Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Neural Food Reward Processing in Successful and Unsuccessful Weight Maintenance

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Objective: Weight loss maintenance is one of the biggest challenges in behavioral weight loss programs. The present study aimed to examine metabolic influences on the mesolimbic reward system in people with successful and unsuccessful long-term weight loss maintenance.

Methods: Thirty-three women with obesity at least 6 months after the completion of a diet were recruited: seventeen women were able to maintain their weight loss, whereas sixteen showed weight regain. Using functional magnetic resonance imaging in combination with the assessment of appetite-regulating hormones, neural reward processing during hunger and satiety was investigated. An incentive delay task was employed to investigate the expectation and receipt of both food-related and monetary reward.

Results: Only participants with successful weight loss maintenance showed a satiety-induced attenuation of brain activation during the receipt of a food-related reward. Furthermore, in successful weight loss maintenance, the attenuation of active ghrelin levels was related to brain activation in response to food-related reward anticipation during satiety.

Conclusions: The findings suggest that an attenuated influence of satiety signaling on the neural processing of food-related reward contributes to unsuccessful weight loss maintenance. Thus, intact satiety signaling to the mesolimbic reward system may serve as a promising target for tackling weight cycling.

Obesity (2018) **26**, 895-902. doi:10.1002/oby.22165

Introduction

Obesity and overweight are major health problems, with increasing prevalence rates worldwide (1). The responsiveness to behavioral weight loss treatment is limited; only a subgroup of people responds with substantial and persistent reduction in body weight. Instead, the majority of individuals with obesity achieve a mere transient reduction in body weight, which is characterized by rapid weight gain after completion of treatment (2). Therefore, weight loss maintenance is one of the biggest challenges in the treatment of obesity.

There is a growing body of evidence showing that food intake is also controlled by the neural reward system. Anticipating food intake and actual food consumption both recruit mesolimbic reward pathways, an observation that has been found to be relevant for both the development as well as maintenance of obesity (3-5). Previous research using different methods has indicated both a hyper- and a hypo-activation of the reward network as potential causal factors for the development and maintenance of obesity (3,5-7). Specifically, it has been proposed that overconsumption of palatable food triggers neuro-adaptive responses in brain reward circuits, driving the development of compulsive eating habits (8). Persistent intake of food with high content may also be driven by a diminished reward response during the consumption of food (9,10), therefore increasing the motivation to compensate by consuming food with high hedonic impact (11). However, individuals with obesity have consistently shown increased activation in mesolimbic and cortical pathways when exposed to food reward in functional magnetic resonance imaging (fMRI) studies (4,12,13). This observation is put forward as indicative of abnormal stimulus-response learning and incentive salience (14), therefore increasing motivational processing of food-related stimuli. These mechanisms

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Funding agencies: This work was supported by the German Competence Network Obesity, funded by the German Federal Ministry of Education and Research (FKZ: 01GI1122E).

Disclosure: The authors declared no conflict of interest.

Additional Supporting Information may be found in the online version of this article.

Received: 21 November 2017; **Accepted:** 11 February 2018; **Published online 24 April 2018. doi:10.1002/oby.22165**

TABLE 1 Group demographics

	Maintain group ($N = 17$), (mean ± SD)	Regain group ($N = 16$), (mean ± SD)	Group differences
Age (y)	31.5 ± 9.8	37.3 ± 14.4	$P = 0.185$
Current BMI (kg/m^2)	29.1 ± 5.2	33.4 ± 6.5	*$P = 0.044$*
BMI before diet	35.6 ± 6.4	32.5 ± 6.8	$P = 0.195$
BMI after diet	28.6 ± 4.9	27.3 ± 5.7	$P = 0.106$
Weight loss during diet (BMI)	6.9 ± 3.9	5.2 ± 2.6	$P = 0.134$
Weight loss during diet (%)	18.9 ± 8.8	15.6 ± 6.2	$P = 0.214$
Difference in BMI: time of investigation - after diet (BMI)	0.5 ± 0.6	6.1 ± 2.8	*$P < 0.001$*
Distance from beginning of diet – time of investigation (mo)	21.9 ± 10.3	31.7 ± 21.5	$P = 0.102$
Total amount of weight fluctuations (kg)[a]	6.1 ± 7.8	7.4 ± 6.8	$P = 0.627$
Maximal lifetime weight (kg)	102.5 ± 22	94.6 ± 15.8	$P = 0.248$
Weighing frequency (per wk)	3.3 ± 1.3	2 ± 1.3	*$P = 0.013$*
Age of first occurrence of overweight	19.3 ± 11.4	14 ± 8.5	$P = 0.138$
Education (y)	14.3 ± 2.2	14.5 ± 2.1	$P = 0.787$
MWT-B	31.7 ± 3.8	30.5 ± 3.6	$P = 0.257$
BDI-II	6.3 ± 7.1	9.5 ± 8.8	$P = 0.259$
EDE-Q	1.7 ± 1	2.4 ± 1.1	$P = 0.093$
DEBQ - restraint eating	22.7 ± 3.8	19.2 ± 7.5	$P = 0.099$
DEBQ - emotional eating	14.5 ± 8.1	15.4 ± 8.6	$P = 0.742$
DEBQ - external eating	19.8 ± 6.7	20 ± 7	$P = 0.921$

