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ORIGINAL ARTICLE

Successful dieters have increased neural activity in cortical areas involved in the control of behavior

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Objective: To investigate whether dietary restraint, a landmark of successful dieting, is associated with specific patterns of brain responses to the sensory experience of food and meal consumption.
Design and subjects: Cross-sectional study of the brain's response to the sensory experience of food and meal consumption in nine successful dieters (age: 38 ± 7 years, body fat (%): 28 ± 3) and 20 non-dieters (age: 31 ± 9 years, body fat (%): 33 ± 9), all women.
Measurements: Changes in brain activity in response to the sensory experience of food and meal consumption were assessed by using positron emission tomography and ^{15}O water as a radiotracer. Body fatness was assessed by dual X-ray absorptiometry. Subjective ratings of hunger and fullness were measured by visual analogue scale. Dietary restraint, disinhibition and hunger were assessed by the Three Factor Eating Questionnaire.
Results: Successful dieters had a significantly higher level of dietary restraint compared to non-dieters. In response to meal consumption, successful dieters had a greater activation in the dorsal prefrontal cortex (DPFC), dorsal striatum and anterior cerebellar lobe as compared to non-dieters. In response to the same stimulation, the orbitofrontal cortex (OFC) was significantly more activated in non-dieters as compared to successful dieters. Dietary restraint was positively correlated with the response in the DPFC and negatively with the response in the OFC. The responses in the DPFC and OFC were negatively intercorrelated.
Conclusion: Cortical areas involved in controlling inappropriate behavioral responses, such as the DPFC, are particularly activated in successful dieters in response to meal consumption. The association between the degree of dietary restraint and the coordinated neural changes in the DPFC and OFC raises the possibility that cognitive control of food intake is achieved by modulating neural circuits controlling food reward.
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Keywords: human brain; dietary restraint; successful dieting; prefrontal cortex

Introduction

Obesity is a progressive, chronic and relapsing disease that represents a common health problem in most countries around the world.[1] Lifestyle interventions remain the cornerstone of obesity treatment, although for those with more severe obesity, drugs and bariatric surgery are options. It is estimated that more than two-thirds of US adults are trying to lose or maintain weight by diet and/or physical exercise.[2]

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Unfortunately, the large majority of people who lose weight gain it back.[3] The reasons for the high rate of recidivism among obese individuals are not clear, and could include both behavioral and metabolic factors that predispose to weight regain. One approach to studying this problem has been to try to learn from those who have succeeded in long-term weight loss maintenance. The National Weight Control Registry (NWCR) includes over 3000 individuals who have successfully maintained at least a 30-lb weight loss for at least 1 year. The average registrant has lost 67 lb and has maintained that loss for roughly 5.5 years. Data from the NWCR indicate that, in general, for people who begin a weight loss program, behavioral factors are stronger predictors of a positive outcome than metabolic factors such as differences in resting metabolic rate, fat oxidation and insulin sensitivity.[3,4]

Specifically, dietary restraint, that is, the cognitive control of food intake, seems to be a key behavioral attribute of people who are successful at losing weight and keeping it off.[3] Individuals who fail to maintain the weight loss report a decrease in dietary restraint as well as an increase in disinhibition (i.e., the susceptibility of eating behavior to emotional factors and sensory cues).[3]

Thus far, the psychology of eating behavior has been studied mainly by means of subjective assessments, mainly collected with self-administered questionnaires, such as the Three Factor Eating Questionnaire (TFEQ)[5] and the Dutch Eating Behavior Questionnaire.[6] The use of neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), now offers the opportunity to describe the patterns of brain activity associated with unconscious and conscious cerebral activity elicited by food-related stimuli and that would give rise to a particular eating behavior.[7]

The aims of the present study were (1) to determine if there were differences in the brain's responses to the sensory experience and consumption of a satiating liquid meal between successful dieters and non-dieters and (2) to identify the behavioral and metabolic determinants of these cerebral responses. Based on the well-established role of the prefrontal cortex in the intentional control of behavior[8] and our previous observation that this area is involved in the response to meal consumption,[9–12] we hypothesized that successful dieters would exhibit a greater response to meal consumption in the prefrontal cortex as compared to non-dieters. Based on our previous report of gender-related differences in the brain response to meal consumption in several cortical areas, including the prefrontal cortex,[13] we have limited this investigation to only women, who constitute, on the other hand, 80% of the successful weight loss maintainers enrolled in the NWCR.[3]

