al. 2003; Gearhardt et al. 2011), bilateral posterior fusiform gyri (Frank et al. 2010; Van der Laan et al. 2011), posterior cingulate cortex (Killgore et al. 2003; Rothemund et al. 2007), parahippocampal gyrus (LaBar et al. 2001), and somatosensory cortex (Stice et al. 2011, who call a nearby fROI "postcentral gyrus"). A higher activation in these regions is considered to represent a higher reward in response to a stimulus or an increase in appetitive motivation; therefore, the activation in these fROIs in the middle of the session is in line with our hypothesis. Similarly, in the remaining 2 of the 9 fROIs—the left FEFs and the left pre-SMA—the group difference was absent at the start and at the end of the exposure session; yet here, brain reward activation in the middle of the session was lower (instead of higher) in the chocolate exposure group, compared with the control group. This pattern of activation fits with the functionality that has previously been linked with these regions: FEF and pre-SMA have been associated with top-down attentional control and with inhibition of responses (Moore and Armstrong 2003; Fox et al. 2005; Muggleton et al. 2010; DiQuattro and Geng 2011). Thus, compared with the control group, a lower activation in these regions in the chocolate exposure group is assumed to represent either a lower amount of effort needed to pay attention to the chocolate pictures versus the neutral ones, or a lower degree of craving suppression when seeing these pictures.

When looking in more detail at the activation pattern in appetitive motivation regions with a 2-way interaction, it can be seen that the transition from similar levels of activation at the start to significant group differences in the middle of the session originated not only from a rise in activation in the chocolate exposure group, but also from a decline in activation in the control group. This control group decline may be due to habituation to the repeatedly shown visual stimuli, also called repetition suppression, which has also been found in previous studies for the majority of our fROIs involved in appetitive motivation like the amygdala (Weierich et al. 2010) and ventral visual stream areas like the posterior fusiform gyri and the parahippocampal gyrus (Vuilleumier et al. 2005; Zweynert et al. 2011). We assume that, in the experimental group, repetition suppression is prevented by the exposure to chocolate, considering that the 2 groups underwent exactly the same procedure except for the cue during the exposures. After the transition from the middle to the end of the session, repetition suppression in the control group seemed to have disappeared, as activation levels in run 7 increased again to a level similar to that of the exposure group. This is probably due to the final prolonged exposure, which lasted 20 min and took place without being interrupted by any brain scans, so there were no picture presentations during this time span.

In the left pre-SMA, 1 of the 2 fROIs with a 2-way interaction involved in inhibitory control, the transition from similar levels of activation from the start of the session to significant group differences in the middle of the session originated mainly from a significant decline in activation in the chocolate exposure group. This can be explained by impaired inhibition in response to the chocolate pictures after the chocolate exposure; inhibition has been previously found to be impaired in cue exposure studies with alcohol (Muraven and Shmueli 2006; Gauggel et al. 2010). In the second inhibitory control region, the left FEF, the transition from similar levels of activation in run 1 to significant group differences in run 5 was the result mainly from a significant increase in activation in the control group, which as discussed before may represent an increased effort in paying attention to the chocolate pictures (DiQuattro and Geng 2011).

When comparing chocolate craving ratings with brain reward activation levels in fROIs with a 2-way interaction, it can be seen that both measures were in accordance at the beginning (no group differences) and in the middle of the session (significant group differences in both measures). However, at the end of the session, there was a dissociation between these measures: Chocolate craving still differed significantly between groups (although a decline in ratings had started in the chocolate exposure group), whereas brain reward activation levels in the 9 identified fROIs returned back to similar levels in both groups. This dissociation could be caused by the tendency of participants to give consistent answers to the same repeatedly asked VAS items (Schubert and Fiske 1973; Schubert 1975). Another explanation for the finding that craving on a neural level had already decreased, at the moment when the subjective report of craving had only started to decrease, could be that brain reward activation levels are a precursor of a decrease in the subjectively experienced craving. After all, before a cue can elicit a subjective feeling, it has to be processed in the brain. This is in line with findings that brain activation accompanying a decision to act occurs prior to the conscious awareness of this decision (Libet

et al. 1983; Soon et al. 2008; Custers and Aarts 2010). Therefore, an investigation of the transient subjective and neural response to food in hungry participants who gradually become satiated would shed more light on this supposedly precursory characteristic of the brain.