[a]Weight fluctuation was assessed via self-evaluation.
BDI-II, Beck Depression Inventory; DEBQ, Dutch Eating Behavior Questionnaire; EDE-Q, Eating Disorder Examination Questionnaire; MWT-B, vocabulary-based test for the assessment of premorbid intelligence.

have previously been related to unsuccessful weight maintenance; a study by Murdaugh and colleagues (15) found that increased activation in reward-related brain areas in response to food pictures was predictive of less success in a weight loss program.

Furthermore, hormonal changes associated with hunger and satiety are known to influence food intake by enhancing or decreasing the hedonic and incentive value of food cues. Ghrelin, as an orexigenic hormone, as well as leptin and insulin as anorexigenic hormones and adiposity signals, is considered to play a pivotal role in food intake by altering the reward value of food (16-18). Hunger seems to sensitize the striatal reward system in normal-weight humans, predominantly during the anticipation of food reward (i.e., incentive motivation), irrespective of the reward magnitude (19). However, in obesity, an increased sensitization of the reward system to food cues is typically observed during satiety (20,21). This is in accordance with behavioral and hormonal studies showing decreased satiety perception and signaling after food intake (22-24). Additionally, weight loss is associated with a long-term upregulation of orexigenic hormones (e.g., ghrelin) and a concurrent long-term downregulation of anorexigenic hormones (e.g., insulin, leptin), signaling a state of nutrient deprivation to the brain resulting in increased hunger as well as lower levels of satiety (25). There is a growing body of evidence showing that hormonal changes associated with maintained weight loss in obesity, including bariatric surgery, play a pivotal role for the success of long-term weight loss maintenance (26,27).

The aim of the present study is to unravel the underlying metabolic and neurobiological mechanisms that are involved in the maintenance of weight loss, as well as weight control. To this end, we investigated whether successful and unsuccessful weight loss maintainers differ in the responsiveness of their neural reward circuitry to food-related reward magnitude as well as metabolic state (24-hour fasting vs. satiety). We employed an event-related fMRI task designed to measure both the anticipation and receipt of food-related and monetary rewards. We previously showed that this task is able to probe typical food and monetary reward–related brain regions (28) and employed the task to investigate the relation between neural food reward processing and hormonal satiety signaling (19) as well as eating disorders (29). Therefore, this task allows us to assess differences between participants during the two phases of reward processing, as well as to establish whether or not altered reward sensitivity is specific to food or extends to more general reward processing. To study the close interaction between the reward system and energy metabolism, we additionally assessed hormonal changes of insulin, leptin, and ghrelin. These hormones directly interact with mesolimbic circuits to modulate reward and motivational aspects of food intake (16-18,30). We hypothesized that compared to successful weight loss maintainers, individuals with unsuccessful weight loss maintenance will (a) show decreased suppression of brain responsiveness in reward pathways to food-related stimuli after food intake, (b) show decreased hormonal satiety signaling after food intake, and (c) display a significant correlation between decreased suppression of brain activation in the reward network and decreased hormonal changes after food intake.

Methods

Participants

Thirty-six overweight women (BMI: 27-40 kg/m^2) took part in the study (Table 1). The group consisted of 18 overweight participants with