Materials and methods

Subjects

Nine successful dieters and 20 non-dieters, all women, were recruited by targeted mailing to members of the NWCR (successful dieters) and by newspaper advertisement in the Phoenix (AZ, USA) metropolitan area (non-dieters). Successful dieters were selected from people who, based on a telephone screening interview, had achieved (by diet and physical exercise) the weight loss necessary to change their body mass index from at least 35 to 25 kg/m^2, and who had successfully kept their weight stable for at least 3 months before the admission. Absence of use of any over the counter or prescription medication for weight loss was confirmed by an accurate medical history collected upon admission. All these subjects but one (who was recruited afterwards) were part of the larger, both male and female post-obese group compared with obese and lean individuals in a previous paper.[14] Non-dieters were selected from people who, based on a telephone screening interview, were not following weight-loss programs and had not experienced any change in body weight for at least 3 months before the admission. These subjects were recruited for a larger study on the neuroanatomical correlates of hunger, sensory experience of food and satiety in lean and obese individuals previously published.[10,13] All subjects were studied while in the follicular phase of the menstrual cycle and were non-smokers, in good health and not taking any medication. Urine screening tests for psychoactive drugs were performed to confirm absence of drug use. Subjects were admitted for 1 week to the Clinical Diabetes and Nutrition Section of the National Institutes of Health in Phoenix and were restricted to the metabolic ward and to sedentary activity for the duration of the study. The protocol was approved by the Institutional Review Boards of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK-NIH), the Indian Health Service and the Good Samaritan Regional Medical Center. Written informed consent was obtained from all subjects before participation.

Experimental protocol

Experimental procedures have been described previously.[15] In brief, on admission all subjects were placed on a weight-maintenance diet (50% carbohydrate, 30% fat, 20% protein). Resting energy expenditure (REE) and respiratory quotient (RQ, a measure of whole body carbohydrate/fat oxidation rates) were measured after an overnight fast by indirect calorimetry (DeltaTrac, SensorMedics, Yorba Linda, CA, USA); body composition was determined by dual-energy X-ray absorptiometry (DPX-L, Lunar, Madison, WI, USA). Characteristics of eating behavior were assessed by using the TFEQ.[5] The TFEQ is a 51-item instrument, composed of three subscales measuring restraint (21 items), disinhibition (16 items) and hunger (i.e., the susceptibility of eating behavior to feelings of hunger; 14 items) using 'true/false' or multiple choice items. An example of the restraint items is 'I often stop eating when I am not really full as a conscious means of limiting the amount that I eat'; an example of the disinhibition items is 'Sometimes things just taste so good that I keep on eating even when I am no longer hungry'; and an example of the hunger items is 'I am always hungry so it is hard for me to stop eating before I finish the food on my plate'.[5] Taste preferences were assessed by using a taste test, as previously described.[16] Briefly, after an overnight fast, subjects were given a standard breakfast, providing 25% of the daily weight-maintenance energy needs. Ninety minutes after breakfast, the subjects were presented with a tray of 16 randomly ordered solutions consisting of non-fat milk (0.1% fat), whole milk (3.5% fat), half and half (11.3% fat) and cream (37.5% fat) and containing 0, 5, 10 or 20% sugar by weight. The subjects rated the solutions for sweetness, creaminess and pleasantness (the hedonic response) by using a 100-mm visual analogue scale (VAS) anchored with the

descriptors 'not at all' and 'extremely' (sweet, creamy or pleasant). Before the brain imaging session, subjects fasted for 36 h. Water and non-caloric, non-caffeinated beverages were provided *ad lib* during the fast.

Imaging procedures

PET and magnetic resonance imaging (MRI) procedures were conducted at the Good Samaritan Regional Medical Center (Phoenix, AZ, USA). MRI of the brain was performed using a 1.5 T Sigma system (General Electric, Milwaukee, WI, USA) to rule out gross anatomical abnormalities and to allow for the identification of regional changes of cerebral blood flow (rCBF), a marker of neural activity. PET maps of rCBF (i.e., neural activity) were obtained for each subject using an ECAT-951/31 scanner (Siemens, Knoxville, TN, USA). During each 1-min scan, subjects rested in the supine position without movement and were asked to keep their eyes closed and pointing forward. For each scan, a 50-mCi intravenous bolus of ^{15}O-water was injected. Two scans (F1 and F2) were obtained in resting conditions after a 36 h fast (*fast*, F), two (T1 and T2) after the oral administration of 2 ml of a liquid meal (Ensure Plus, 1.5 kcal/ml, 56% carbohydrate, 29% fat, 15% protein; Ross-Abbott Laboratories, Columbus, OH, USA) (*taste-sensory experience of food*, T) and two (S1 and S2) after the administration (over 25 min) of a satiating amount of the same meal (*satiety*, S), which provided 50% of the individual REE. There was an interval of 10 min between F1 and F2, T1 and T2, and S1 and S2. To control for swallowing, 30 s before each scan at F and S, subjects were asked to retain and swallow 2 ml of water at room temperature administered from a syringe through a plastic tube into the mouth. Immediately after each scan, subjects were asked to rate feelings of desire to eat, hunger, prospective food consumption, thirst and fullness on a 100-mm VAS, ranging from 0 ('not at all hungry', etc.) to 100 ('very hungry', etc.). Blood samples were also drawn immediately after each scan. For T, 30 s before each scan, subjects were asked to retain and swallow 2 ml of the liquid formula meal at room temperature administered in the same manner as for the water at F and S. The experimental session continued with the administration of the same liquid meal to induce satiety (S). The subjects were anticipating being fed until sated, as they had been fully familiarized with the experimental protocol in order to minimize the risk of learning-related artifacts (before the imaging session, the procedure was performed twice in the research ward).

