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Loss of lateral prefrontal cortex control in food-directed attention and goal-directed food choice in obesity

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ABSTRACT

Loss of lateral prefrontal cortex (lPFC)-mediated attentional control may explain the automatic tendency to eat in the face of food. Here, we investigate the neurocognitive mechanism underlying attentional bias to food words and its association with obesity using a food Stroop task. We tested 76 healthy human subjects with a wide body mass index (BMI) range (19–35 kg/m^2) using fMRI. As a measure of obesity we calculated individual obesity scores based on BMI, waist circumference and waist-to-hip ratio using principal component analyses. To investigate the automatic tendency to overeat directly, the same subjects performed a separate behavioral outcome devaluation task measuring the degree of goal-directed versus automatic food choices. We observed that increased obesity scores were associated with diminished lPFC responses during food attentional bias. This was accompanied by decreased goal-directed control of food choices following outcome devaluation. Together these findings suggest that deficient control of both food-directed attention and choice may contribute to obesity, particularly given our obesogenic environment with food cues everywhere, and the choice to ignore or indulge despite satiety.

Introduction

Obesity is reaching pandemic proportions and is associated with major health problems. Although many factors contribute to obesity, altered neural regulation of appetite has been repeatedly associated with body mass index (BMI) variation (Dagher, 2012). Through a lifetime of conditioned responses, high caloric foods act as strong rewards. This may lead to loss of control and the automatic tendency to overeat (Papies et al., 2008; Johnson, 2013), particularly in our obesogenic environment with an abundance of high caloric food cues. Individual differences in controlling the automatic tendency to eat when facing food cues, may therefore explain some variation in obesity. Lateral prefrontal cortex (lPFC) has been consistently associated with exercising control over food choices (Hare et al., 2009, 2011; Lopez et al., 2014) and regulating food craving (Giuliani et al., 2014; Silvers et al., 2014; Dietrich et al., 2016). However, obesity-related loss of lPFC-mediated attentional control in the face of food cues has not yet been shown.

In drug addiction, which is suggested to show neurocognitive parallels with obesity (Volkow et al., 2008, 2013; Hebebrand et al., 2014; but see Ziauddeen et al. (2012)), there is evidence for loss of attentional control in, for example, emotional color-naming Stroop tasks (Field and Cox, 2008; Hester and Luijten, 2014). In these tasks, the simple goal is to name the color of a word as fast and accurately as possible. When words are related to their target of abuse, and thus highly salient, individuals are generally distracted from their goal, resulting in an attentional bias to those words reflected by slower response times. In substance addiction, attentional bias has been found to correlate with craving and drug use severity (Franken, 2003; Field and Cox, 2008), as well as with altered lateral and medial prefrontal and striatal (e.g. putamen) responses (Chase et al., 2011; Hester and Luijten, 2014). In addition, BOLD responses in putamen for smoking-related attentional bias were found to correlate positively with craving in smokers (Luijten et al., 2011). Similar to addiction, using a color-naming Stroop task, attentional bias to palatable food words has been related to (future) obesity in children and adults (Braet and Crombez, 2003; Calitri et al., 2010). However, two other studies have not found a relationship between attentional bias to food words and obesity (Nijs et al., 2010a; Phelan et al., 2011). The neural mechanisms underlying attentional bias to food words and their relation to obesity has not yet

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been investigated, and could shed light on these inconsistent behavioral findings.

Attentional bias is often interpreted as decreased control over the automatic tendency to attend to salient cues, possibly leading to craving and habitual intake (Field et al., 2009). However, the automatic tendency to attend to salient cues is different from automatic, or habitual, choices when faced with these cues. The latter can be measured more directly with instrumental tasks implementing an outcome devaluation procedure. Such tasks have revealed that habitual behavior, as opposed to goal-directed control, in animals and humans is associated with responses in dorsolateral striatum (i.e. putamen) (Tricomi et al., 2009; Balleine and O'Doherty, 2010) and with reduced white matter strength between putamen and premotor cortex in humans (de Wit et al., 2012). However, whether increased food attentional bias is paralleled by the failure to exert goal-directed control during food choices is unknown. Here, we investigated these two types of control as a function of obesity.

Our aim was to investigate the neurocognitive mechanisms underlying food attentional bias and choice. We tested 76 healthy human subjects with a wide body mass index range (19–35 kg/m^2) using fMRI, while performing a food Stroop task (Nijs et al., 2010a). We hypothesized that increased obesity would be related to a stronger behavioral and neural attentional bias to food words. Increased neural food attentional bias would be reflected in reduced lPFC-control and perhaps altered lPFC-connectivity with putamen, associated with habitual behavior. In addition, we included a separate behavioral outcome devaluation task (adapted from Hogarth et al. (2012)) to measure the degree to which subjects make goal-directed versus automatic food choices. We hypothesized that enhanced attentional bias effects would be paralleled by decreased goal-directed – and thus increased automatic – food choices with increased obesity.