successful weight loss maintenance (defined according to criteria from Wing and Hill (24)) of $\geq 10\%$ of their initial body weight for at least 6 months after weight loss treatment ("Maintain" group), as well as 18 overweight participants with successful weight loss of $\geq 10\%$ of their initial body weight but with weight regain to at least their initial body weight within 6 months after weight loss ("Regain" group). Furthermore, exclusively women with weight fluctuations of $< 5\%$ during the last 3 months were included. All participants employed caloric restriction ($N = 23$, Maintain group: 10, Regain group: 13) or a combination of caloric restriction with increased physical activity ($N = 13$, Maintain group: 7, Regain group: 6) as a weight loss method. The mean duration of the diet was 5.8 months in both groups (Maintain group: 5.9 months, Regain group: 5.7 months). Both groups were matched regarding age, BMI, and education level. All participants underwent the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (31) and filled out the Beck Depression Inventory (32). All participants were right-handed and over the age of 18 years. Exclusion criteria included claustrophobia, metallic implants, current or lifetime diagnoses of an eating disorder, any type of psychiatric medication, bipolar disorder, borderline personality disorder, psychosis or alcohol or drug abuse, and current diagnoses of affective or anxiety disorders. One of the Maintain participants and two of the Regain participants were excluded from the analysis because of excessive head motion. Thus, data from 17 Maintain participants and 16 Regain participants are reported. Furthermore, for one participant of the Regain group, the data from the "monetary incentive delay" (MID) task could not be included because of technical difficulties. Participants were recruited via advertisements and flyers. The present study was approved by the local ethics committee of the Medical School of the University of Heidelberg. All participants provided written and oral informed consent. Participants received a fixed reimbursement for their participation in the study (100 euro [EUR]) in addition to the amount of money (maximum of 30 EUR per measurement and 60 EUR in total) and "snack points" (SP; maximum of 300 SP per measurement and 600 SP in total) won. Power calculations for this study were based on reports from previous investigations employing similar protocols. These studies observed brain activation during processing of food-related cues with P values between 0.05 and 0.001. The sample sizes in these studies ranged from 10 to 16, suggesting effect sizes between $d = 1.15$ and $d = 2.6$ (4,12,33,34). Furthermore, because we used a region of interest (ROI) analysis in this study, we increased power by substantially limiting the correction for multiple comparisons.

Procedure

Participants were scanned on two separate days with a mean interval of 11.2 days (SD = 4.8) between measurements. The order of the two experimental sessions was randomized in a within-subject crossover design. Every scan occurred at lunchtime, starting at 12:00 PM and ending at 2:00 PM. During the hunger condition, participants were asked to refrain from consuming anything except drinking water or herbal tea 24 hours prior to the measurement. During the satiety condition, participants received a standardized meal containing ~650 kcal 1 hour prior to scanning. Participants were free to eat until they were sated. On both days, blood samples were taken shortly before the fMRI measurement (at around 11:45 AM) in order to assess leptin, glucose, insulin, and active ghrelin as well as total ghrelin and free fatty acid levels. Additional details of the procedure are given in the Supporting Information.

fMRI task

We used two types of incentive delay tasks designed to assess the neural processing during different types of reward. Specifically, both tasks measure neural processing during the "anticipation" and the "receipt" of either monetary or food-related reward. Both tasks were previously and were found to reliably induce neural reward processing (28,29,35). In the MID task, participants were able to win a certain amount of money that was paid out immediately after scanning, whereas they could win SP in the "food incentive delay" (FID) task, which could be exchanged for sweet and salty snacks as well as beverages and fruits immediately after the MRI measurement. In both tasks, each trial started with the presentation of a visual cue (750 milliseconds) indicating the amount of money or number of SP participants could win with a correct response (i.e., 1 EUR, 0.20 EUR, 0 EUR, or 10 SP, 2 SP, 0 SP, respectively). After a delay period (3,000 milliseconds) participants had to correctly react to one of two symbols (triangle inclined to the right or to the left), with a left or right button press corresponding to the direction of the triangle (index or middle finger of dominant hand) within a fixed interval of 1,000 milliseconds. Immediately after target presentation, feedback appeared (1,500 milliseconds), notifying participants about the amount of money or the number of SP they had won and about their cumulative total. Further details of the tasks and a graphical depiction are given in Supporting Information Figure S1.

fMRI acquisition and analysis

Images were collected using a TIM Trio 3-T whole-body magnetic resonance scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard 32-channel head coil. Each of the four functional runs lasted 9.15 minutes with 275 volumes per run. Further details of the employed fMRI parameters and image preprocessing are given in the Supporting Information. The fMRI data were preprocessed and analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). At the first-level analysis, a general linear model was constructed by separately modeling regressors for the three different anticipation phases (i.e., anticipation of 1 EUR, 0.20 EUR, 0 EUR outcomes in the MID task and anticipation of 10 SP, 2 SP, and 0 SP outcomes in the FID task) and the five different outcome phases (i.e., receipt or omission of 1 EUR, 0.20 EUR, 0 EUR and receipt or omission of 10 SP, 2 SP, and 0 SP). The anticipation phase consisted of the entire duration of the cue and delay phase (3,750 milliseconds), whereas the receipt phase consisted of the feedback phase (1,500 milliseconds).

The targets and error trials were included as additional regressors of no interest. Based on our a priori hypothesis, we then extracted the mean percent signal change for each regressor using MarsBaR (36) in predefined ROIs. For the analysis of the expectation phase, we defined masks for the bilateral ventral striatum (VS); for the receipt phase, we defined masks in the bilateral and medial orbitofrontal cortex (OFC). Details of the employed ROIs are given in the Supporting Information.