Analytical measurements

Plasma glucose and insulin concentrations were determined by the glucose oxidase method (Beckman Instruments, Fullerton, CA, USA) and by an automated radioimmunoassay (Concept 4; ICN, Costa Mesa, CA, USA), respectively; serum free fatty acid (FFA) concentrations were determined by an enzymatic colorimetric method (Wako Chemicals, Richmond, VA, USA).

Image processing and statistical analysis

Using SPM99 (The Wellcome Institute of Neurology, London, UK), automated algorithms were implemented to align each subject's sequential PET images,[17] spatially normalize them to the stereotactic space as defined by the template provided by the Montreal Neurological Institute (MNI) and smooth the images with a 15 mm full-width-at-half-maximum Gaussian filter. To test our hypothesis, we evaluated the effects of condition (stimulus vs baseline) within each group (as reported in Figures 2 and 3) and condition*group interaction (as reported in Tables 2 and 3) using the 'multistudy: replicated conditions & covariates' SPM99 design, accounting for the whole brain–blood flow and age by Analysis of Covariance (ANCOVA).[18] The resulting T-score maps were then superimposed onto the SPM-MRI template using the standard MNI coordinates to allow visual inspection of the composite images. A critical $P<0.001$ (not corrected for multiple comparisons) was used to characterize significant changes in rCBF and condition*group interactions. For the *post hoc* analysis of the behavioral and metabolic determinants of the brain responses, average CBF was determined in 5-mm radius spherical regions of interest (ROIs) centered on peaks of condition*group interactions. Because TFEQ scores were not normally distributed, the relationships of ROIs CBF with TFEQ variables were assessed by Spearman rank correlation analysis.

Repeated-measures analysis of variance was used to determine within-subject differences in the hedonic response to taste owing to sugar and fat content (taste test). The response surface method, calculated by using the SAS RSREG procedure (SAS Institute Inc., Cary, NC, USA), was used to approximate a maximal hedonic response and the corresponding sugar and fat concentrations at this maximum.[19] The procedure determines an optimal quadratic response surface by least-squares regression using the hedonic values of all combinations of sugar and fat concentrations. Group differences ($P<0.05$) in age were assessed by Student's *t*-test; group differences in percentage of body fat, hedonic response to taste, serum FFA, plasma glucose and insulin concentrations were assessed by general lineal models adjusted for age. Group differences in TFEQ scores and VAS ratings (variables that were not normally distributed) were assessed by Wilcoxon rank-sum tests after adjusting for age. The procedures of the SAS Institute (Cary, NC, USA) were used for these statistical analyses.

Results

Successful dieters were older than controls and slightly leaner (although this difference did not reach statistical significance) (Table 1). REE and fasting RQ were not

Table 1 Anthropometric and energy metabolism variables, eating behavior factors, hedonic response to taste and subjective ratings of hunger and satiety in successful dieters and non-dieters