Materials and methods

Subjects

The reported results are based on data from 76 healthy right-handed subjects (65 women; mean age: 31.5 years old, SD: 10.7, range: 18–53; mean BMI: 26.4 kg/m^2, SD: 3.8, range: 19–35) with adequate demand of Dutch and with normal or corrected-to-normal vision. Subjects were recruited from Nijmegen and surroundings through advertisement. To be eligible for the study, subjects were required to be motivated to change their eating habits (not per se losing weight, but also targeting unhealthy snacking or irregular eating patterns), as this study was part of a larger protocol including a behavioral intervention program to change eating habits. Here, only data acquired prior to the intervention are presented. Subjects were excluded from participation if they reported any (history of) clinically relevant neurological or psychiatric disorders, current psychological treatment, current use of psychotropic medication, (history of) taste or smell impairments, eating disorders (including binge eating disorder), extremely high restrained eating scores (Dutch Eating Behaviour Questionnaire, males≥4.0, females≥3.6; van Strien et al. 1986), current dieting (i.e. following a strict diet to lose weight and/or being in treatment with a dietitian), changes in body weight > 5 kg during the last two months, and contra-indications for MRI. Following scanning, seven subjects (3 males, 4 females) were excluded from the analyses due to: being extreme outliers in terms of task performance (n=3; see Behavioral Analyses below), bad image quality (n=2; excessive signal intensity spikes and signal dropout), incidental finding (n=1), and no longer meeting the inclusion criteria due to a concussion (n=1). All subjects provided written informed consent, which was approved by the regional research ethics committee (Commissie Mensgebonden Onderzoek, regio Arnhem-Nijmegen, Registration Number: 2013/188, Date: 20 June 2013), and received financial compensation for participation.

Obesity score

As a measure of obesity we calculated an obesity score, which reflects common variance in three highly correlated variables that have been related to degree of obesity and the associated health risks: body mass index (BMI), waist-to-hip ratio (WHR) and waist circumference (all r's > 0.4, all p-values < 0.001) (Huxley et al. 2009). We z-scored these variables and ran principal component analysis on the z-scored variables using the built-in function 'princomp' in MATLAB (version 7.9.0, Mathworks, Natick, MA) for reducing the number of correlated variables under consideration whilst retaining most of the information in the data (Jolliffe 2002). We then selected the first principal component, which explained 80.1% of the common variance in these measures. Finally, to correct the resulting score for gender and age, which are known to co-vary with obesity, we regressed them against the first principal component and saved the unstandardized residuals as the obesity score.

Procedure

Test sessions started at 11 a.m. or 12:30 p.m. and lasted approximately 3.5 h. Subjects were asked to refrain from eating and drinking anything else than water 4 h prior to testing. They were also asked to abstain from recreational drugs one week, and from alcohol 24 h prior to testing. Compliance was assessed by administering a self-report compliance questionnaire. The tasks described below were part of a larger protocol and were performed approximately 1 h after the start of the test session. The order of the tasks was the same across subjects. All tasks were programmed with Presentation software (Version 16, Neurobiobehavioral Systems, Inc.).

Weight (in kg), height (in cm), and waist and hip circumference (in cm) were measured at the start of the test session. During scanning, subjects performed a color-naming Stroop task to assess attentional bias. Before the task started, they rated how hungry they felt using a visual analogue scale ranging from 0 (not hungry) to 10 (very hungry) on the screen. After scanning, subjects performed a food-choice satiety task to assess the degree of goal-directed control over their choices after outcome devaluation. In between these tasks, subjects also performed an incentive delay task in the scanner in which small monetary and caloric rewards could be earned. This task was programmed such that the accumulative earnings were similar across subjects. Data from the incentive delay task are not reported here. On a separate intake session prior to the test days, subjects were screened for exclusion criteria, rated the Stroop words (see below), and the Dutch version of the National Adult Reading Test (NART) was administered to assess education level ranging from 0 (no degree) to 7 (college degree) (M: 6.3, SD: 0.6, range: 5–7) and verbal IQ (M: 104.7 SD: 9.9, range: 83.0–127.0) (Schmand et al. 1991).

Paradigms

Stroop task

Subjects were instructed in the Stroop task before going into the scanner and were further familiarized with the task by practicing the color-button contingency and performing 10 practice trials with feedback (correct/incorrect) in the scanner. For task details see Fig. 1A. In short, subjects had to indicate the color of the word presented on the screen pressing the button reflecting that color as fast and accurately as possible. Subjects were presented with food, positively valenced emotional and neutral words. All task stimuli were presented with a digital projector on a screen at the back end of the MRI scanner bore, which was visible via a mirror mounted on the head coil. Responses were made using an MRI-compatible button box. Twenty generally high-calorie, palatable food words were selected from word lists reported in previous studies (Nijs et al. 2010a; Phelan et al. 2011). Twenty positively valenced emotional words were selected from the Dutch

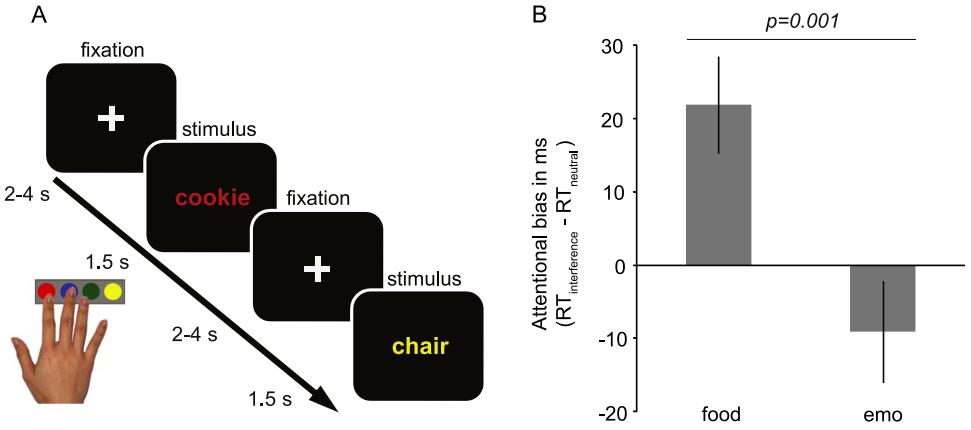

Fig. 1. Food Stroop task. (A) On each trial, subjects had to name the color of the word presented in the center of the screen as fast and accurately as possible by pressing one of four buttons using their right hand. The buttons reflected the four colors in which the words could be displayed (i.e. red, blue, yellow or green). Button-color contingencies remained the same throughout the task and were counterbalanced across subjects. Subjects were presented with interference words (i.e. 20 food and 20 positively valenced emotional words), and matched neutral words in an event-related design. During scanning, each word was presented twice, and always in a different color, resulting in 160 trials and a task duration of approximately 10 min. Halfway, subjects had a 30-s break. Each trial consisted of a jittered fixation period of 2–4 s (drawn from a Poisson distribution, mean=2.6 s) followed by a colored word, which remained on the screen for 1.5 s. No feedback was given. The order of words was pseudorandomized and counterbalanced across subjects. (B) Behavioral attentional bias for food and positively valenced emotional (emo) words versus neutral words. Error bars represent 1 SEM.

