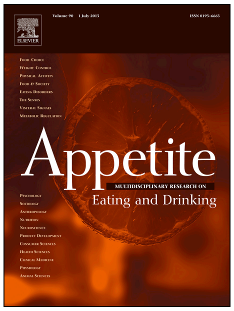

Increased food choice-evoked brain activation in adolescents with excess weight: Relationship with subjective craving and behavior

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Abstract

Objective: We used functional magnetic resonance imaging (fMRI) to assess brain regions associated with food choices between appetizing (i.e., high sugar, high fat) and plain food in adolescents with excess weight and those with normal weight. The associations between choice-evoked brain activation and subjective food craving and behavioral food choices were also evaluated.

Methods: Seventy-three adolescents (aged 14-19 years), classified into excess weight (n=38) or normal weight (n=39) groups, participated in the study. We used a food-choice fMRI task, between appetizing and plain food, to analyse brain activation differences between groups. Afterwards, participants assessed their "craving" for each food presented in the scanner.

Results: Adolescents with excess weight showed higher brain activation in frontal, striatal, insular and mid-temporal regions during choices between appetizing and standard food cues. This pattern of activations correlated with behavioral food choices and subjective measures of craving.

Conclusions: Our findings suggest that adolescents with excess weight have greater food choice-related brain reactivity in reward-related regions involved in motivational and emotional responses to food. Increased activation in these regions is generally associated with craving, and increased dorsolateral prefrontal cortex is specifically associated with appetizing food choices among adolescents with excess weight, which may suggest greater conflict in these decisions. These overweight- and craving-associated patterns of brain activation may be relevant to decision-making about food consumption.

Keywords: Appetizing; high-calorie; reward; obesity; addiction; adolescence

Increased food choice-evoked brain activation in adolescents with excess weight: Relationship with subjective craving and behavior

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INTRODUCTION

The prevalence of adolescent overweight and obesity has steeply increased over the last two decades, reaching epidemic levels (1). In most cases, overweight and obesity are the result of food choices characterized by high calorie intake. When these choices are consolidated at an early age, obesity is more severe and associated with worse long-term consequences (2).

Although food consumption is an essential human behavior, factors that regulate dietary choices are complex and poorly understood. Food intake is influenced by a variety of factors besides homeostatic regulation, like sensory cues (e.g., taste, smell, texture and appearance), availability, motivational and affective states, pleasure seeking, etc. All of these aspects influence what, and how much, humans eat even when they are satiated. These factors are associated with specific patterns of regional cerebral blood flow (rCBF), particularly within brain regions commonly implicated in motivation, emotion, memory, and behavioral control (3).

Previous studies have demonstrated that brain activation in response to food pictures is a useful measure to examine both sensitivity to food cues and vulnerability to the development or maintenance of overweight (4, 5). High-fat foods evoke activation in brain regions associated with reward value processing (e.g. dorsal/ventral striatum, orbitofrontal cortex [OFC]), as well as with the representation of internal body states such as hunger (insula) (6, 7).

Comparisons of rCBF between obese and normal-weight individuals have shown differential responses to food cues associated with weight status (6, 8, 9). Obese individuals show greater activation to food cues in comparison to normal-weight participants in multiple brain regions, including reward system-related ones, like the prefrontal cortex (PFC), OFC, anterior cingulate cortex (ACC), insula, amygdala, and striatum during hunger states (10); the PFC, caudate, hippocampus, and temporal lobe immediately after eating (8); and the striatum, insula, hippocampus, and parietal lobe during neutral appetitive states (neither hungry or satiated) (6). In addition, differential activation to food types (high- and low-calorie) has also been examined in relation to weight. The majority of reported results of direct comparisons between normal-weight and obese/overweight groups indicate greater activation in response to high-calorie food cues in similar brain regions among overweight/obese individuals (6, 8, 10).

Another way to study brain activation during eating behavior is by using food choice paradigms. Food decisions concern what, when, and how much to eat. Food choices can lead to overconsumption, when more energy is consumed than expended. The brain mechanisms underpinning food choices have been examined in neuroimaging studies. Several neural processes are involved in feeding behavior. Firstly, the visual system is very important to guide food selection. Inputs from the visual system elicit a specific pattern of brain activation related to preparation for food ingestion, which evokes the desire to eat, as well as cognitive processes such as memory retrieval and hedonic evaluation of the specific food (11, 12). Secondly, visual food cues activate the reward neural circuitry (e.g., PFC, OFC, amygdala, dorsal and ventral striatum, hypothalamus, and insula) (10). Moreover, high-calorie food cues specifically elicit a greater response in these regions relative to low-calorie food images (3, 6, 9, 10).