	Successful dieters	*Non-dieters*	*Comparison (P)*
Age	38.0±6.5	31.3±8.6	0.05*
Height (m)	1.66±0.07	1.64±0.04	0.3*,¶
Weight (kg)	64±5.7	86.0±27.6	0.05*,¶
Body fat (%)	28±3	33±9	0.2#,¶
Resting energy expenditure (kcal/day)	1251±156	1562±380	0.2#,†
Respiratory quotient	0.87±0.04	0.89±0.06	0.8#,‡
Three factor eating questionnaire			
Restraint (1–21)	15 (9–18)	9 (1–17)	0.002¶,§
Disinhibition (1–16)	6 (2–15)	5 (1–12)	0.5¶,§
Hunger (1–15)	4 (1–10)	4 (0–9)	0.9¶,§
Hedonic response to taste			
Maximum hedonic response (0–100 mm)	68.0±15.9	71.7±13.5	0.5#,¶
Sugar % at the maximum hedonic response	8.4±9.3	14.3±8.1	0.1#,¶
Fat % at the maximum hedonic response	10.7±15.5	19.9±18.0	0.2#,¶
Subjective ratings (0–100 mm)			
Desire to eat (S-F)	−53 ((−90)–(−14))	−54 ((−100)–(−11))	0.8¶,§
Hunger (S-F)	−57 ((−92)–(−16))	−57 ((−100)–(−12))	0.9¶,§
Thirst (S-F)	−38 ((−93)–(−3))	−34 ((−96)–10)	0.9¶,§
Fullness (S-F)	66 (23–90)	68 (1–100)	0.5¶,§
Prospective food consumption (S-F)	−56 ((−89)– (−21))	−51 ((−98)– (−17))	0.6¶,§

*Student's *t*-test (two-tailed); # General linear model (two-tailed); ¶Adjusted for age; †Adjusted for age, fat mass and fat free mass; ‡adjusted for age, and body fat (%); §Wilcoxon rank-sum test (two-sided).

significantly different between successful dieters and non-dieters. The level of dietary restraint was higher in successful dieters than in non-dieters, whereas no group differences were observed in disinhibition and hunger scores (Table 1). The subjective hedonic response to taste was not different (Table 1). After consuming a satiating meal, subjective ratings of hunger, desire to eat, prospective food consumption, fullness and thirst showed the expected changes in both successful dieters and non-dieters, without group differences. Fasting plasma glucose was lower in successful dieters as compared to non-dieters (Figure 1). Fasting serum FFA were higher in successful dieters than in non-dieters (Figure 1). After accounting for body fatness, the group differences in serum FFA remained significant, whereas the group differences in plasma glucose disappeared. After consuming the meal, in both groups plasma glucose and insulin increased, whereas serum FFA decreased, without significant meal*group interaction.

Brain responses

In response to T as compared to F, successful dieters were distinguished from non-dieters by the absence of activation in the occipital cortex, hippocampus and parahippocampal gyrus (Table 2).

In response to S as compared to F, successful dieters were distinguished from non-dieters by significantly greater activation in the dorsal prefrontal cortex (DPFC) (Figure 2), dorsal striatum (DS) and anterior lobe of the cerebellum (ACL) (Table 3). In response to the same stimulation, in the orbitofrontal cortex (OFC, bilaterally), non-dieters had activation (Table 3 and Figure 3), whereas successful dieters showed a trend towards deactivation (Figure 3). Because changes in the left OFC were tightly correlated with changes in the right OFC ($r=0.71$; $P<0.0001$), ROI changes in the OFC in both hemispheres were averaged for correlation analyses.

In the whole group, changes in neural activity in the DPFC were inversely correlated with changes in the OFC (r = -0.36; $P=0.05$) (Figure 4).

Behavioral and metabolic determinants of the brain responses

None of the changes in neural activity observed in response to T (as compared to F) were associated with behavioral or metabolic variables.

In the whole study population, simple correlation analysis revealed that dietary restraint was positively associated with changes in neural activity in S (as compared to F) in the DPFC ($r=0.43$; $P=0.02$) (Figure 4) and in the ACL ($r=0.40$; $P=0.03$) and negatively with changes in neural activity in the OFC ($r=-0.44$; $P=0.02$) (Figure 4). In stepwise regression models with percentage of body fat, changes in circulating glucose, insulin and FFA, and dietary restraint, disinhibition and hunger as covariates, dietary restraint was the only variable associated with changes in neural activity in S (as compared to F) in the DPFC ($P=0.04$; $R^2=0.15$) and in the ACL ($P=0.03$; $R^2=0.18$). Changes in plasma insulin and serum FFA were associated with changes in neural activity in the OFC ($P=0.03$ and $P=0.05$, respectively;