Words Database (Moors et al. 2013) based on reported arousal and positive valence ratings (> 5). Forty neutral words with low arousal and positive valence ratings (3–5) were selected from the same database. Food and emotional words were matched to twenty neutral words each in terms of word length, number of syllables and frequency of use according to the SUBTLEX-NL norms (Keuleers et al. 2010). On the intake session, subjects rated all stimuli in terms of arousal (from not arousing to highly arousing) and valence (from negative to positive) using visual analogue scales to confirm that the food and emotional words were rated higher than neutral words (see Supplemental materials).

Food-choice satiety task

Following scanning, subjects performed a food-choice satiety task (adapted from Hogarth et al. (2012)) outside the scanner that was presented on a computer screen. The food-choice satiety task is an outcome devaluation task consisting of three phases (i.e. training, devaluation and test (nominal extinction)) and measures changes in snack choices after sensory-specific satiety in terms of devaluation magnitude (%choices training phase-%choices test phase). For task details see Fig. 4A. A high devaluation magnitude shows that subjects adjusted their choice behavior after devaluation of the snack, whereas a score around zero shows that subjects did not adjust their behavior, signaling reduced goal-directed control over their choices following sensory-specific satiety. Unbeknownst to subjects, we calculated the amount of kilocalories (kcal) consumed by weighting the bowl before and after the satiation phase, and by multiplying the amount of grams consumed by the amount of kcal/gram of that particular snack. Before the devaluation phase we asked subjects again how hungry they felt on a scale from 0 (not hungry) to 10 (very hungry).

Behavioral analyses

Mean reaction times (RTs) and accuracies on the Stroop task, as well as valence and arousal ratings, were analyzed using repeated measures ANOVA (SPSS 19, Chicago, IL) with Condition (interference, neutral) and Type (food, emotional) as within-subject factors. The interaction with degree of obesity was analyzed by adding Obesity score as a continuous covariate of interest to the model. Devaluation magnitude (%choices training - test phase) on the food-choice satiety task was analyzed using non-parametric statistics because the assumption of normality was violated. We used one-sample Wilcoxon signed rank test to test whether median devaluation magnitude was significantly greater than 0 (i.e., goal-directed rather than automatic choices) and Spearman's rho (r_s) to investigate the relationship with Obesity score.

Subjects who were outliers in terms of response times when color-naming words (i.e., > 3 SD above the mean for each condition; n=2), Stroop accuracies (i.e., accuracy=50%; n=1), or devaluation magnitude in the food-choice satiety task (i.e., > 3 SD above the mean; n=1) were excluded from the corresponding analyses. Grubb's test (also known as the maximum-normed residual test; Barnett and Lewis (1994)) was used to identify outliers.

Imaging and fMRI analyses

To measure blood oxygen level dependent (BOLD) contrast, whole-brain functional images were acquired on a Siemens 3T Skyra MRI scanner (Siemens Medical system, Erlangen, Germany) using a 32-channel coil. A multi-echo echo-planar imaging (EPI) sequence was used to acquire 34 axial slices per functional volume in ascending direction (voxel size 3.5×3.5×3 mm; repetition time (TR) 2070 ms; TE 9 ms, 19.25 ms, 29.5 ms, and 39.75 ms; flip angle 90°; field of view 224 mm). This is a method that uses accelerated parallel imaging to reduce image artifacts (in plane acceleration 3) and acquire images at multiple TEs following a single excitation (Poser et al. 2006). Before the acquisition of functional images, a high-resolution anatomical scan was acquired (T1-weighted MPRAGE, voxel size 1×1×1 mm, TR 2300 ms, TE 3.03 ms, 192 sagittal slices, flip angle 8°, field of view 256 mm).

Data were pre-processed and analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm). The volumes for each echo time were realigned to correct for motion (estimation of the realignment parameters was done for the first echo and then copied to the other echoes). The four echo images were combined into a single MR volume based on 31 volumes acquired before the actual experiment started using an optimised echo weighting method (Poser et al., 2006). Combined functional images were slice-time corrected by realigning the time-series for each voxel temporally to acquisition of the middle slice. Structural and functional data were then co-registered and spatially normalised to a standardized stereotactic space (Montreal Neurological Institute (MNI) template). After segmentation of the structural images using a unified segmentation approach, the mean of the functional images was spatially coregistered to the bias-corrected structural images. The transformation matrix resulting from segmentation was then used to normalize the final functional images into MNI space (resampled at voxel size 2×2×2 mm). Finally, the normalised functional images were spatially smoothed using an isotropic 8 mm full-width at half-maximum Gaussian kernel.