Recent theoretical models highlight that decision-making skills are a key factor in controlling caloric intake in modern environments, since these are characterized by open access to food and strong media-driven appeals to eat high-calorie food (13). Decision-making skills are particularly pertinent in the case of adolescents, in whom transitions in brain development appear to be geared towards maximizing reward at the expense of risk (14). Neuroimaging studies have confirmed that adolescents have hypersensitive striatal responses to reward prediction (15, 16) and high activation of brain areas implicated in the promotion of risk-taking (OFC) during decision-making (17).

However, the neural correlates of food choices in adolescents have been less well-studied. This matter is particularly important, as the probability that an obese adolescent develops into an obese adult is much higher than that of a normal-weight adolescent (18). Moreover, once people have become overweight or obese, it is quite difficult for them to regress to a stable healthy weight. The important increase in the prevalence of obesity in children and adolescents, the complications of overweight / obesity for health and the greater tendency to continue being overweight or obese in adulthood make prevention of obesity the alternative of choice and the optimal strategy to stop the spread of the obesity epidemic.

In this study, we used functional magnetic resonance imaging (fMRI) to assess brain regions associated with food choices between appetizing (i.e., high sugar, high fat) and plain food in adolescents with excess weight (i.e., overweight and obese) versus normal weight. We also aimed to evaluate the association between choice-evoked brain activation, subjective self-reported food craving and choice behavior. We hypothesized that excess weight participants, in comparison with the normal weight ones, would show greater neural responsiveness in the corticolimbic reward system during food choices between appetizing and plain foods (i.e., OFC, ACC, insula, ventral striatum and amygdala). We also hypothesized that this choice-evoked activation in these areas would correlate with food craving and selection of appetizing foods in the excess-weight group.

METHODS

Participants

Seventy-three adolescents (age range: 14-19 years) participated in the study. They were classified into two groups, excess weight [n=38] (27 adolescents with obesity and 11 adolescents with overweight) or normal weight [n=39], according to their age- and sex-adjusted body mass index (BMI) percentile, following the International Obesity Task Force (IOFT) criteria (19). There were no significant differences in age or sex between groups. Demographic and body composition data are summarized in Table 1.

The recruitment of participants was carried out throughout the province of Granada (Andalusia, Spain) in hospitals and high schools, as well as via press and radio advertisements. The inclusion criteria were defined as follows: (i) aged between 14 and 19 years; (ii) BMI percentiles falling within the intervals categorized as overweight or obesity (≥85: Excess weight group), or normal weight (5 to 84: Normal weight group); (iii) absence of any history or current evidence of neurological mental disorders as assessed via interviews with participants and their parents; (iv) absence of any history or current evidence of eating disorders (e.g., binge eating, bulimia nervosa, anorexia nervosa) assessed with the Eating Disorders Inventory-2 (EDI-2) (20) and (v) absence of any contraindication to undergo the fMRI session (i.e. metal prosthesis or claustrophobia). All participants had normal or corrected-to normal vision.

The Ethics Committee for Human Research of the Universidad de Granada approved the study. Both the participants and their parents/tutors signed an informed consent form.

Insert Table 1 here.

Procedure

This study consisted of two sessions. In the first session, all participants were pre-exposed to foods in a catered tasting session conducted 1 week before scanner acquisition. The participants tasted all foods included later in the fMRI task in order to become familiar with the specific foods (and their corresponding flavours, textures and sizes) that were going to be used in the fMRI tasks. The purpose of the tasting was to establish a context closer to real life in the food choice task. Then, they had to rate the different foods on a 1- to 10-point self-report scale indexing how much they liked each meal.

In the second session, we conducted the fMRI task. When participants arrived at the lab, we used an automated scale (Tanita BC-420 GP Supplies Ltd., London) to measure their weight and body fat percentage. Body fat percentage was estimated via Bioelectrical Impedance Analysis. All of the sessions were carried out at the same time of day (4 p.m.), and always fMRI tasks were carried out between one and three hours after lunch. The teenagers finished their lessons in the high school about 2.30 p.m., after that they ate lunch and at 4 p.m. they started the session. Given the study had a more extensive protocol that included measures assessed before fMRI, participants usually started the fMRI tasks at about 5 p.m. Just before the fMRI session, before beginning the task inside the scanner, and after finishing the fMRI session, participants rated their hunger from 0 to 100 points on a visual analogue scale in response to the question of "how hungry are you now?"