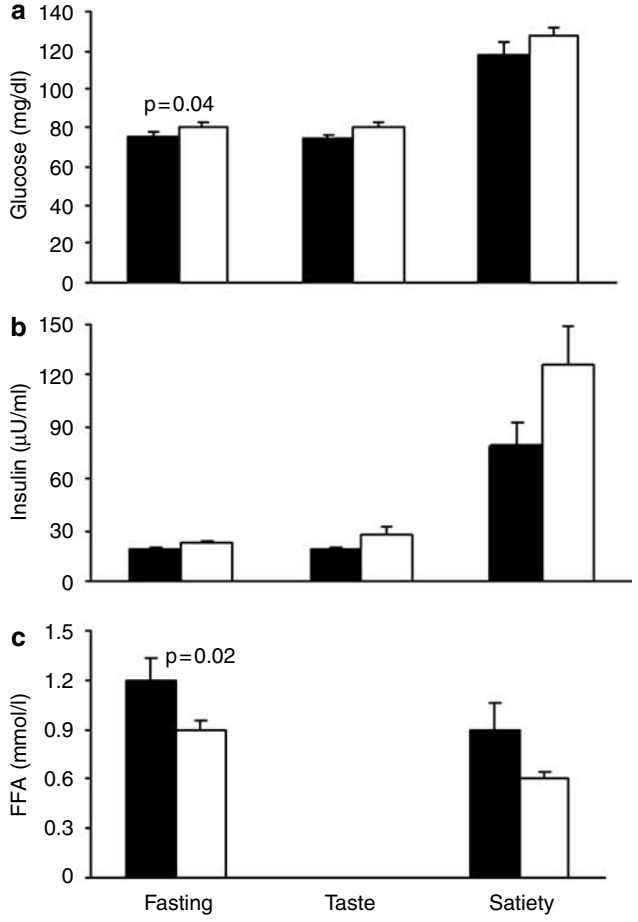

Figure 1 (**a**) Plasma glucose (mean and standard error) in successful dieters (■) and non-dieters (□) after 36-h fast (fasting), after sensory stimulation (taste) and after meal consumption (satiety). Group differences were assessed by general linear models (two-tailed), after adjustment for age. (**b**) Plasma insulin (mean and standard error) in successful dieters (■) and non-dieters (□) after 36-h fast, after sensory stimulation and after meal consumption. Group differences were assessed by general linear models (two-tailed), after adjustment for age. Values were $\log_{10}$ transformed before group comparison to approximate a normal distribution. (**c**) Serum FFA (mean and standard error) in successful dieters (■) and non-dieters (□) after 36-h fast and after meal consumption (serum FFA were not measured after sensory stimulation). Group differences were assessed by general linear models (two-tailed), after adjustment for age. Values were $\log_{10}$ transformed before group comparison to approximate a normal distribution.

$R^2 = 0.24$). Changes in plasma insulin were associated with changes in neural activity in the DS ($P = 0.02$; $R^2 = 0.21$). Group differences in changes in neural activity in these four regions remained significant, although attenuated, after adjustment for these covariates.

Discussion

We have previously reported activation in the DPFC in response to consuming a satiating meal and hypothesized that this cortical region may play an important role in the central regulation of eating behavior.[9–12,20] The results from the present study extend our previous observation by showing that the response of this cortical region to the consumption of a meal is enhanced in successful dieters and that it is associated with the level of dietary restraint.

Table 2 Group differences in increases in brain activity in response to the taste-sensory experience of food

Non-dieters > successful dieters				
Region	*Local maxima coordinates*[a]			P[#]
	x	Y	z	
Middle occipital gyrus	−31	−81	0	0.0001
Parahippocampal gyrus	−23	−41	4	0.0004
Hippocampus	23	−31	−4	0.0009

[a]Montreal Neurological Institute standard brain; *x* is the distance in mm to the right (+) or left (−) of midline, *y* is the distance in mm anterior (+) or posterior (−) to the anterior commissure and *z* is the distance in mm superior (+) or inferior (−) to a horizontal plane through the anterior and posterior commissures; [#]not corrected for multiple comparisons.

The DPFC is the cortical region that underwent the greatest phylogenetic enlargement in humans[21] and has been consistently implicated in the conscious experience of emotion, in the initiation, monitoring or modulation of emotion, and in the inhibition of the expression of emotion.[22] Altogether, the DPFC is considered to be the pivotal site of the cognitive control of behavior,[23] especially when 'behavior must be guided by internal states or intentions',[8] the so called 'top-down' processing. Lesions of the prefrontal cortex result in the lack of restraint of inappropriate behavior in social situations[24] and disrupt the balance between internal mental representations and reflex responses to environmental stimuli, favoring the latter.[25] Here we show that dietary restraint, as other forms of behavioral restraint, is functionally associated with the activation of the DPFC. Nevertheless, dietary restraint explained only 15% of the variability of the DPFC response to the consumption of a meal and did not entirely account for the group difference in this response. This indicates that other group characteristics, not considered in this study, play a role. Furthermore, we did not observe a relationship between dietary restraint and the DPFC response within each group: although this could be related to limitations in statistical power, we need to consider this relationship with caution.

