



# Neural correlates of the energetic value of food during visual processing and response inhibition



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## ABSTRACT

Previous research showed that human brain regions involved in reward and cognitive control are responsive to visually presented food stimuli, in particular high-energy foods. However, it is still to be determined whether the preference towards high-energy foods depends on their higher energy density (kcal/gram), or is based on the difference in energy content of the food items (total amount of kcal). Here we report the results of an fMRI study in which normal-weight healthy participants processed food images during a one-back task or were required to inhibit their response towards food stimuli during a Go/No-Go task. High-energy density (HD) and low-energy density (LD) foods were matched for energy content displayed. Food-related kitchen objects (OBJ) were used as control stimuli. The lateral occipital complex and the orbitofrontal cortex showed consistent higher activity in response to HD than LD foods, both during visual processing and response inhibition. This result suggests that images of HD foods, even when the amount of food shown is not associated with a higher energy content, elicit preferential visual processing - possibly involving attentional processes - and trigger a response from the reward system. We conclude that the human brain is able to distinguish food energy densities of food items during both active visual processing and response inhibition.

## 1. Introduction

Food is essential for our survival and therefore it is important that our brain efficiently recognizes edible items in the environment and categorizes them, especially according to their energetic value (Toepel et al., 2009; Foroni, Pergola and Rumiati, 2016a; Foroni, Rumiati, Coricelli and Ambron, 2016b; Rumiati and Foroni, 2016; Foroni and Rumiati, 2017; Pergola et al., 2017).

Every food has its own value of *energy density* (kcal/gr). The energy density is intrinsic and unique to each type of food. Examples of foods with high energy density are chocolate bars or French fries, whereas examples of foods with low energy density are lettuce or carrots. When considering the picture of a food, the *energy content* of the food stimulus (i.e., total amount of kcal) will not depend only on the type of food displayed (whether chocolate or carrots), but also on the amount of food depicted, in other words on the portion size. A small portion of a high energy-dense food (a piece of chocolate) can have the same energy

content of a large portion of a low energy-dense food (a large salad). Both types of information are important, however the information concerning energy density and energy content of food stimuli have never been disentangled in prior studies investigating the neural processing of food items.

Using fMRI in a group of normal-weight participants, we investigated the functional relevance of the energy density and the energy content of foods when food images are processed within two different cognitive tasks chosen to provide a comprehensive comparison with the extant literature. Previous studies used imaging techniques to investigate how different types of foods modulate the activity of the brain network involved in food perception (Killgore et al., 2003; Beaver et al., 2006; Toepel et al., 2009; Frank et al., 2010). Images depicting food seem to be preferentially processed by the visual stream, analogously to other biologically relevant stimuli such as faces (Huerta et al., 2014). Additionally, Toepel et al. (2009) using electroencephalography (EEG) showed that high- and low-energy foods were differentially processed as early as at

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165 ms post-stimulus onset. We first investigated visual processing of food items and the role of energy density while participants performed a one-back task. In order to ensure an active processing of the food stimuli, we avoided passive viewing paradigms. Indeed, the one-back task is held to require continuous monitoring of the stimuli, mildly engaging attentional processes and working memory. The food images were divided into high energy-dense (HD) and low energy-dense (LD) foods, and presented in three different portion sizes. Two sizes were defined by the actual energy content of the foods displayed, namely 80 or 160 kcal. In this way, the energy density of the foods differed, while the energy content of the foods displayed was kept constant. The third portion size was based on the amount of food (in grams) shown. In this latter condition, the food stimuli were displayed in a *fixed amount* of 250 gr, while the energy content varied across foods with different energy densities. The activity of the regions responsive to food images was first compared to the activity of the regions responsive to images of food-related kitchen objects, and then differences in BOLD activity due to differences in energy density and energy content of the food items were analyzed.