fMRI task

A food preference decision-making task was used. The food pictures used in the task were taken earlier in the tasting session. All pictures were shot ad hoc for the study using standardized presentation and lighting conditions. Therefore, all images were matched for visual properties (size, brightness, clarity and contrast) and serving size (about a portion for all food images). Furthermore, all the photographs were taken in the same place and with the same ambient light. Three types of food were utilized: appetizing (food with high levels of fats and sugars), plain (defined as natural food or low in fats and/or sugars) and functional (foods that are prepared not only for their nutritional characteristics but also to fulfil a specific function, such as improving health and reducing the risk of disease). Appetizing cues included, for instance, sausages, chocolate, cake, cheese and chips and plain cues included, for instance, fruits, yoghurt, cereals and salads. In each trial, pairs of these different types of food were presented to participants (appetizing vs. plain, appetizing vs. functional and plain vs. functional). Participants were instructed to choose between these two options taking into account their own preference for one or the other meal. The question presented was: “If you had to eat one of these foods, which would you choose?” Each trial began with a fixation cross, which appeared for 4 seconds. Then, images of the two options appeared for 5 seconds (one on the left side of the screen and the other one on the right side). The order of presentation of the images was counterbalanced among the participants. Then, the fixation cross was presented again (Fig 1). There were a total of 36 choice trials with 12 choices for each decision type. Participants were instructed to press a button in order to choose the food that they preferred. Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology Inc., Northridge, CA, USA), and responses were recorded with the Evoke Response Pad System (Resonance Technology Inc.). Participants were instructed to press the button with their thumb if they preferred the food on the left side, or the button with their forefinger for food on the right side. According to the objectives of this study, we focused only on the choice between appetizing food and plain food. The primary behavioral measure was the number of selections of appetizing and plain foods. Additionally, we calculated the percentage of appetizing choices when participants had to choose between appetizing and plain foods (“Percentage of Appetizing vs. Plain Food Choices”).

After the fMRI session, participants assessed their "craving" for each food presented earlier in the scanner on a 9-points scale (1, they did not desire the meal; 9, desired the meal excessively). Valence and arousal for each meal were also assessed via Self-Assessment Manikin (SAM) (21). The stimuli were presented using a computer task programmed using e-Prime software, in which each stimulus was presented on the screen for 5 seconds. Differences between scores for subjective ratings of craving in response to appetizing versus plain food (referred to as “Appetizing vs. Plain Food Craving Ratings”) were calculated.

Insert Figure 1 here.

Imaging data acquisition and processing

A 3.0 T clinical MRI scanner (Intera Achieva; Philips Medical Systems, Eindhoven, The Netherlands), equipped with an eight-channel phased-array head coil, was used to obtain a T2*-weighted echo-planar imaging sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, field of view (FOV) = 230 × 230 mm, 96 × 96 matrix, flip angle = 90°, 21 4 mm axial slices, 1 mm gap, 162 scans. A sagittal three-dimensional T1-weighted turbo-gradient-echo sequence (3DTFE) (160 slices, TR = 8.3 ms, TE = 3.8 ms, flip angle = 8°, FOV = 240 × 240, 1 mm^3 voxels) was also obtained in the same experimental session to discard gross anatomical abnormalities.

Functional images were analyzed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK), running on MATLAB R2009 (MathWorks, Natick, MA). Prior to preprocessing, all images were visually inspected for artifacts. Preprocessing included reslicing to the first image of the time series, slice timing correction, normalization (using affine and smooth nonlinear transformations) to an EPI template in Montreal Neurological Institute (MNI) space, and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum = 8 mm). No participant was excluded due to excessive motion, defined as a degree of movement above 3 mm or 3 degrees in either direction.

Data analysis

Group comparisons of sociodemographic, task, and self-reported variables were performed with independent-sample t-tests (two-tailed).

For the neuroimaging analysis, the conditions of interest were modelled from the time at which the food choice was presented to the time at which participants responded. Baseline was modelled as the time that the fixation cross was on the screen. Task regressors were convolved with the SPM8 canonical hemodynamic response function. The key contrast of interest was "appetizing vs. plain > baseline", defined in first-level (single subject) and between-group analyses.

One-sample t-tests were conducted to assess intra-group activations (healthy weight and excess weight) in the contrasts of interest. Between-group comparisons were conducted using two-sample t-tests. The statistical threshold used was $p<0.05$ family wise error (FWE) for the within-group analysis and $p<0.05$ false discovery rate (FDR) for the between groups analysis whole-brain corrected, with a minimum cluster size extent

(KE) of 10 contiguous voxels. To exclude the potential effect of the age in the results, we replicated all the analysis including age as confounder variable. Results were similar in both approaches, so we only report the original non-covaried results.

Finally, in order to examine the association between brain activation during exposure to appetizing and plain food cues during the food decision task and behavioral food choices and subjective food craving, the peak beta eigenvalues from each cluster of significant brain differences between groups were extracted for each participant and correlated with the "Percentage of Appetizing vs. Plain Food Choices" (food choice) and the "Appetizing vs. Plain Food Craving Ratings" (food craving), respectively.

RESULTS

There were not significant group differences in self-report measures (see Table 2).

Insert Table 2 here.

Brain activation during exposure to appetizing and plain food cues during the food decision task compared to baseline (fixation cross)

Both groups showed extensive activation in several areas of the frontal cortex (dorsolateral prefrontal cortex [dlPFC], dorsomedial prefrontal cortex [dmPFC] and ventrolateral prefrontal cortex [vlPFC]), supplementary motor area (SMA), occipital cortex (visual cortex), supramarginal gyrus, middle temporal gyrus, and subcortical regions (caudate, putamen, hippocampus and amygdala) (see table S1).