The OFC is another cortical area of the frontal lobe that we have previously reported as activated in response to meal consumption, as a component of the early satiety response.[9–12,20] In this study, contrary to the expected increase of the OFC activity in non-dieters, we found a trend towards a decrease of activity in successful dieters. We also found that in the whole group the response in the OFC was inversely correlated with the response in the DPFC. The OFC is a multimodal associative area, where sensory and visceral inputs elicited by food ingestion converge[26–30] and

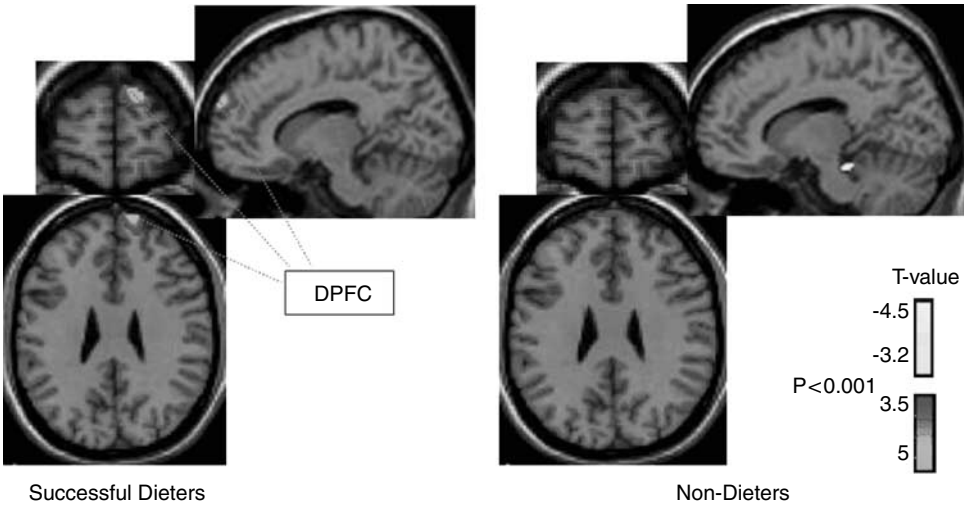

Figure 2 Statistical parametric maps of changes in blood flow at $P \leqslant 0.001$ in response to consumption of a meal in successful dieters and non-dieters at the level of the DPFC. According to the increasing *T*-value of the within-group analysis, increases of blood flow are represented in different colors from blue to green, and decreases are represented in yellow from dark to light. Axial (bottom), coronal (upper left) and sagittal (top) sections (the stereotaxic coordinates of the DPFC are reported in Table 3) are shown for the successful dieters (left side of the picture) and non-dieters (right side of the picture) groups. For the interpretation of the references to color in this figure legend, the reader is referred to the web version of the paper.

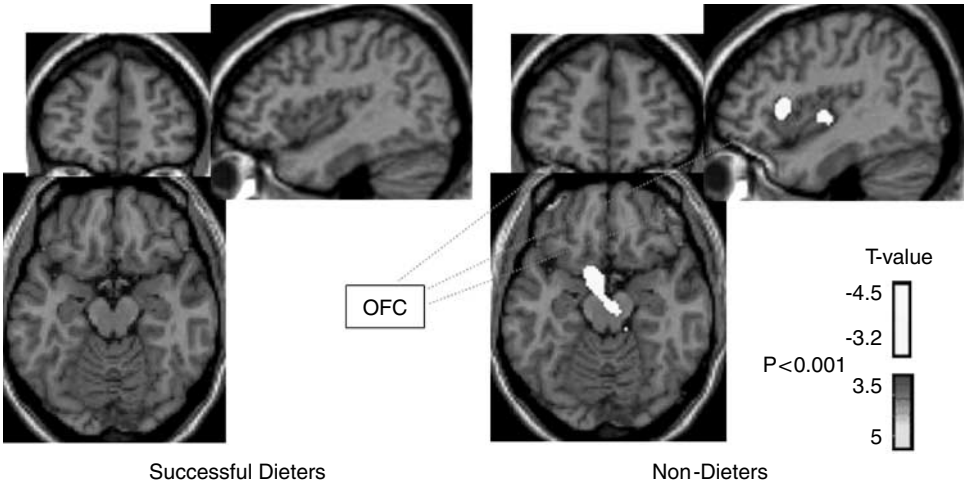

Figure 3 Statistical parametric maps of changes in blood flow at $P \leqslant 0.001$ in response to consumption of a meal in successful dieters and non-dieters at the level of the OFC. According to the increasing *T*-value of the within-group analysis, increases of blood flow are represented in different colors from blue to green, and decreases are represented in yellow from dark to light. Axial (bottom), coronal (upper left) and sagittal (top) sections (the stereotaxic coordinates of the OFC are reported in Table 3) are shown for the successful dieters (left side of the picture) and non-dieters (right side of the picture) groups. For the interpretation of the references to color in this figure legend, the reader is referred to the web version of the paper.

are decoded in their reward value.[31] In this region, the bottom-up processing of information about the internal state (homeostasis) initiated in subcortical structures interfaces with the cognitive level.[32] The correlation that we report between the OFC response and meal-induced changes in circulating insulin and FFA is consistent with this functional pattern.