Statistical analyses

Analyses were performed using SPSS Statistics version 22 (IBM Corp., Armonk, New York). Repeated-measures analyses of variance (ANOVA) with satiety state as the repeated/within factor and group as the between factor were used to assess differences in homeostatic parameters between groups. Post hoc tests were performed using t tests. P values below 0.05 were considered statistically significant. At the group level, percent signal change was extracted from the ROIs and entered into a repeated-measures ANOVA to assess influences of metabolic state and reward

level on brain activation (2 × 3 repeated-measures ANOVA). To assess the influence of successful versus unsuccessful weight maintenance, we performed a mixed-model ANOVA by entering group as a between-subject factor in our repeated-measures ANOVA. Because of the small group size, ANOVAs were performed separately for the expectation (using signal change extracted from the VS) and receipt phase (using signal change extracted from the OFC), as well as performed separately for the FID and MID tasks. To compare modalities, we performed an additional 2 (modality) × 3 (reward level) repeated-measures ANOVA. Similarly, reaction times during the MID and FID tasks were analyzed separately using a repeated-measures ANOVA with metabolic state and reward level as within factors and group as a between factor. Post hoc tests were performed using two-tailed t tests. Correlational analyses between percent signal change in ROIs during satiety or hunger and weight loss or weight loss maintenance were performed separately for the two groups. Furthermore, differences between the hunger and satiety condition regarding hormonal satiety signaling (insulin, leptin, and ghrelin) and brain activation in ROIs were correlated separately for the two groups using the Pearson product-moment correlation coefficient (two-tailed). P values below 0.05 were considered significant.

Results

Group demographics

Demographic and clinical characteristics of participants are summarized in Table 1. Both groups showed a comparable, statistically significant weight loss of 6.9 kg/m^2 (Maintain group, SD = 3.9) and 5.2 kg/m^2 (Regain group, SD = 2.6) of their body weight during their last diet. Regarding weight maintenance, the Maintain group showed a mean difference in BMI of 0.5 (SD = 0.6) between the end of the diet and the time of the investigation, whereas the Regain group showed a mean BMI increase of 6.1 (SD = 2.8). After initially matching the groups regarding their BMI at the time of investigation, because of the exclusion of three subjects because of excessive head movements, the groups were no longer matched regarding their BMI ($P = 0.044$) at the time of investigation. However, it has to be noted that there were no differences between groups regarding BMI before or after the diet (Ps > 0.106, Table 1). In both groups, participants reported significantly higher hunger ratings during the hunger than during the satiety condition (Ps < 0.001). We furthermore observed a significant effect of group on mood ratings ($F[1,31] = 9.19$, $P = 0.005$); only the Maintain group displayed higher mood levels during the satiety relative to the hunger condition (Supporting Information Table S1).

Hormonal satiety parameters

Our repeated-measures ANOVAs with satiety state as the repeated/within factor and group as the between factor indicated a significant effect of satiety status on all hormonal parameters (Fs > 10.3, Ps < 0.003). However, results remained unaffected by group (Fs < 1.91, Ps > 0.177, Supporting Information Table S1). Furthermore, one participant may have had an impaired glucose tolerance, as her fasting glucose showed a value between 100 and 125 mg/dL.

Behavioral performance

We observed a significant effect of reward level and metabolic state on reaction times in all participants ($F[2,62] = 6.65$, $P = 0.002$, $F[1,31] = 14.15$, $P = 0.001$, respectively); however, there was no group interaction effect. Post hoc tests revealed that participants reacted faster during both tasks when hungry (expectation of 10 SP: $t = -3$, $P = 0.005$, expectation of 1 EUR: $t = -3.8$, $P = 0.001$). There were no group differences regarding the amount of money or number of SP won during both the hungry and sated states (Ps < 0.11, Supporting Information Table S1).

fMRI blood oxygen level–dependent signal change during the expectation of food-related and monetary rewards

We found that in all participants (combining successful and unsuccessful weight loss maintenance), activation in the VS during the expectation of food-related reward was influenced by reward level (right VS: $F[2,62] = 6.88$, $P = 0.002$, left VS: $F[2,62] = 8.34$, $P = 0.001$) but unaffected by satiety state (Ps > 0.604), and we observed no significant group interaction effect (Ps > 0.168, Figure 1).