Statistical analysis of fMRI data was performed using a general linear model (GLM) approach. At the first level, subject-specific data were analysed in an event-related design using a fixed effects model, which included four regressors of interest that reflected the onset of presentation of *food*, neutral matched to food (*fneu*), emotional (*emo*), and neutral matched to emotional (*eneu*) words. Incorrect responses and misses were modeled in two separate regressors. All onsets were modeled using a stick function and convolved with the canonical hemodynamic response function. Time and dispersion derivatives of the hemodynamic response function were included, as well as out-of-brain signal variation. To account for head movement the six movement parameters resulting from the realignment procedure and their six time derivatives were included. High pass filtering (128 s) was applied to the time series of the functional images to remove low-frequency drifts and correction for serial correlations was done using an autoregressive AR(1) model.

We investigated whole-brain group effects in a random effects analysis (second level). To investigate the main task effect of Condition (interference, neutral), we contrasted food to neutral activations (food-fneu), and emotional to neutral activations (emo-eneu) across all subjects. To investigate the interaction between the Condition (interference, neutral) and Type (food, emo), we contrasted food to neutral activations versus emotional to neutral activations ([food-fneu]-[emo-eneu]). In a separate analysis, we investigated the relationship between obesity and our effect of interest (food-fneu) by adding obesity score as a covariate on the second level in line with our behavioral analyses. Statistical inference (pFDR < 0.05) was performed at the peak-level, correcting for multiple comparisons over the search volume, i.e. whole brain or *a priori* defined small search volume: lateral prefrontal cortex (i.e. combination of left and right superior frontal gyrus (dorsolateral), middle frontal gyrus and inferior frontal gyrus (opercular, triangular and orbital parts) from the Automated Anatomical Labeling (AAL) atlas; Tzourio-Mazoyer et al. (2002)). The intensity threshold necessary to determine the peak-level threshold was set at $p < 0.001$, uncorrected. Upon significant effects, we extracted the mean betas from the significant functional cluster within the lPFC search volume and correlated them with the behavioral food attentional bias effect.

In addition, we performed a generalized psychophysiological interaction (gPPI; McClaren et al., 2012) analysis to investigate obesity-related differences in functional connectivity with lateral prefrontal cortex. As a seed, we used the region of lateral prefrontal cortex activated in the main effect for food words (food-fneu) masked by the interaction between food and emotional words ([food-fneu]-[emo-eneu]) extracted at intensity threshold $p < 0.001$ (uncorrected). The rationale for this approach was that the seed should be a task-specific region involved in attentional bias for food words. To further enhance the task specificity and reduce the extent of the seed, we specifically selected a task-related region in lateral prefrontal cortex that was more activated for food (versus neutral) words than for emotional (versus neutral) words (Fig. 2C). To estimate the neural activity producing the physiological effect in the seed region for each subject, the BOLD signal was extracted from this region and deconvolved (Gitelman et al., 2003). This was included in the model as the physiological regressor, as were the onset times for each of the task conditions (food, fneu, emo and eneu words), and the psychophysiological interaction was entered by multiplying the estimated neural activity by the onset times for each of the task conditions separately convolved with the HRF, resulting in nine regressors of interest on the first level (i.e., one physiological, four psychological, and four interaction regressors). Two PPI contrasts were created for each subject: food-fneu, and the interaction effect [food-fneu]-[emo-eneu]. On the second level, these PPI contrasts were analyzed separately using a one-sample t-test with obesity score again as a continuous covariate of interest. Statistical inference (pFDR < 0.05) was performed at the peak-level, correcting for multiple comparisons over the a priori defined small search volume: bilateral putamen (AAL atlas; Tzourio-Mazoyer et al. (2002)). The intensity threshold necessary to determine the peak-level threshold was set at $p < 0.001$, uncorrected. We extracted mean betas from a functional region of interest based on an independent contrast (i.e. main task contrast: food-fneu, at threshold $p < 0.001$), and subsequently correlated them with the obesity score and the behavioral food attentional bias effect.

Results

Behavioral attentional bias

All subjects were included in the analyses of the color-naming Stroop task (n=76). We observed an attentional bias effect in RTs for food words, relative to emotional words (Condition (interference, neutral)×Type (food, emotional): $F(1,74)=11.038$, $p=0.001$) (Fig. 1B). Specifically, subjects were slower to name the color of food relative to neutral words ($F(1,74)=10.950$, $p=0.001$), but not slower to name the color of positively valenced emotional relative to neutral words ($F(1,74)=1.903$, $p=0.172$). We did not observe a 3-way interaction between Condition, Type and Obesity ($F(1,74)=0.290$, $p=0.592$). However, we did find an interaction between Condition and Obesity ($F(1,74)=4.677$, $p=0.034$), suggesting that obesity was associated with a differential response to interference words (food+emo) versus neutral words (fneu+eneu), although this was not driven by any significant simple effects (main effect Obesity: interference: $F(1,74)=0.983$, $p=0.325$; neutral: $F(1,74)=3.519$, $p=0.065$). There was no main effect of Obesity for both RTs and accuracies, suggesting that performance was unrelated to obesity scores (Table 1), neither did the behavioral food attentional bias effect correlate with the observed neural effects described below (Table S1). There were no correlations between obesity scores and valence or arousal ratings of the Stroop words (Table S1).

Subjects reported moderate hunger prior to the Stroop task (M: 5.9, SD: 2.5, range: 0–9.4), which showed a trend towards correlating negatively with obesity score ($r_s=-0.214$, $p=0.066$). Feelings of hunger have previously been associated with increased food attentional bias (Nijs et al. 2010b). However, we did not find such a correlation ($r_s=-0.148$, $p=0.201$) (Table S1).