Food images also appear to be an appealing stimulus for the brain triggering reward and inhibition processes (Killgore et al., 2003; Beaver et al., 2006; Toepel et al., 2009; Batterink et al., 2010; Frank et al., 2010). Notably, the ability to exert inhibitory control seems to be critical for maintaining a healthy body weight, and there is plenty of evidence that points towards dysfunctional inhibitory processes in obese individuals and people with eating disorders (Stoeckel et al., 2008; Kenny, 2011; Volkow et al., 2011; Nummenmaa et al., 2012; Lavagnino et al., 2016; Schiff et al., 2016; Aiello et al., 2018a). The clinical implications of the investigation of inhibitory processes in the context of food makes this research of extreme relevance. In particular, investigating how the difference in energy density and energy content of foods might affect inhibition towards food items in normal-weight participants is important in order to understand the basic cognitive mechanisms involved in processing the energetic value of food when response inhibition is required. In the present study, the participants that performed the one-back task also carried out the Go/No-Go task that required them to inhibit their motor response when food items were presented (Aiello et al., 2017, 2018a). The aim was to investigate the role of the energy density of food stimuli during response inhibition. Similarly to the one-back task, HD and LD food items were presented in portion sizes of 80 or 160 kcal. Previous evidence in a similar task with food stimuli (Batterink et al., 2010) highlighted the recruitment of regions typically involved in response inhibition like the superior and inferior frontal gyri, but also regions frequently involved in food processing like the insula when inhibition towards high-energy foods was required. Moreover, Batterink et al. (2010) showed that the Body Mass Index (BMI) correlated with inhibition performance both at the behavioral and at the neural level. Additional evidence (see Lavagnino et al., 2016 for a review) suggests that BMI might be an important factor to consider when investigating the efficiency of inhibitory processes towards food items. In the Go/No-Go task, we aimed to compare participants' behavioral performance and brain activity when response inhibition towards high energy-dense and low energy-dense foods was required. In addition, the role of the differences in BMI was investigated.

## 2. One-back task

### 2.1. Experimental methods

#### 2.1.1. Participants

Twenty-six healthy participants gave written informed consent to take part in the study. One participant was ambipreferent whereas all other participants were right-handed as measured with the Edinburgh Handedness Inventory (Oldfield, 1971); they all had normal or corrected to normal vision, and did not suffer from any neurological or psychiatric conditions. None of the participants reported food restrictions such as

vegetarianism or avoidance of specific foods because of religion, allergy, medical conditions, or reported symptoms of eating disorders. All participants had a BMI within normal range (BMI normal range: 18.5–24.99; Keys et al., 1972). Participants were measured for height and weight at the end of the experimental session.

All participants performed the two tasks (i.e., one-back task and Go/No-Go task) in one single fMRI session and in a satiated state. One participant was excluded from the analyses due to a technical problem of the scanner. Therefore, data from 25 participants were analyzed (14 females; mean age 23.5 years, age range 19–30 years). The average BMI of the final sample was 22.3 ( $\pm 1.3$ ; range = 19.8–24.2). The study had been approved by the 'Comitato Etico Unico Regionale (C.E.U.R.)' and conducted in accordance with the Declaration of Helsinki. All participants were scanned between 2:00 p.m. and 7:00 p.m. to limit possible circadian rhythm effects on hunger.

In order to have equal level of satiety in all the participants, participants were asked to avoid eating for four hours prior to the experiment. During the preparatory procedures they were provided with three sandwiches, and they were allowed to eat until satiation. After completing the tasks in the fMRI, participants were presented with additional questionnaires to assess possible symptoms of aberrant eating patterns (Eating Disorder Inventory-3; Garner et al., 1983), restrictive eating habits (Restraint eating scale-revised, RS-R; Herman and Polivy, 1980), impulsivity (Barrat Impulsiveness Scale-11, Fossati et al., 2001) and general information on current health and dietary habits.