Differences in brain activation between participants with excess weight and normal weight

During exposure to appetizing and plain food cues in the food decision task, adolescents with excess weight, compared to those with normal weight, had increased activation in the dlPFC (bilaterally), superior temporal cortex (bilaterally), hippocampus, medial temporal cortex, putamen, superior frontal cortex, thalamus (bilaterally), globus pallidus, inferior temporal cortex, OFC, vlPFC, dorsal ACC, insula and dorsal caudate (see Table 3). The reverse contrast (i.e., normal weight > excess weight) yielded non-significant results (see Figure 2).

Insert Table 3 here.

Insert Figure 2 here.

Association between brain activation during exposure to appetizing and plain food cues in the food decision task and food choice

The Percentage of Appetizing vs. Plain Food Choices positively correlated with dorsolateral prefrontal cortex (dlPFC) activation in participants with excess weight (r=0.370, p=0.024), but not in healthy-weight controls (r=0.086, p=0.618).

In contrast, the Percentage of Appetizing vs. Plain Food Choices negatively correlated with the activation of the ACC (r=0.338, p=0.044) and the thalamus (r=0.356, p=0.033) among healthy-weight controls, but not among participants with excess weight (r=0.138, p=0.417 and r=-0.084, p=0.619 respectively).

Association between brain activation during exposure to appetizing and plain food cues in the food decision task and food craving

In participants with excess weight, “Appetising vs. Plain Food Craving Ratings” positively correlated with activation in the dlPFC, vlPFC, ACC, insula, superior/medial/inferior temporal cortices, dorsal caudate, putamen and thalamus. In contrast, only insula activation was correlated with "Appetising vs. Plain Food Craving Ratings" in normal-weight participants (see Table 4). We performed an FDR adjustment for multiple comparisons and the regions that remained significant were the right dlPFC, dorsal caudate and superior temporal cortex only in the excess-weight group.

Insert Table 4 here.

DISCUSSION

We found that adolescents with excess weight, compared to those with normal weight, show greater brain activation in frontal, striatal, insular and mid-temporal regions during exposure to appetizing and plain food cues in a food decision task. This pattern of activations correlated with behavioral food choices and subjective measures of craving. The pattern of brain activation of excess weight participants was consistent with that of previous cue-reactivity studies (4, 6, 8-10, 22, 23). However, there is limited research on exposure to food cues during a food decision task in adolescents. The link between brain activation and selection of appetizing foods and related craving illustrate the relevance of brain function for eating behavior during this period, which is associated with high prevalence of obesity in the Western world (24).

Group differences in brain activation may reflect hypersensitivity to food stimuli in adolescents with excess weight. Brain differences encompass regions involved in cognitive control, attention, interoception and memory and habit formation, which have been collectively or discreetly associated with overweight and obesity (6, 8, 9, 22, 23). Increased activation seems to suggest heightened reward valuation during preference formation and/or greater effort during action selection, which are two critical components of decision-making (25). However, the non-specific control condition precludes conclusions about decision-making mechanisms, and thus we use correlations with behavioral measures to refine our interpretation.

The positive association between dlPFC activation and appetizing food choices in excess-weight adolescents can be explained by the role of this region in conflict-based decision-making. Activation of the dlPFC increases with a rising amount of conflict, regardless whether it is emotional (preference formation) or cognitive (action selection) (26). This interpretation fits with previous findings that suggest that children and adolescents with excess weight show increased activation of this region in response to food versus other non-food related pleasant stimuli (23). In addition, recent meta-analyses have concluded that the dlPFC engages during different forms of conflict monitoring, including incongruent trials of the Stroop task, task switching, and high working memory loads (27-29). Based on this evidence, we reason that increased dlPFC reflects greater conflict associated with selection of appetizing food choices among adolescents with excess weight. In contrast, a positive association between anterior cingulate and thalamic activation and appetizing food choices has been found only in the normal weight group. These results are consistent with the role of these regions on attention orientation to task-relevant stimuli (30).

The correlations between most of the regions activated by the cues in the decision-making task and craving further support the general notion that excess-weight adolescents are hypersensitive to appetizing food cues (23, 31, 32). This hypersensitivity may influence craving for specific foods in daily life (i.e., high fat, high sugar food) (33). Subjective craving in response to food cues is a well-validated experimental model of sensitivity to the high-calorie foods we frequently encounter in the current “obesogenic” environment (33-36). Therefore, prevention policies that reduce exposure to cues of foods high in sugar and fat are important to control adolescent obesity. Although cue-related changes in fronto-limbic activity are also observed in drug addiction, our findings do not directly speak to the concept of food addiction. Future studies are needed to establish if the reported differences in brain activation correlate with self-report measures of food addiction (Yale Food Addiction Scale, YFAS) (37) and related behaviors such as emotional eating (The Dutch Eating Behavior Questionnaire, DEBQ) (38). In addition, multimodal studies linking brain activation and direct measures of dopamine concentrations are needed to clarify dopaminergic involvement in food cue reactivity (as it has been shown for drugs of abuse) (35, 39, 40).