Neuroimaging results

Neural attentional bias

First, we investigated the neural network involved in the attentional bias to food and emotional words. BOLD responses in frontoparietal, temporal, and cerebellar regions were significantly increased for food relative to neutral words (Fig. 2A; Table 2). In addition, we found a significant interaction effect when contrasting activation in response to food relative to emotional ([food-fneu]-[emo-eneu]) words in left angular gyrus (Fig. 2B; Table 2). No significant clusters were found for positively valenced emotional relative to neutral words, which is in line with the absence of a behavioral attentional bias to the emotional words. Also, in contrast to the behavioral Condition×Obesity interaction reported above, we observed no such interaction at the neural level in a *post hoc* analysis ([food+emo]–[fneu+eneu]).

Second, we investigated the interaction between neural responses to food words and obesity score, and found that BOLD responses in left superior frontal gyrus (BA9/8) during food attentional bias (food-fneu) correlated negatively with obesity score (Fig. 3A and B; Table 2). For the interaction contrast ([food-fneu]-[emo-eneu]) we found no correlation with obesity score.

Functional frontostriatal connectivity

To investigate the relationship between functional connectivity with lPFC and obesity scores, we performed generalized PPI analysis. As a seed we used the region of lPFC (BA8/6) that showed greater responses for food than neutral words (food-fneu), masked by the interaction effect between food and emotional words ([food-fneu]-[emo-eneu]) to increase the specificity to food words and to confine the number of

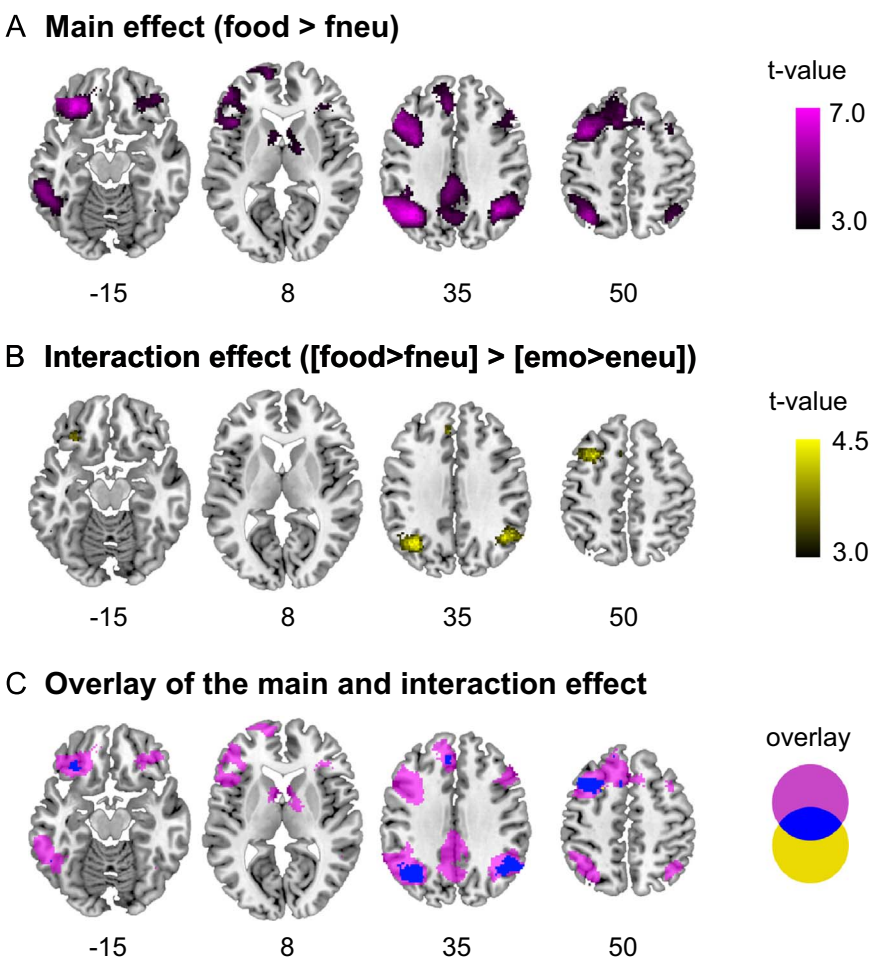

Fig. 2. Neural attentional bias effect. (A) Contrast of food versus matched neutral words (food > fneu). (B) Contrast of food minus matched neutral versus positively valenced emotional minus neutral words ([food > fneu] > [emo > eneu]). (C) Overlay of (A) in violet and (B) in yellow to show the overlap in activation maps in blue. All statistical parametric maps were overlaid onto a T1-weighted canonical image. Images are shown in neurological convention (left=left) and with axial slice coordinates as defined in MNI152 space. For illustrative purposes full brain statistical parametric maps were thresholded at $p < 0.001$ (uncorrected).

voxels of the seed (Fig. 2C). Note that this region was located more posterior in lPFC (BA8 extending into premotor cortex (BA6)) than the region in left superior frontal gyrus (BA9/8) that showed a significant interaction between neural responses to food attentional bias and obesity score (see Fig. 3A). This seed region did not show a correlation with obesity ($r=-0.153$, $p=0.188$; $r_s=-0.192$, $p=0.097$). On a low threshold ($p < 0.001$ uncorrected) we found that obesity score was related to increased functional connectivity between this more posterior region in lPFC and left posterior putamen during food attentional bias (peak-coordinates [x,y,z]: [−26,−12,6], k=1, t-value: 3.26). However, this did not survive the appropriate corrections for multiple comparisons (i.e., FDR < .05, peak level), neither did a *post hoc* analysis show a significant correlation between the obesity score and premotor-connectivity in the bilateral, anatomical putamen region of interest ($r=0.014$, $p=0.903$; $r_s=0.114$, $p=0.327$).

Outcome devaluation effect

Finally, we investigated whether the observed neural effects during food attentional bias would be accompanied by decreased goal-directed, i.e. increased automatic, food choices in subjects with increased obesity scores. We measured automatic behavioral tendencies by assessing the degree of goal-directed control over food choices on an instrumental outcome devaluation paradigm, i.e. a food-choice satiety task.