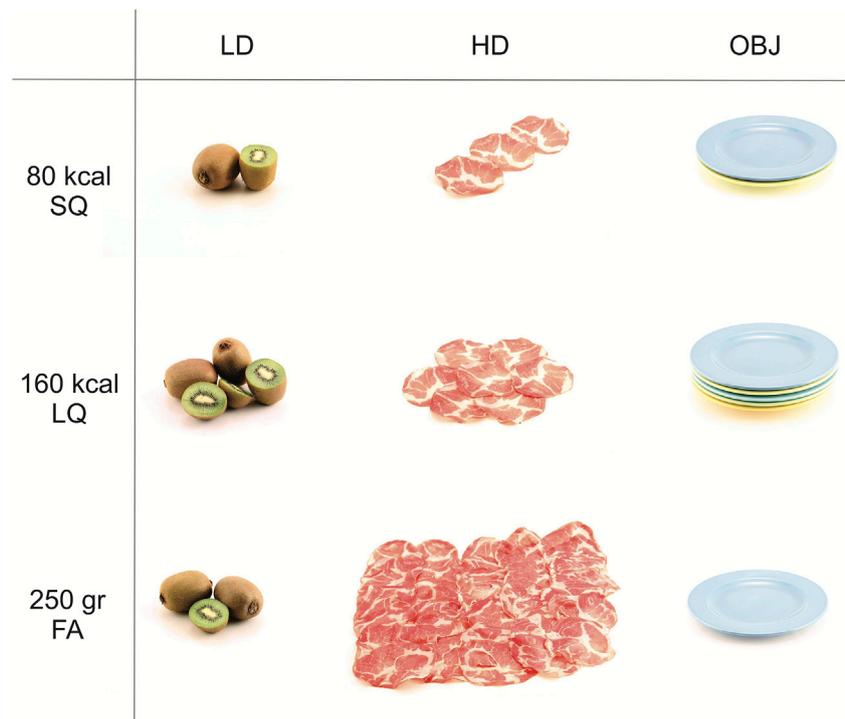
#### 2.1.2. Stimuli and experimental paradigm

During the one-back task, participants saw 20 different high energy-dense (HD) and 20 low energy-dense (LD) foods and 60 pictures of food-related objects (OBJ; i.e., kitchen utensils). Food items and food-related kitchen objects were shown in three different quantities:

- i) *small quantity (SQ)* – in this condition pictures presented food stimuli of exactly 80 kcal (e.g., a small piece of chocolate providing 80 kcal), or 2 objects ( $n = 20$ );
- ii) *large quantity (LQ)* – in this condition pictures presented food stimuli of exactly 160 kcal (e.g., a larger piece of chocolate providing 160 kcal), or 3–6 objects ( $n = 20$ );
- iii) *fixed amount (FA)* – in this condition pictures presented food items in fixed portion size of 250 g each with varying in energy content, or a single food-related kitchen object ( $n = 20$ ).

Each food item was presented in three different portion sizes (80 kcal, 160 kcal, 250 g fixed amount). However, food-related objects were usually different for the SQ and the LQ although they looked similar. For instance, the plates associated with the SQ could be slightly different in the color or in the shape from the plates associated with the LQ.

The images are part of a large database presenting high-quality pictures of foods and food-related objects in different quantities (Foroni, Pergola, Serra, & Rumiati, in prep). The food images were evaluated on multiple dimensions by a group of 127 healthy young participants (see also FRIDA database, Foroni et al., 2013). Foods with an energy density from 0 to 1.50 kcal/gr were classified as LD foods, whereas foods with an energy density from 1.52 to 6 kcal/gr were classified as HD foods. Exemplars of the stimuli used are presented in Fig. 1 and a table with the complete list of food stimuli and their energy densities is provided in the Supplementary materials (Table S1). Stimuli were selected in order to match as much as possible the stimulus types on rating scores for arousal, familiarity, valence, and some relevant perceptual factors (i.e., spatial frequency, percentage of red/green/blue color, size, brightness, normalized complexity) associated with the stimuli. We additionally tested for differences in the hedonic pleasure associated with the food items (i.e. how pleasurable would be to eat the food in the picture). Results of the analyses are showed in the Supplementary materials (S1.1, Tables S2 and S3, and S1.2).



**Fig. 1.** Examples of the stimuli used for food items and kitchen-related objects for the three different portion sizes or quantities. LD: low energy-dense foods; HD: high energy-dense foods; OBJ: food-related kitchen objects; SQ: small quantity; LQ: large quantity; FA: fixed amount.