During the expectation of monetary reward, activation in the VS was related to reward level in all participants (right VS: $F[2,60] = 12.46$, $P < 0.001$, left VS: $F[2,60] = 12.02$, $P < 0.001$) but remained unaffected by satiety state and there was no group interaction effect (Ps > 0.266, Supporting Information Figure S2). However, we observed an interaction between satiety and reward level for the right VS ($F[2,60] = 3.72$, $P = 0.03$), and post hoc tests indicated that this was due to a stronger activation in the right VS during the expectation of 0 EUR when sated than when hungry ($t = -1.82$, $P = 0.079$). Finally, when comparing the expectation of food-related reward with monetary reward, we observed no differences (Ps > 0.466).

fMRI blood oxygen level–dependent signal change during the receipt of food-related and monetary rewards

Analyzing activation in the OFC in the combined group during the receipt of food-related reward revealed an influence of reward level (right OFC: $F[2,62] = 14.16$, $P < 0.001$, left OFC: $F[2,62] = 4.85$, $P = 0.011$, medial OFC: $F[2,62] = 9.29$, $P < 0.001$) but not of satiety (Ps > 0.144). However, we observed a significant group effect on the interaction between satiety and reward level for the left OFC ($F[2,62] = 7.69$, $P = 0.001$). When looking at separate groups, we found that the Maintain group showed a significant interaction between satiety and reward level in the left OFC ($F[2,32] = 5.76$, $P = 0.007$, Figure 2). Post hoc tests revealed a difference between satiety states in signal change extracted from the left OFC during the receipt of 10 SP that did not quite reach significance ($t = 2.11$, $P = 0.051$) and a significant difference during the receipt of 2 SP ($t = 2.67$, $P = 0.017$). The Regain group did not show a significant effect of reward level in the left OFC ($P = 0.162$), and there was no effect of satiety in this group (Figure 2).

During the receipt of monetary reward, activation in the OFC was unaffected by reward level (Ps > 0.066), and there was no effect of satiety or group (Ps > 0.278, Supporting Information Figure S3).

Relation between brain activation and dietary success

To further specify the relation between brain activation during the processing of rewards and dietary success, we correlated signal change during the processing of food-related reward with amount of weight loss (difference in weight before vs. after diet) and long-term weight

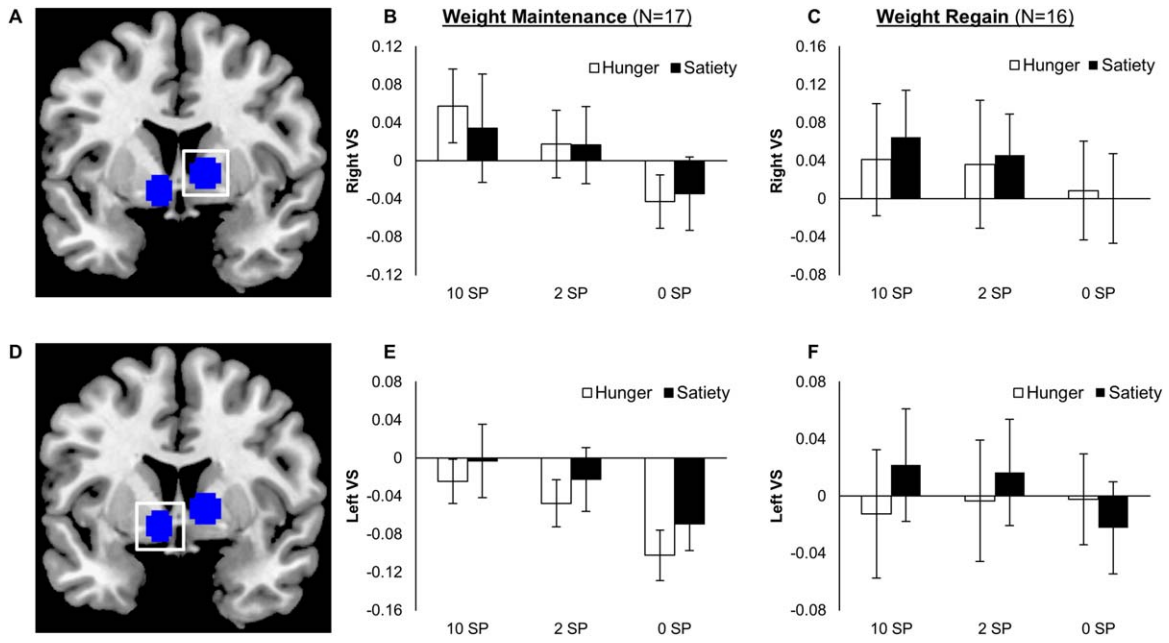

Figure 1 Masks used to extract percent signal change of blood oxygen level–dependent activation from the (**A**) right and (**D**) left ventral striatum (VS). In overweight participants with successful weight maintenance, activity in the (**B**) right and (**E**) left VS was related to reward level ($F[1,16] = 7.48$, $P = 0.002$ and $F[1,16] = 4.96$, $P = 0.013$, respectively) during the expectation of food-related reward. There was no influence of satiety status ($P > 0.324$). In overweight participants with unsuccessful weight maintenance, there was no influence of reward level or satiety status on activity in the (**C**) right and (**F**) left VS ($P > 0.134$) during the expectation of food-related reward. Error bars depict SEM. [Color figure can be viewed at wileyonlinelibrary.com]