In sum, the main funding of this study is that adolescents with excess weight have increased activation in several regions involved in reward valuation, salience detection and conflict monitoring when they are faced with decisions between appetizing versus plain food. Our results also suggest that brain activations are meaningfully linked to the subjective value of appetizing food, as we found significant correlations with appetizing food choice and related cravings.

These findings have to be appraised in the context of relevant limitations, such as the type of contrast that we used (appetizing and plain food cues vs. baseline), since some of the activations could not be specifically related to decision making. In addition, the lack of attention measures makes impossible to know if participants could be looking at healthy or unhealthy foods. Direct attentional measures (e.g. eye tracking) should be included in future research. However, this limitation was partially overcome by the significant correlation of brain activation with food choice behavior and craving measures. On the other hand, although we observed clear and extensive differences between our obese and control samples, because we used a cross-sectional experimental design, it was not possible to determine whether the observed effects represent the causes or consequences of obesity. Moreover, it would be interesting if the functional implications of the current results could be addressed in longitudinal studies. Furthermore, research is needed to compare the results obtained between participants in fasted and satiated states. Finally, the effects of the menstrual cycle should be taken into account in future studies, since a number of studies have reported that brain activation and decision making processes are modulated by the hormonal stage of the menstrual cycle during exposure to food cues (41, 42).

Notwithstanding these limitations, the findings of the study may have important treatment implications. Interventions for adolescent obesity should focus not only on physiological endpoints, but also in decision-making mechanisms such as reward valuation and conflict monitoring. The ability to resist reward-related temptations and cravings in response to high-calorie food is extremely important to prevent unhealthy eating behaviors. Therefore, prevention policies that promote a reduction in exposure to high in fat and/or sugar food cues in the environment of adolescents with excess weight could be useful. Furthermore, more research into the neural correlates of food choice may provide better insight into the effects of age, sex, and weight on food-related decision-making processes, and provide targets for healthy eating interventions. Since an overweight child or adolescent has a high probability of developing into an overweight adult, prevention of overconsumption of unhealthy foods and formation of healthy eating habits in children is crucial in order to reverse the prognosis.

CONCLUSION

We show that adolescents with excess weight have heightened activation in a distributed set of frontal, temporal, insular and striatal regions during exposure to food cues in a decision-making task. Increased activation in these regions is generally associated with craving, and increased dorsolateral prefrontal cortex is specifically associated with appetizing food choices among adolescents with excess weight, which we interpret as greater conflict in these decisions. The main implication of this finding is that policy, prevention and treatment interventions for obesity need to tackle vulnerabilities in brain-cognitive-affective decision-making systems.

Author contributions: MMP and JVR carried out the experiments and analyzed data. MMP wrote the paper with the contributions and approval of all authors.

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REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA* 2012;307:483-490. 1
2. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *Int J Obes* 2011;35:891. 2
3. Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Cortical and limbic activation during viewing of high-versus low-calorie foods. *Neuroimage* 2003;*19*:1381-1394. 3

4. Castellanos EH, Charboneau E, Dietrich MS, et al. Obese adults have visual attention bias for food cue images: evidence for altered reward system function. *Int J Obes* 2009;33:1063. 4
5. Lawrence NS, Hinton EC, Parkinson JA, Lawrence AD. Nucleus accumbens response to food cues predicts subsequent snack consumption in women and increased body mass index in those with reduced self-control. *Neuroimage* 2012;63:415-422. 5
6. Rothemund Y, Preuschhof C, Bohner G, et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage* 2007;37:410-421. 6
7. Stoeckel LE, Kim J, Weller RE, Cox JE, Cook EW, Horwitz B. Effective connectivity of a reward network in obese women. *Brain Res Bull* 2009;79:388-395. 7
8. Bruce AS, Holsen LM, Chambers RJ, et al. Obese children show hyperactivation to food pictures in brain networks linked to motivation, reward and cognitive control. *Int J Obes* 2010;34:1494. 8
9. Carnell S, Benson L, Pantazatos SP, Hirsch J, Geliebter A. Amodal brain activation and functional connectivity in response to high□energy□density food cues in obesity. *Obesity* 2014;22:2370-2378. 9
10. Stoeckel LE, Weller RE, Cook EW, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage* 2008;41:636-647. 10
11. Van der Laan LN, De Ridder DTD, Viergever MA, Smeets PA. The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues. *Neuroimage* 2011;55:296-303. 11