Results of the stricter 3-way analysis corroborate the interpretation of neural craving correlates as a precursor of subjective craving. The activation pattern showed that, in all 6 fROIs with a 3-way interaction, activation in run 7 (i.e. after the last prolonged exposure) was lower in the exposure group than it was in the control group. The sign of this group difference before the last prolonged exposure (in run 1 or 5) was reversed (i.e. the exposure group had a higher activation than the control group). Five of the 6 fROIs with a 3-way interaction of group, picture type, and time of measurement have been found to be active in previous studies investigating the response either to food or to food pictures versus control pictures. These were the left and right caudate nuclei, very close to locations found by St-Onge et al. (2005), aside from studies that found activation of other parts of the caudate nuclei (Small et al. 2001, 2003; Rothemund et al. 2007; Malik et al. 2008; Stoeckel et al. 2008). Further, there was a region in the left striate cortex (Rothemund et al. 2007; Führer et al. 2008; Malik et al. 2008; Tang et al. 2012), as well as 2 regions in the extrastriate cortex (Rothemund et al. 2007; Malik et al. 2008; Schienle et al. 2009). Finally, the sixth fROI on the border of the right lingual gyrus, the posterior cingulate gyrus, and the parahippocampal gyrus has been found to have a smaller gray matter volume with increasing participants' BMI in a previous study (Walther et al. 2009). The fact that the exposure group had a lower activation than the control group in run 7, combined with findings that most of the fROIs have been implicated in food reward, leads to the interpretation that, at the end of the session, the exposure group had a lower reward of chocolate versus neutral pictures than the control group. Keeping in mind that, at this point in time, the subjective craving reports were still higher in the exposure group than those in the control group, this is in line with the assumption that neural correlates of craving could be a precursor of subjectively experienced craving. Regarding the activation pattern before the last prolonged exposure, where the group difference was reversed compared with run 7, this could indicate that the prolonged chocolate exposure was effective in reducing chocolate reward on a neural level, although subjective ratings did not (yet) indicate this. Aside from this, the fact that the exposure group had a higher activation in run 1 in some of the fROIs than the controls could be due to the instructions: They had been told before the start of the session that they were going to smell chocolate and therefore may have viewed the chocolate pictures in a different way than the controls did right from the start.

Our findings that the brain might have precursory characteristics are in line with results from studies with alcoholics (Grüsser et al. 2004) and treatment-seeking cocaine-dependent participants (Kosten et al. 2006). In these participants, brain activation in reward regions in response to cues of the respective drug of abuse proved to be a better predictor of relapse than subjective craving reports. Even when participants were asked to rate their implementation intentions (instead of craving), brain activation was a better predictor of subsequent behavior than were subjective reports, as shown in studies with smokers (Falk et al. 2011) and in people who were exposed to persuasive messages regarding the value of regular sunscreen use (Falk et al. 2010). This shortcoming of subjective reports with regard to predictive validity may be due to interoceptive awareness being limited in some of the individuals (Craig 2004; Herbert and Pollatos 2012).

In the present study, we did not find the hypothesized decrease in subjective craving with repeated exposure to chocolate. This may be due to the frequent interruption of the exposures by the brain scans. This interruption may have prevented the extinction of subjective craving in the chocolate exposure group. In addition, the duration of the final prolonged exposure was probably not long enough. However, a slight decrease in craving in the chocolate exposure group was found at the very end of the final prolonged exposure, and this might have continued with further exposure. Apart from these considerations, the use of a different food cue than chocolate might have yielded different results, because chocolate is a generally highly preferred food. It has been found to resist extinction in a previous study that studied the effects of context change on acquisition and extinction of conditioned chocolate craving (Van Gucht, Vansteenwegen, Beckers, Van den Bergh 2008). In addition, there was a marginally significant group difference of BMI in our sample, which may have influenced the results (Table 1). However, the mean BMI of each group was well within the healthy-weight range, and only one participant was slightly overweight. Finally, no menstrual cycle data were collected, which may have introduced some additional noise, since the neural response to food cues fluctuates throughout the menstrual cycle (Dreher et al. 2007).

Taken together, the results of this study indicate that the changes in brain reward activation during CERP are linked to the changes in craving, at least for a short exposure. This is substantiated by an increase of these measures in the experimental group, compared with constant values for the control group. Therefore, a short cue exposure can be considered effective in increasing both craving and brain reward activation. Regarding the long exposure, the expected extinction of subjective craving did not occur, although a decrease of craving was found at the very end of the prolonged exposure, which might have continued if the exposure would have been even longer. At the same time, brain reward activation did decrease at the end of the session. Therefore, the decreased brain reward activation may be considered a precursor of a decrease in craving. To test this possibility, brain activation and subjective measurements before and after a longer CERP would be necessary. In any case, these results show that CERP is an effective intervention for the reduction in brain reward activation as a form of food cue reactivity. This treatment should be further investigated as a possible therapy for overweight or obese people to cope with their excessive food craving.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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