maintenance (difference in weight after diet over time of investigation) in both groups. We found a negative correlation between brain activation during the expectation of food-related reward when sated (i.e., percent signal change extracted from the right VS during the expectation of 10 SP) and amount of weight loss in the Maintain group ($r = -0.565$, $P = 0.018$, Figure 3) but not in the Regain group. When excluding one apparent outlier ($z = 2.81$) from the correlation between weight loss and signal change from the right VS during the expectation of 10 SP, the results still remained significant ($r = -0.541$, $P = 0.031$). As for long-term weight maintenance, the Maintain group displayed a positive correlation with brain activation in the medial OFC during the receipt of food-related reward (10 SP) when sated ($r = 0.670$, $P = 0.003$, Figure 3). Finally, we observed a significant positive correlation between satiety-induced differences of brain activation in the left VS and active ghrelin values in the Maintain group ($r = 0.62$, $P = 0.014$, Figure 3). This indicates that a lower satiety-induced decrease in active ghrelin is related to a similar lower decrease in left VS activity. We failed to observe a similar observation in the Regain group.

Discussion

To our knowledge, this is the first study investigating the influence of hunger and satiety on the responsiveness of the mesolimbic reward system to food-related reward in participants with and without successful weight loss maintenance. We found that in both groups taken together, neural processing during both the expectation and the receipt of food-related reward was influenced by reward level but not by satiety state. However, only the Maintain group showed an influence of satiety state on brain activation during the receipt of rewards. Furthermore, in the Maintain group, greater diet-induced weight loss as well as long-term weight loss maintenance was related to reduced activation in both the VS during the expectation and medial OFC during the receipt of food-related reward when sated. Finally, satiation-induced decreases in active ghrelin levels were related to satiation-induced decreases in the VS during the expectation of food-related reward in the Maintain group.

In contrast to our findings in normal-weight controls using the same study protocol (19), participants with obesity showed no reward level-independent decrease of striatal activity when sated. This observation is in line with the often-observed detachment of neural food processing from homeostatic aspects toward a more reward-based food intake in obesity (21). Because we compared successful with unsuccessful weight loss maintenance, we were able to differentiate between different levels of obesity persistence. We observed a reduced influence of satiety state on neural processing in the Regain group. Furthermore, only the Maintain group showed a relation between satiety-induced reduction in brain activation and satiety-induced reduction in active ghrelin levels. Taken together, this indicates that in less persistent types of obesity, where behavioral interventions are still successful, a certain amount of influence of metabolic satiety signaling is still present, which may allow for an adequate coupling of homeostatic and hedonic mechanisms related to eating behavior.

Although we did not observe a significant influence of group on satiety-induced reduction in ghrelin levels, we observed that the