12. Smeets PA, Charbonnier L, van Meer F, van der Laan LN, Spetter MS. Food induced brain responses and eating behaviour. *Proc Nutr Soc* 2012;7:511–520. 12
13. Morrison CD, Berthoud HR. Neurobiology of nutrition and obesity. *Nutr Rev* 2007;65:517-534. 13
14. Ernst M, Fudge JL. A developmental neurobiological model of motivated behavior: anatomy, connectivity and ontogeny of the triadic nodes. *Neurosci Biobehav Rev* 2009;33:367-382. 14
15. Cohen JR, Asarnow RF, Sabb FW, et al. A unique adolescent response to reward prediction errors. *Nat Neurosci* 2010;13:669-671. 15
16. Galvan A, Hare TA, Parra CE, et al. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *J Neurosci* 2006;26:6885-6892. 16
17. Van Leijenhorst L, Moor BG, de Macks ZAO, Rombouts SA, Westenberg PM, Crone EA. Adolescent risky decision-making: neurocognitive development of reward and control regions. *Neuroimage* 2010;51:345-355. 17
18. Guo SS, Wu W, Chumlea WC, Roche AF. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. *Am J Clin Nutr* 2002;76:653-658. 18
19. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut□offs for thinness, overweight and obesity. *Pediatr Obes* 2012;7:284-294. 19
20. Garner DM. Eating Disorder Inventory2 professional manual. Odessa, FL: Psychological Assessment Resources, Inc. 1991. 20
21. Bradley MM, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. *J Behav Ther Exp Psychiatry*, 1994;25:49-59. 21

22. Scharmüller W, Übel S, Ebner F, Schienle A. Appetite regulation during food cue exposure: a comparison of normal-weight and obese women. *Neurosci Lett* 2012;518:106-110. 22
23. Davids S, Lauffer H, Thoms K, et al. Increased dorsolateral prefrontal cortex activation in obese children during observation of food stimuli. *Int J Obes* 2010;34:94–104. 24
24. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. *Jama* 2018;319:1723-1725.
25. Rangel A, Camerer C, Montague PR. A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci* 2008;9:545.
26. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron* 2006;51:871-882. 27
27. Derrfuss J, Brass M, Neumann J, von Cramon DY. Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. *Hum Brain Mapp* 2005;25:22–34. 28
28. Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci* 2000;23:475–483. 29
29. Wager TD, Jonides J, Reading S. Neuroimaging studies of shifting attention: a meta-analysis. *Neuroimage* 2004;22:1679–1693. 30
30. Downar J, Crawley AP, Mikulis DJ, Davis KD. The effect of task relevance on the cortical response to changes in visual and auditory stimuli: an event-related fMRI study. *NeuroImage* 2001;14:1256–1267. 53

31. Yokum S, Ng J, Stice E. Attentional bias to food images associated with elevated weight and future weight gain: an fMRI study. *Obesity* 2011;19:1775-1783. 33
32. Batterink L, Yokum S, Stice E. Body mass correlates inversely with inhibitory control in response to food among adolescent girls: an fMRI study. *Neuroimage* 2010;52:1696-1703.
33. Boswell RG, Kober H. Food cue reactivity and craving predict eating and weight gain: a meta□analytic review. *Obes Rev* 2016;17:159-177. 55
34. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *The Lancet* 2011;378:804-814. 56
35. Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci* 2011;15:37-46. 57
36. Polivy J, Herman CP. 2014. Eating in response to external cues. *Managing and Preventing Obesity: Behavioural Factors and Dietary Interventions* 2014;12:181-192. 58
37. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale food addiction scale. *Appetite* 2009;52:430-436. 52
38. Van Strien T, Frijters JER, Bergers GPA, Defares PB. The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. *Int J Eat Disord* 1986;5:295– 315. 51
39. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev* 2013;14:2-18.
40. Volkow ND, Wang GJ, Tomasi D, Baler RD. The addictive dimensionality of obesity. *Biol Psychiatry* 2013;73:811-818.

41. Barr SI, Janelle KC, Prior JC. Energy intakes are higher during the luteal phase of ovulatory menstrual cycles. *Am. J. Clin. Nutr* 1995;61:39–43. 65

42. Frank TC, Kim GL, Krzemien A,Van Vugt DA. Effect of menstrual cycle phase on corticolimbic brain activation by visual food cues. *Brain res* 2010;1363:81-92. 666

Table 1

Socio-demographic characteristics, BMI and percentage of fat for each group.

	Excess weight (n=38) Mean (SD[b])	Normal weight (n=39) Mean (SD)	t[c]/chi square[d]	p-value
Age	16.47 (1.66)	16.58 (1.36)	-0.30[c]	0.768
Sex (%men/women	47.37/52.63	48.72/51.28	0.00[d]	0.991
BMI[a]	29.89 (3.72)	21.36 (2.07)	12.58[c]	< 0.001
Fat (%)	29.03 (10.28)	15.61 (7.39)	6.56[c]	< 0.001

[a]: Body Mass Index; [b]: Standard Deviation; [c]: value of Student's t; [d]: value of Chi-square χ2

Table 2

Means (±SD) of food choices and self-reported measures (tasting, valence, arousal, percentage of appetizing choices, craving and hunger).