The reported results for the food-choice satiety task are based on data from 76 subjects. Two subjects did not perform the task. One other subject was an outlier in terms of devaluation magnitude and was therefore excluded (see Materials and Methods). Note that the outliers

Table 1
Raw data of the Stroop task for low versus high obesity scores.

	Food words		Emotional words		Neutral words	
	M(SEM)	Range	M(SEM)	Range	M(SEM)	Range
Response time (in ms)	841.4 (11.4)	648.0–1110.4	816.0 (10.8)	625.5–1045.1	822.3 (11.3)	630.7–1168.7
Accuracy (in %)	95.2 (0.5)	80–100	95.8 (0.5)	80–100	95.9 (0.4)	76–100
Arousal[a] (not arousing(1)-very arousing(100))	44.4 (2.3)	0–76.9	65.1 (2.0)	12.6–91.1	23.0 (2.0)	0–63.2
Valence[a] (negative(1)-positive(100))	60.2 (1.4)	25.2–80.9	84.4 (0.9)	64.5–98.6	51.1 (0.4)	37.3–58.1

Values represent mean (SEM) and range.
[a] Arousal and valence ratings were available for n=75.

Table 2
Summary of brain regions exhibiting main and interaction task effects, and interactions with obesity score.

Region	Side (L/R)[a]	MNI-coordinates x, y, z (mm)			Size (# voxels)	pFDR (voxel-level)	t-Value (peak)
Main effect Food > Neutral							
Angular gyrus	L	−36	−62	38	2933	< 0.001	8.02
Angular gyrus	L	−44	−60	34		< 0.001	6.84
Supramarginal gyrus	L	−58	−52	30		< 0.001	6.78
Middle temporal gyrus	L	−56	−38	−8	1510	< 0.001	7.04
Middle temporal gyrus	L	−48	−42	−6		0.009	5.41
Inferior temporal gyrus	L	−48	−52	−14		0.045	4.73
Inferior orbitofrontal cortex	L	−30	32	−10	8218	< 0.001	7.03
Precentral gyrus	L	−34	10	44		0.001	6.60
Middle orbitofrontal cortex	L	−22	34	−14		0.001	6.35
Angular gyrus	R	38	−58	34	1808	0.001	6.59
Inferior parietal cortex	R	38	−52	40		0.002	6.02
Angular gyrus	R	46	−48	30		0.003	5.88
Middle temporal gyrus	R	60	−42	−2	475	0.009	5.41
Middle temporal gyrus	R	54	−34	−8		0.036	4.84
Inferior frontal gyrus	R	52	34	24	1125	0.012	5.31
Inferior frontal gyrus	R	44	30	24		0.012	5.30
Inferior frontal gyrus	R	34	26	18		0.044	4.75
Middle cingulum gyrus	L	−4	−34	36	1388	0.018	5.14
Precuneus	L	−6	−64	40		0.021	5.07
Posterior cingulum gyrus	L	−4	−42	32		0.024	5.01
Cerebellum	R	14	−84	−34	377	0.036	4.83
Inferior orbitofrontal cortex	R	30	30	−20	238	0.041	4.77
Interaction effect [Food > Neutral] > [Emo > Neutral]							
Angular gyrus	L	−34	−62	38	564	0.044	5.66
Interaction effect [Food > Neutral]×Obesity score[b]							
Middle frontal gyrus	L	−28	32	50	53	.030	4.49

[a] L=left, R=right.
[b] p < 0.05, small volume, FDR corrected.

on the Stroop task were no outliers on this task and were therefore included in the analyses reported below. Across the group, we observed a significant devaluation effect (Fig. 4B; Wilcoxon signed rank test, p < 0.001), suggesting that subjects generally adjusted their choices following devaluation, which is a sign of goal-directed (as opposed to automatic) choice behavior. Importantly, we found that devaluation magnitude was significantly decreased with increased obesity scores (Fig. 4C; r_s=−0.325, p=0.004). Thus, higher obesity scores were associated with less goal-directed control over food choices. The group difference in devaluation magnitude could not be explained by the amount of kilocalories consumed in the devaluation phase (M: 307.7, SD: 222.0, range: 31.3–1800.7), as this was not related to obesity score (r_s=0.142, p=0.223), nor did the amount of kilocalories consumed correlate with devaluation magnitude (r_s=−0.060, p=0.607). Before the devaluation phase, subjects still reported moderate feelings of hunger (M(SD): 6.9(2.2)), which was not correlated with obesity score, devaluation magnitude or amount of kilocalories consumed during devaluation (all p's > 0.11).

Between-task correlations

Despite the differences in stimuli and outcomes between the tasks in this study, we ran *post hoc* (non-parametric) correlational analyses to investigate the relationship between devaluation magnitude and the observed behavioral and neural food Stroop effects, as well as correlations with possible confounding factors such as arousal and valence ratings of the Stroop words, hunger ratings, and the amount of kilocalories consumed in the food-choice satiety task. However, no significant between-task correlations were found (Table S1).