Anatomical studies have documented that the DPFC and the OFC are reciprocally interconnected;[26] therefore, we can hypothesize that in response to meal ingestion, an inhibitory feedback circuit links the DPFC and the OFC in successful dieters. The inhibition of food reward is probably the goal of this prefrontal–orbitofrontal loop as a peculiar case of the top-down control (DPFC) over a bottom-up processing of information (OFC).

The DS has been implicated in the representation of food reward by neuroimaging studies documenting changes in the local neural activity in accordance with changes of

Table 3 Group differences in increases in brain activity in response to satiety, after consumption of a meal

Region	*Local maxima coordinates*[a]			P[#]
	x	y	z	
Successful dieters > non-dieters				
Dorsal prefrontal cortex	13	63	28	0.0005
Dorsal striatum (putamen)	−29	−3	0	0.0009
Anterior cerebellar lobe	5	−41	−20	0.0006
Non-dieters > successful dieters				
Orbitofrontal cortex	−39	51	−16	0.0002
	43	49	−16	0.00002

[a]Montreal Neurological Institute standard brain; *x* is the distance in mm to the right (+) or left (−) of midline, *y* is the distance in mm anterior (+) or posterior (−) to the anterior commissure and *z* is the distance in mm superior (+) or inferior (−) to a horizontal plane through the anterior and posterior commissures; [#] not corrected for multiple comparisons.

reward[33] or local dopamine release in response to the consumption of a favorite meal.[33] Interestingly, Volkow *et al.*[34] reported that the dopamine release in the DS in response to the sensory stimulation from food was positively correlated with the level of dietary restraint, suggesting that dopamine release is involved in the cognitive control of eating behavior. We found a greater DS response in successful dieters, but not a correlation between the DS response and dietary restraint. This is not surprising, given that dietary restraint is a typical cognitive dimension of eating behavior, whereas DS operates at an unconscious level.

Studies in non-human primates, as reviewed by Wise *et al.*[36], showed that the PFC–basal ganglia (of which the DS is part) system is involved in different aspects of response learning. The PFC is primarily implicated in conditional associations, to set the 'if-then' rules of voluntary behavior,[35] and the basal ganglia are more involved in potentiating learned rules, by cortico-striatal positive feedback loops. Although in our study the DPFC and DS activations are not correlated, both are greater in successful dieters compared to non-dieters.

Furthermore, as suggested by a recent neuroimaging study, different cortico-striatal networks are recruited at different timescales in expectation of rewards. The cognitive and motor loops, including the DPFC and DS, seem to be involved in the prediction of large future rewards rather than immediate rewards that elicit activation of the OFC and ventral striatum (limbic loop).[37] This leads us to speculate that the greater activation of the DS in successful dieters compared to non-dieters may represent the expectation of the great reward of keeping the weight off prevailing over the immediate reward of consuming a meal (as represented in the OFC).

Limitations in the study design also must be acknowledged. Although our sample size is comparable to most human neurofunctional studies, we could have increased our chances of missing brain responses and group differences. This being a women-only study, further investigation in both genders is warranted to ascertain if there is a gender-specific pattern of brain responses associated with successful weight loss. We also recognize the potentially confounding effects of scan order, but we note that we could not counterbalance the fast and satiety conditions in a within-session study, acknowledging that between-session studies have more