	Excess weight (n=37) Mean (SD)	Normal- weight (n=36) Mean (SD)	p-value
Appetizing food			
Food Tasting	7.59 (1.09)	7.74 (1.15)	0.571
Valence	6.45 (1.09)	6.58 (1.19)	0.633
Arousal	5.32 (1.63)	5.48 (1.45)	0.657
Craving	5.61 (1.29)	5.75 (1.49)	0.679
Plain food			
Food Tasting[a]	7.43 (1.06)	7.28 (1.08)	0.552
Valence	6.22 (1.04)	6.2 (1.19)	0.956
Arousal	5.15 (1.43)	5.23 (1.22)	0.801
Craving	5.35 (1.13)	5.26 (1.38)	0.745
Percentage of appetizing[b] choices	53.24 (20.57)	54.81 (18.97)	0.734
Appetizing vs. Plain Craving	0.26 (0.93)	0.49 (0.73)	0.238
Hunger1[c]	20.69 (21.2)	19.84 (18.9)	0.861
Hunger2[d]	18.42 (21.06)	27.7 (24.56)	0.102
Hunger3[e]	36.68 (27.67)	46.43 (28.15)	0.156

[a]: Catered tasting session; [b]: Percentage of appetizing choices when comparing to Plain food; [c]: Hunger evaluation before entering the resonance machine; [d]: Hunger evaluation before food-choice task; [e]: Hunger evaluation after fMRI task

Table 3

Brain regions that show greater activation in “appetizing versus plain choices > baseline” in excess weight group than in the normal weight group.

Region	Side	MNI coordinates			Ke[a]	t-value
		X	Y	Z		
dlPFC[b]	Right	32	34	36	133	4.12
	Left	-34	44	10	199	5.26
STCx[f]	Right	60	-20	2	364[c]	4.58
	Left	-52	-30	6	131	4.19
Hippocampus	Right	42	-16	-18	945[d]	4.46
MTC[g]	Right	46	-36	2	364[c]	4.37
Putamen	Right	34	-16	0	945[d]	4.34
SFCx[h]	Right	10	36	48	241	4.32
Thalamus	Right	10	-8	2	945[d]	4.3
	Left	-6	-20	0	152	3.82
GlobusPallidus	Left	-12	-2	-4	51	4.22
ITC[i]	Left	-60	-4	-18	93	4.15
OFC[j]	Right	38	48	-6	182[e]	4.13
vlPFC[k]	Right	30	30	-20	182[e]	3.96
Dorsal ACC[l]	Right	6	48	4	91	3.88
ACC	Left	-10	36	16	96	3.82
Insula	Right	40	6	-4	48	3.7
DorsalCaudate	Right	12	10	8	23	3.74

[a]: Cluster size (voxels); [b]: Dorsolateral Prefrontal Cortex; [c,d,e]: Part of the same cluster;[f]: Superior Temporal Cortex; [g]: Medial Temporal Cortex; [h]: Superior Frontal Cortex; [i]:Inferior Temporal Cortex; [j]: Orbitofrontal Cortex; [k:] Ventrolateral Prefrontal Cortex; [l]: Dorsal Anterior Cingulate Cortex.

Table 4

Correlations between craving scores (Appetizing vs. Plain Food Craving Ratings) and “appetizing versus plain choices > baseline” brain activation as a function of group. Only areas with significant correlations are displayed.

	Side	MNI coordinates			Excess weight		Normal weight		Fisher
		x	y	Z	p-value	r	p-value	r	p
dlPFC[b]	Left	-34	44	10	**0.04**	**0.35**	0.43	-0.136	**0.017**
	Right	32	34	36	**0.001**[a]	**0.53**	0.819	-0.04	**0.004**
TSC[c]	Right	60	-20	2	**0.003**[a]	**0.49**	0.84	0.035	**0.017**
TMC[d]	Right	46	-36	2	**0.04**	**0.34**	0.221	0.209	0.274
Putamen	Right	34	-16	0	**0.01**	**0.43**	0.385	0.149	0.097
TIC[e]	Left	-60	-4	-18	**0.03**	**0.38**	0.628	0.083	0.092
vlPFC[f]	Right	30	30	-20	**0.03**	**0.38**	0.388	0.148	0.145
Thalamus	Left	-6	-20	0	**0.02**	**0.4**	0.892	-0.023	**0.03**
ACC[g]	Left	-10	36	16	**0.009**	**0.44**	0.381	0.15	0.089
Insula	Right	40	6	-4	**0.03**	**0.38**	**0.049**	**0.33**	**0.405**
DorsalCaudate	Right	12	10	8	**0.004**[a]	**0.48**	0.738	0.058	**0.025**

[a]: These results survived FDR correction for multiple comparison;[b]: Dorsolateral Prefrontal Cortex; [c]: Temporal Superior Cortex; [d]: Temporal Medial Cortex; [e]: Temporal Inferior Cortex; [f]: Ventrolateral Prefrontal Cortex; [g]: Anterior Cingulate Cortex