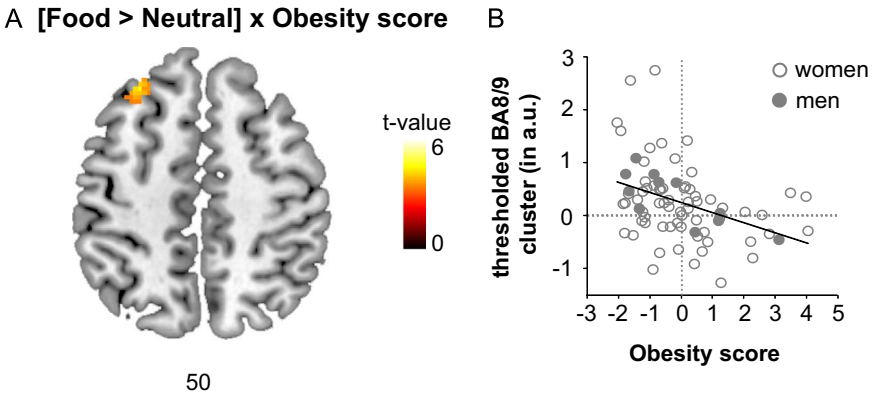

Fig. 3. Obesity-related neural attentional bias effect. (A) Whole brain effect of obesity score on BOLD responses when color-naming food versus neutral words (food > fneu) (p=0.030). Image is shown in neurological convention (left=left) and with axial slice coordinate as defined in MNI152 space. The statistical parametric map was thresholded at p < 0.001. For illustrative purposes the extracted betas are shown in (B). Increased obesity score was associated with diminished BOLD responses in left lPFC (BA9/8) when color-naming food versus neutral words. In the scatter plot open circles (o) represent females, filled circles (•) represent males.

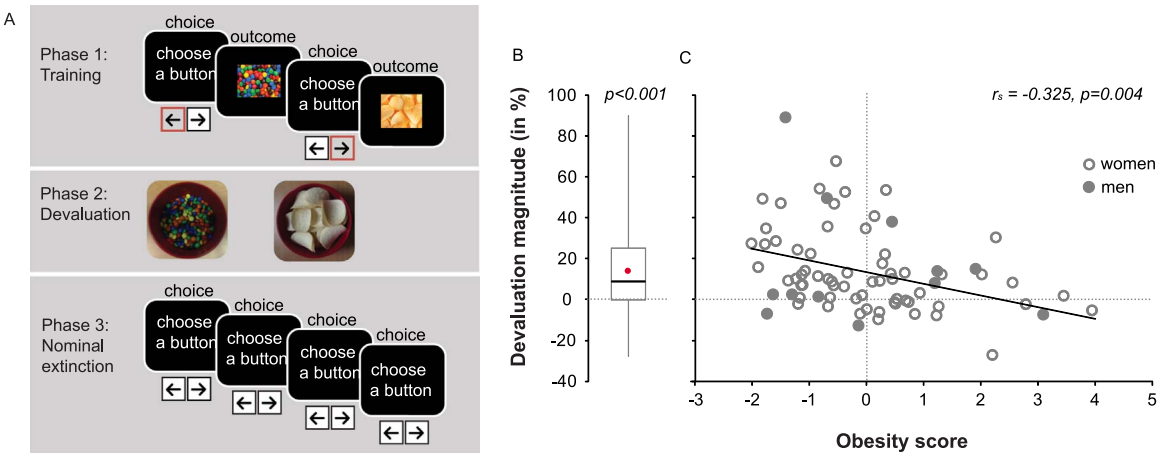

Fig. 4. Food choice satiety task. A) In phase one (i.e., training), subjects were instructed to choose between a left or right button press on each trial (80 trials, approximate duration: 10 min). Each of the two buttons was associated with either a sweet or salty snack that they could win in 50% of the trials. Prior to the task, subjects selected their preferred sweet snack (wine gums, Skittles or chocolate M & M's) and salty snack (Pringles (original), TUC-crackers (paprika) or cocktail nuts). Immediately after the training phase, subjects received 1/5 of their winnings and consumed the snacks. Key-reward assignment was counterbalanced across subjects, and learnt by trial and error. Responding was self-paced. In phase two (i.e., devaluation), a bowl filled with one of the snacks was placed in front of the subjects, and they were asked to eat to satiation. Which reward they were satiated on (sweet or salty) was counterbalanced across subjects. The duration of phase two was self-paced and varied between 2 and 18 min (M(SD): 7.6(3.3) minutes). Phase three (i.e., test) was similar to phase one (72 trials, approximate duration: 8 min), except that no direct feedback was delivered (i.e., nominal extinction). Subjects again received 1/5 of their winnings afterwards, of which they were informed beforehand. Devaluation magnitude was calculated by subtracting the percentage of the devalued snack in phase 1 and 3 (%choices training phase-%choices test phase), and reflected how well subjects adjusted their choice behavior after devaluation of the snack. (B) On average subjects adjusted their food choices after devaluation as reflected in the median devaluation magnitude (black line) that was significantly greater than 0 (Wilcoxon signed rank test, $p < 0.001$). The red dot represents the mean. (C) Increased obesity score was related to decreased devaluation magnitude across the sample (r_s=−0.325, p=0.004). In the scatter plot open circles (o) represent females, filled circles (•) represent males.

Discussion

In this cross-sectional study we aimed to unravel the neurocognitive mechanism underlying food attentional bias and choice. More specifically, we determined whether lPFC responses and connectivity during attentional bias to food words are associated with obesity, and whether we could find evidence of decreased goal-directed control of food choice in the same subjects. Our findings suggest that higher degree of obesity is associated with reduced control over both attention as well as choice in the face of food. We found that high obesity scores were associated with diminished lPFC BOLD-responses in left superior frontal gyrus (BA9/8) during food attentional bias relative to subjects with low obesity scores. We also found reduced goal-directed, and thus more automatic food choices with increased obesity scores on a separate outcome devaluation task, which was not correlated with loss of lPFC-based attentional control.