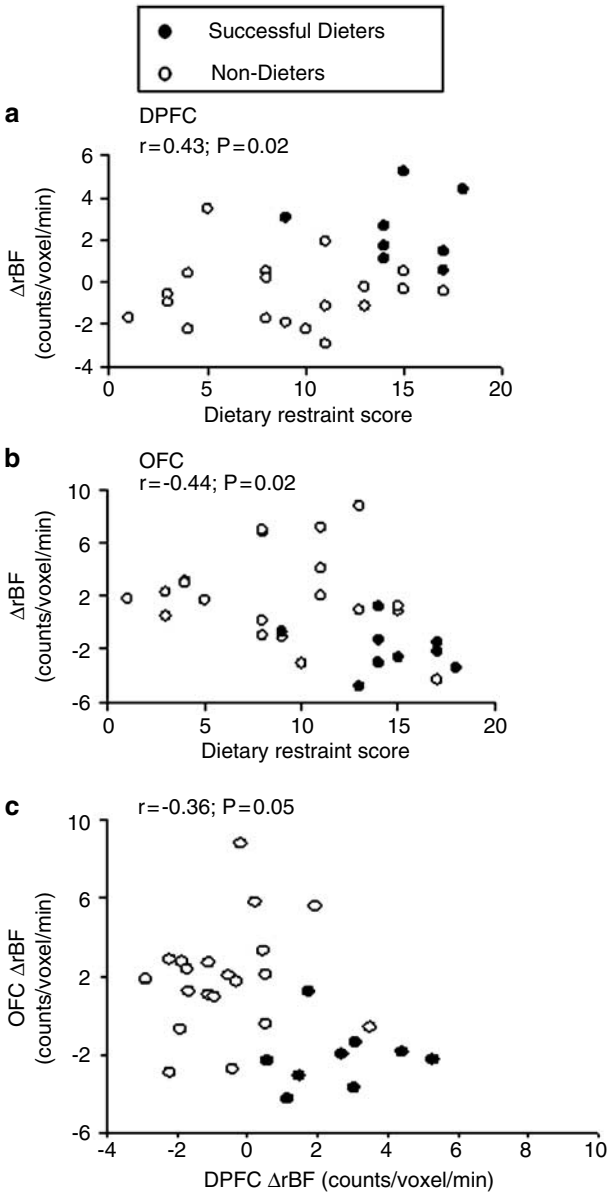

Figure 4 (**a**) Relationship of changes in the neural activity (ΔrBF) in response to consumption of a meal from baseline in the DPFC with dietary restraint score, assessed by Spearman rank correlation analysis. (**b**) Relationship of changes in the neural activity (ΔrBF) in response to consumption of a meal from baseline in the OFC with dietary restraint score, assessed by Spearman rank correlation analysis. (**c**) Relationship between changes in neural activity (ΔrBF) in the DPFC and OFC, assessed by Pearson correlation analysis.

limited statistical power. The baseline condition was characterized by a rather accentuated state of hunger after a 36-h fast. This was done to produce behavioral states of sufficient intensity to maximize our chances of detecting regional brain responses selectively elicited by the consumption of a satiating meal. On the other hand, from both a metabolic (as indicated by the higher serum FFA concentration) and a behavioral standpoints, successful dieters likely are better equipped to tolerate such a prolonged fasting in comparison with non-dieters.

Furthermore, whereas the brain responses reported here are indicative of neurofunctional patterns associated with a stabilized weight loss, rather than elicited by dieting *per se*, the experimental design of the study is such that it is not possible to distinguish whether the specificity of brain responses in successful dieters is due to the meal delivery modality (predetermined set of circumstances that cannot be modified by an act of volition) or the size of the meal (amount of food larger than successful dieters would choose if eating *ad libitum*). This is an important distinction because if the former is true, then the pattern of brain activity we describe in this study may not be meal-specific at all, but more generally related to a perceived loss of control over the external environment. If the latter is true, then it would be important to determine if administration of smaller meals (down to the size that successful dieters would choose if eating *ad libitum*) is always accompanied by greater neural activity in areas of the brain involved in the cognitive control of behavior in successful dieters compared to non-dieters. This would more convincingly support the hypothesis that the associated inhibition of reward circuits is a strategy used in real life by successful dieters to exert cognitive control over their dietary habits when faced with large amounts of food.

How and when this cognitive control of eating behavior is learned/acquired, if it is common to less extreme phenotypes of behavioral control and if it is a function of the duration of dietary restraint are also fundamental questions that cannot be addressed in this study. The personal history of our successful dieters as formerly obese individuals who still harbor putative neural risk factors of weight gain[14] increases the complexity of the neurophysiological mechanisms that may be at play in this group of individuals. Nevertheless, carefully designed longitudinal studies describing the pattern of brain activity before, at the onset of, during and after weight loss should permit building on these initial observations and understanding better how the brain adapts or reacts to the long-term changes in energy homeostasis that these individuals have experienced throughout their lives.

Conclusions

Cortical areas involved in controlling inappropriate behavioral responses, such as the DPFC, are particularly activated in successful dieters in response to meal consumption. The association between the degree of dietary restraint and the coordinated neural changes in the DPFC and OFC raises the possibility that cognitive control of food intake is achieved by modulating neural circuits controlling food reward.

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