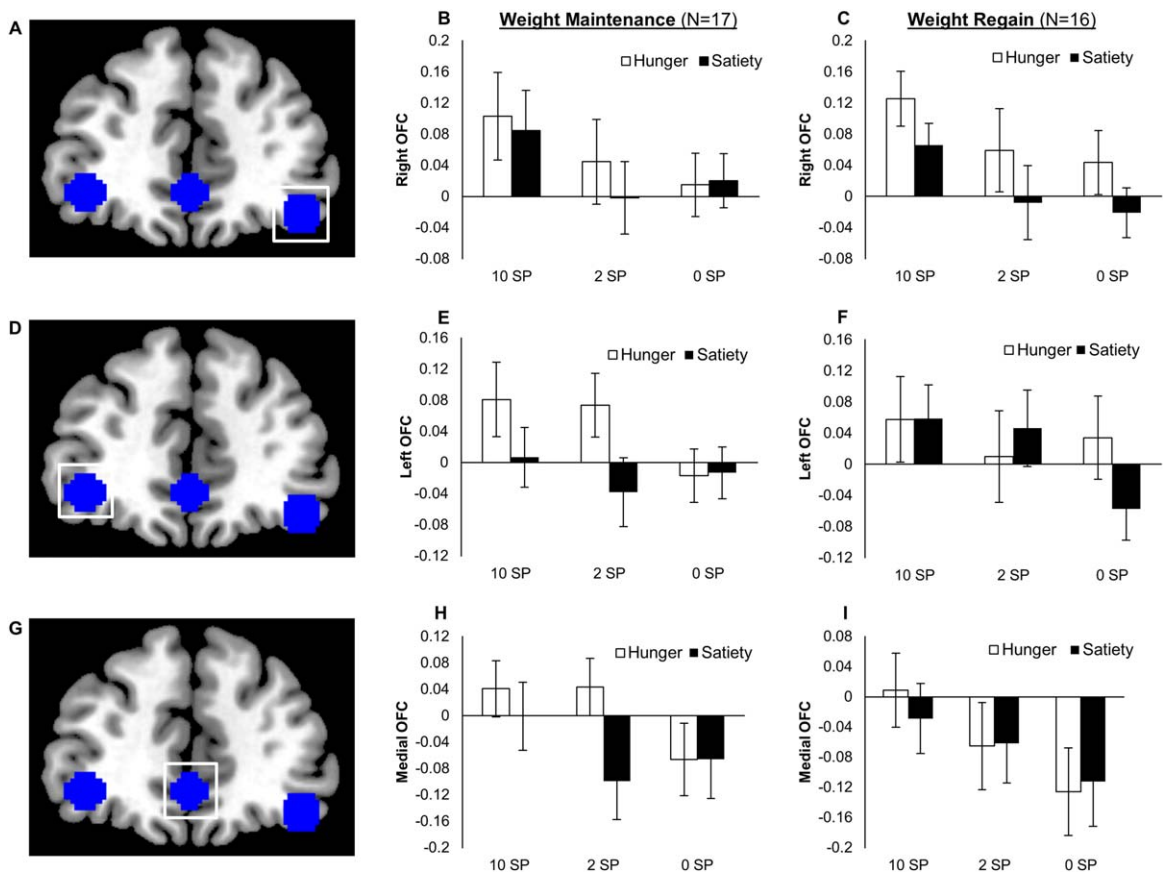

Figure 2 Masks used to extract percent signal change of blood oxygen level–dependent activation from the (**A**) right, (**D**) left, and (**G**) medial orbitofrontal cortex (OFC). In overweight participants with successful weight maintenance, activity in the (**B**) right, (**E**) left, and (**H**) medial OFC was related to reward level ($F[2,32] = 3.53$, $P = 0.041$, $F[2,32] = 6.1$, $P = 0.006$, and $F[2,32] = 4.8$, $P = 0.015$, respectively) during the receipt of food-related reward, and we observed a significant interaction between satiety and reward level in the left OFC ($F[2,32] = 5.76$, $P = 0.007$). In overweight participants with unsuccessful weight maintenance, there was an influence of reward level in the (**C**) right OFC ($F[2,30] = 8.52$, $P = 0.001$) and (**I**) medial OFC ($F[2,30] = 4.56$, $P = 0.019$), but not in the (**F**) left OFC ($P = 0.162$), and there was no influence of satiety state ($P > 0.682$). Error bars depict SEM. [Color figure can be viewed at wileyonlinelibrary.com]

suppression of active ghrelin was related to an equal suppression of brain reward processing only in successful weight maintenance. This finding contributes to the growing body of evidence indicating that intact suppression of ghrelin levels during satiety may play a pivotal role in successful weight loss maintenance (25,37).

Our findings are not in support of the "Incentive-Sensitization Theory" (38), as unsuccessful weight maintenance was not related to increased neural processing of food-related reward. This theory postulates that an increased mesolimbic reactivity to food cues triggers craving (i.e., "wanting") even when pleasure during the actual consumption of food (i.e., "liking") is reduced or absent (39), which has been proposed to explain the often compulsive nature of overeating. However, we observed a negative association between both short- and long-term weight loss and brain activation in the reward network in the Maintain group during satiety. Although not conclusively substantiating incentive sensitization in obesity, it indicates that lower neural responses during the expectation of food-related reward support short-term weight reduction. Specifically, decreased assignment of salience to food-related cues may reduce the allocation of attentional resources to food, therefore facilitating self-regulatory control of food intake. On the other hand, diminished neural processing during hedonic evaluation was related to weight stability in successful weight maintenance. Therefore, successful weight loss maintainers may be less dependent on food to compensate for the often-observed reward deficiency in obesity (11), and their food intake seems to be driven less by hedonic factors than by homeostatic needs. This assumption is corroborated by the satiety-induced improvement in mood ratings in the Maintain group, which could decrease the need for compensation via food intake. Since we employed a cross-sectional design, it remains unclear whether this correlation represents a change in the motivational value of food or a trait inherent to successful weight loss maintainers.