Our neural effects are generally consistent with literature showing that activation of lateral prefrontal cortex predicts the ability of individuals to exercise self-control on food choices (Hare et al., 2009, 2011; Lopez et al., 2014). For example, Hare et al. (2009) found greater left dorsolateral prefrontal BOLD-responses when dieters successfully controlled their food choices relative to when they failed to do so. In another study, successful weight-loss maintainers showed greater BOLD-responses to food pictures in left superior frontal gyrus than both obese and normal-weight controls not restraining their food intake (McCaffery et al., 2009). Diminished lateral prefrontal activity has also been related to greater BMI when regulating craving responses in both adults (Giuliani et al., 2014) and children (Silvers et al., 2014), and when inhibiting prepotent responses to appetizing foods in adolescents (Batterink et al., 2010). Furthermore, a meta-analysis by Jansen et al. (2013) showed that non-invasive stimulation of dorsolateral prefrontal cortex can reduce craving to food and other substances of abuse. In this context, and given the addiction model of Franken (2003), which explains craving in terms of attentional bias, our finding of diminished lPFC activation may reflect decreased attentional control in more obese subjects when attentional bias to food words needs to be overcome.

We did not find a larger behavioral attentional bias to food words for subjects with increased obesity scores as we had hypothesized. This is inconsistent with previous studies that did find a relationship between (future) BMI and attentional bias to food words (Braet and Crombez, 2003; Calitri et al., 2010). However, some other studies also did not find a difference in attentional bias to food words between healthy weight and overweight/obese individuals when using a food Stroop task (Nijs et al., 2010a; Phelan et al., 2011). These mixed results in obesity are in contrast to more consistent behavioral drug attentional bias effects in addicts (for a review see Field and Cox (2008)). In spite of the suggested similarities in the underlying neurocognitive mechanism of obesity and addiction (Volkow et al., 2008; Volkow et al., 2013; Hebebrand et al., 2014), a key difference should be noted in the saliency of the used stimuli. Everyone in the Western world is conditioned for high caloric foods, whereas being conditioned for drug cues only applies to substance users. It is therefore not surprising that group differences in attentional bias to substance-related words are generally shown for addicted versus non-addicted individuals who are not conditioned for these cues (with the exception of alcohol). Differences in food attentional bias between individuals may be more subtle and have been shown to depend on factors such as craving as well as worry towards high caloric foods rather than obesity per se (Werthmann et al., 2015). For example, individuals who strongly restrain their food intake and are preoccupied to maintain a healthy weight or lose weight also show behavioral food attentional bias (Papies et al., 2008; Hollitt et al., 2010). In the current sample, all subjects were motivated to change their eating habits independent of their BMI, and were therefore likely to be more preoccupied with healthy eating habits and a healthy weight. This may explain why we do not find obesity-related differences in attentional bias to food words. Although a limitation of the study is that we did not systematically record preoccupation, or the intention to change eating habits. Despite the absence of an attentional bias to food stimuli in terms of reaction times, we show that the neural measures underlying the process of overcoming food attentional bias may be better associated with obesity.

Attentional bias is often interpreted as decreased control over the automatic tendency to attend to salient cues, possibly leading to craving and habitual intake (Field et al., 2009). However, the links between attentional bias and craving or habitual intake are indirect. In

order to address whether increased food attentional bias is paralleled by the failure to exert goal-directed control during food choices more directly, we administered a separate instrumental outcome devaluation task to the same subjects. We extend previous findings by Horstmann et al. (2015) who showed decreased goal-directed food choices following sensory-specific satiety with increased BMI in a group of exclusively male subjects, whereas our sample consisted predominately of female subjects. However, we observed no correlations between goal-directed food choices and either the neural or behavioral food attentional bias effect in a relatively large sample. A likely explanation is that the food words in the Stroop task are not associated with a particular response, therefore, the task cannot assess instrumental habit-like behavior, such as automatic food choice. This concurs with the present absence of significant obesity-related differences in functional connectivity between premotor cortex and putamen during this non-instrumental food attentional bias task. One might rather expect to find obesity-related differences in connectivity with putamen for the outcome devaluation task, in line with previous studies showing that dorsal frontostriatal connectivity was associated with habitual slips of action (de Wit et al., 2012). This hypothesis should be confirmed by future studies implementing an fMRI version of the outcome devaluation task. Together, our findings suggest that food attentional bias and habit-like food choice are largely separate constructs, and that loss of both lPFC-based attentional control and goal-directed food choice may independently contribute to obesity.

Note that we operationalized obesity in terms of an obesity score reflecting common variance in BMI, waist-circumference and waist-to-hip ratio to capture more obesity-related information relative to BMI. Whereas BMI is widely used as a measure of obesity and has been shown a relatively accurate predictor of obesity-related health risks, it might not be an accurate predictor of the cognitive processes and underlying neural mechanism of obesity because it is a poor indicator of percent body fat (Nuttall, 2015). Indeed, this is reflected in the inconsistent results in functional neuroimaging studies on brain responses to food and food-related stimuli in relation to BMI (Ziauddeen et al., 2012). Combining obesity-related variables can capture more information and give us a better measure of obesity and overeating. A limitation of this study is that we only combined simple anthropometrics, rather than more sophisticated bodily measurements (e.g. body composition) or behavioral indices of compulsive eating. Future studies are required to address which (combination of) variables might more accurately predict cognitive processes and the underlying neural mechanisms (see also Ziauddeen et al. (2012)).

In conclusion, we found diminished lateral prefrontal control with increasing obesity when resisting the distraction of food words in a food attentional bias task. This was accompanied by less goal-directed, i.e. more automatic food choices following satiation on a separate outcome devaluation paradigm. Our findings suggest that both reduced lPFC-based control during food-related distraction, and increased automatic food choices, at the expense of goal-directed control, may contribute to obesity. Treatments to increase control over food-directed attention and choices could therefore be a fruitful target to reduce overeating.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuroimage.2016.11.015.

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