Figure 1

Schematic representation of the fMRI task through depiction of the sequence of one experimental trial

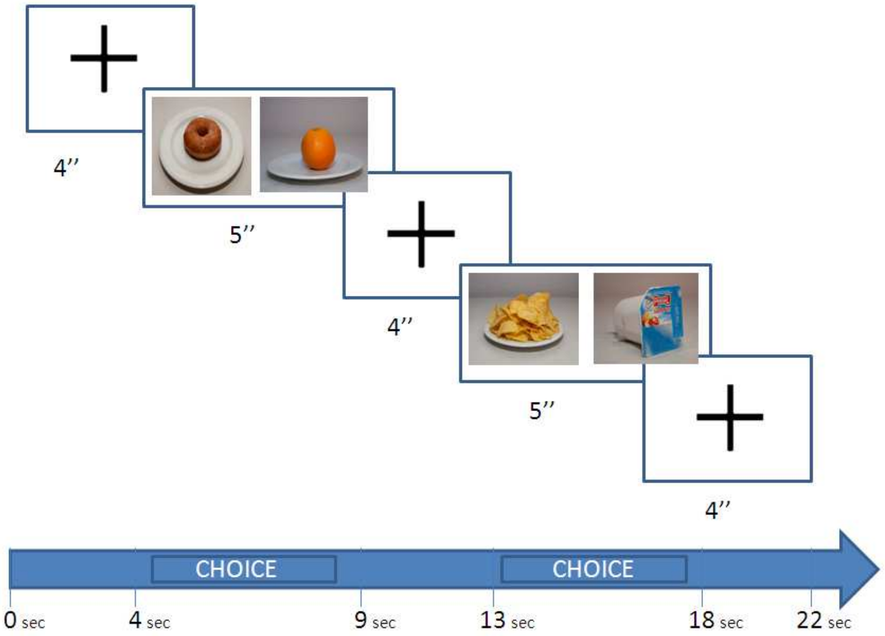
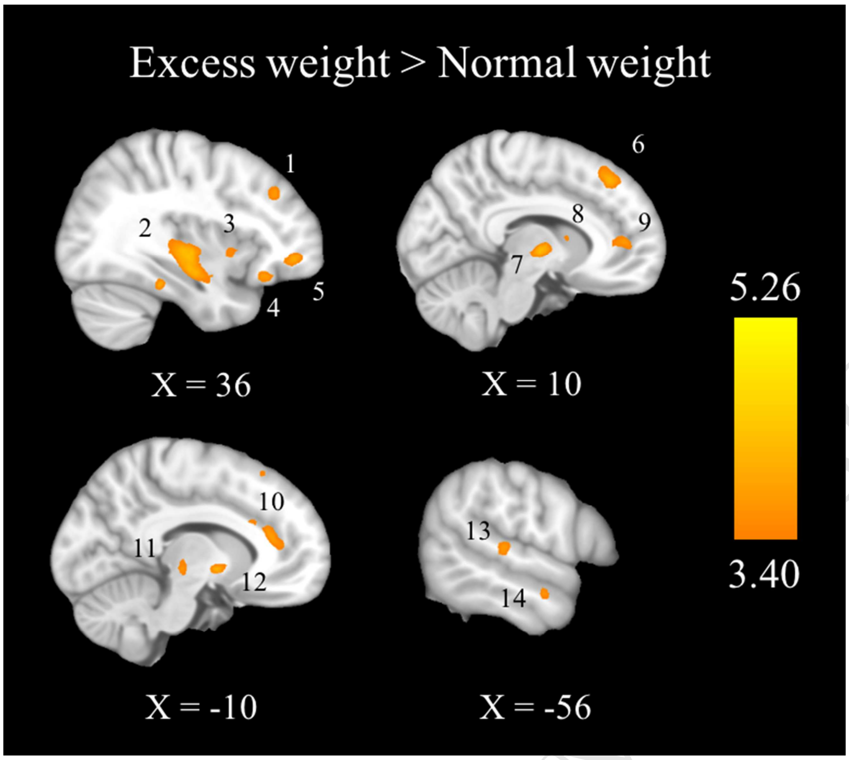


Figure 2

Between-group differences during "appetizing vs. plain > baseline" contrast.



1: dlPFC: dorsolateral prefrontal cortex; 2: Putamen; 3: Insula; 4: vlPFC: ventrolateral prefrontal cortex; 5: OFC: orbitofrontal cortex; 6: SFC: superior frontal cortex; 7: Thalamus; 8: Dorsal Caudate; 9: Rostral ACC: rostral anterior cingulate cortex; 10: ACC: anterior cingulate cortex; 11: Thalamus; 12: Globus Pallidus; 13: STC: superior temporal cortex; 14 ITC: inferior temporal cortex.