There are several limitations to our study that need to be taken into account. Because we included only female participants in our study, the reported results should be generalized to men with caution. Because of the exclusion of three participants, our group differed regarding the individual BMIs of participants. To ascertain the influence of this observation on our results, we correlated each individual BMI with the percent signal change extracted from all ROIs. Although we observed no significant results ($P > 0.125$), this

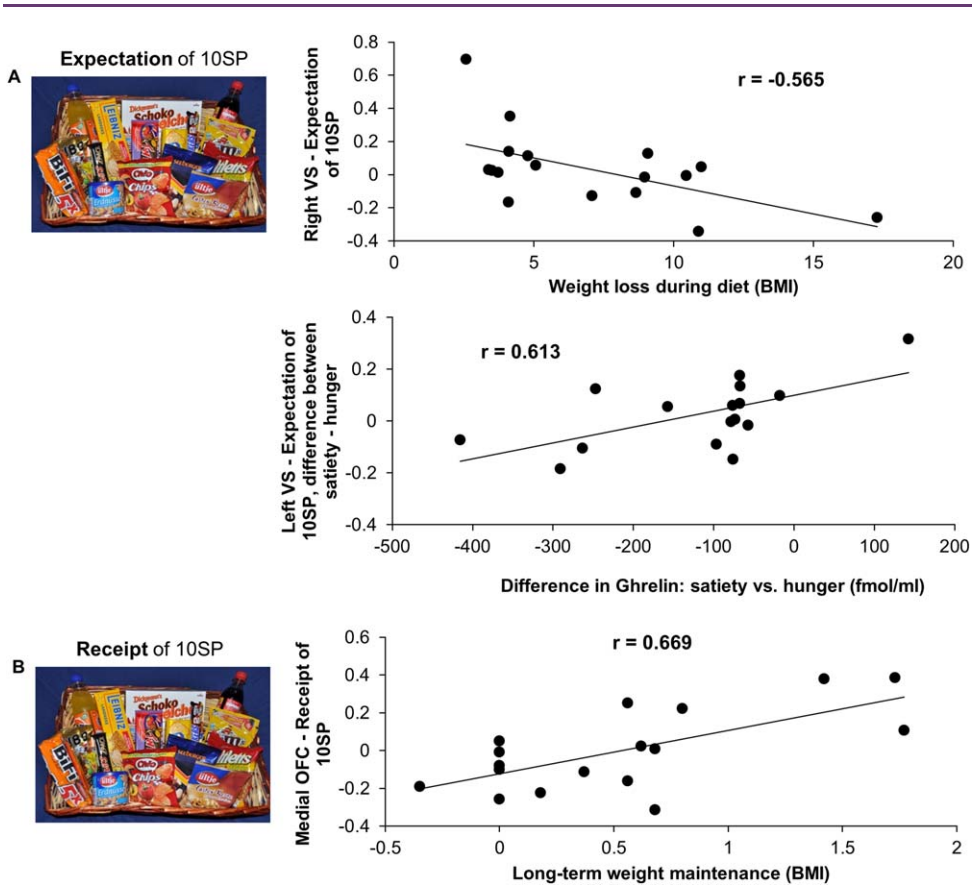

Figure 3 (**A**) Correlation analyses between percent signal change extracted from the right ventral striatum (VS) during the expectation of 10 SP ($r = -0.565$, $P = 0.018$) in the sated state and differences in BMI before and after diet in overweight participants with successful weight maintenance (top). Correlation analysis between differences in active ghrelin values (satiety minus hunger) and differences in left VS activation during the expectation of 10 SP (satiety minus hunger, $r = 0.613$, $P = 0.014$) (bottom). (**B**) Correlation analyses between percent signal change extracted from the medial orbitofrontal cortex (OFC) during the receipt of 10SP ($r = 0.669$, $P = 0.003$) in the sated state and long-term weight maintenance (amount of weight gain since end of the diet) in overweight participants with successful weight maintenance. [Color figure can be viewed at wileyonlinelibrary.com]

remains an important limitation of our results. Because measuring the exact number of calories consumed in cases in which participants did not eat the whole meal proved to be unfeasible, we cannot exclude the possibility that differences in food intake might have influenced the observed results. Although most participants ate the whole meal, this remains a limitation of the study. Furthermore, although it was previously shown that the task used in this study was able to provoke neural reactions similar to those observed during actual food consumption (28), further studies should investigate food reward processing in response to tangible food stimuli. Additionally, since we employed a cross-sectional design, we can draw only limited inferences about the relevance of our findings for the development and maintenance of obesity.

Taken together, these results indicate that intact hormonal satiety signaling as well as a pronounced coupling of homeostatic and hedonic mechanisms is a crucial aspect in long-term weight maintenance. Therefore, studying the responsiveness of the reward system to food cues in people with obesity during different states of satiety could give new insights in the underlying mechanisms of altered food reward sensitivity in obesity and the neurobiological factors that predispose to unsuccessful weight loss maintenance. O

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