In a block design, participants saw two blocks consisting of 10 food items or 10 objects for each of the portions/quantities, repeated in the two blocks. As in any one-back task, one item in each block was randomly chosen and repeated twice in a row, leading to 11 trials per block. On every trial, participants saw the picture of a food (or an object) for 1500 ms on a white background followed by a jittered inter-trial interval (i.e., white background alone) ranging from 400 to 600 ms, in incremental steps of 50 ms. A total of 198 trials were presented for a total duration of about 7 min. Participants had to indicate if the presented image was the same or different to the one presented in the previous trial by pressing one of two buttons with their right hand.

Prior to the main task, participants completed a short practice of two blocks of 11 trials (including one image repeated), with pictures of food-related objects different from those used in the experimental session. Stimuli were presented using Presentation (Neurobehavioral Systems, Albany, CA) and projected to a NordicNeuroLab VisualSystem goggles that subtended  $30^\circ \times 23^\circ$  (horizontal  $\times$  vertical) of visual angle.

### 2.1.3. Behavioral data analysis

The one-back task was aimed at keeping participants motivated to look at the images and to pay attention to them and, thus, maintaining an active monitoring of the stimuli. Therefore, we expected a high performance and we only analyzed accuracy data performing a repeated-measures ANOVA with factors *stimuli* (HD, LD, OBJ) and *quantity* (80 kcal/SQ, 160 kcal/LQ) on accuracy scores. The fixed amount quantity (250 gr/one object) was analyzed separately in a one-way ANOVA with the factor *stimuli* (HD, LD, OBJ).

### 2.1.4. MRI data acquisition

A Philips Achieva 3-T scanner was used to acquire both T1-weighted anatomical images and gradient-echo planar T2\*-weighted MRI images with blood oxygenation level dependent (BOLD) contrast. Functional images were scanned using an echo-planar imaging (EPI) pulse sequence with a TR of 2500 ms, an echo time (TE) of 35 ms, a flip angle of  $90^\circ$ , a slice thickness of 3 mm, and no gap interval between the slices. Each volume comprised 37 axial slices with an in-plane resolution of

$128 \times 128$  voxels and voxel size of  $1.8 \times 1.8 \times 3$  mm<sup>3</sup>, field of view (FOV) of 230 mm.

The functional images were acquired during three separate runs, one for the one-back task and two for the Go/No-Go task. The first six volumes of each run were discarded from the analysis to allow for T1 equilibration effects. The remaining volumes (one-back: 187; Go/No-Go:  $2 \times 340$ ) were analyzed using the Statistical Parametric Mapping software SPM12 (Wellcome Department of Imaging Neuroscience, London; Friston et al., 1995; <http://www.fil.ion.ucl.ac.uk/spm>). Images were spatially realigned and a mean EPI image was computed for each subject and spatially normalized to the MNI template using the segmentation function. Subsequently, the obtained transformation was applied to the individual EPI volumes to translate the images into standard MNI space and resample them into  $2 \times 2 \times 2$  mm<sup>3</sup> voxels. Finally, the normalized images were spatially smoothed using a 6 mm full-width half-maximum Gaussian kernel.

For the anatomical images the following parameters were used: TR = 8.2 ms, TE = 3.7 ms, number of slices = 190, slice thickness = 1 mm, no interslice gap, in-plane resolution of  $1 \times 1$  mm<sup>2</sup> and flip angle =  $8^\circ$ .

### 2.1.5. fMRI data analysis

Data were analyzed using a random-effects general linear model (GLM). Nine regressors of interest were defined at the single-subject level (the three types of stimuli – HD, LD, OBJ – in the three quantities – 80 kcal/SQ, 160 kcal/LQ, 250 g/FA) by specifying the onsets and durations (22 s) of the task blocks. The spatial realignment parameters were added to the design matrix as conditions of no interest. Resulting box-car functions were convolved with the canonical hemodynamic response function. Data were high-pass filtered at 1/128 Hz to remove low frequency noise from the BOLD signal. The first-level individual images describing the parameter estimates associated with each of the nine experimental conditions were then fed to a second-level flexible factorial design with a within-subjects factor with nine levels, using a random effects analysis. Contrasts were thresholded at  $p < 0.05$  familywise error whole-brain corrected at the cluster-level (with a voxel-level cutoff of

$p < 0.001$ ). For exploratory purposes we also considered activated regions thresholded at  $p < 0.001$  at the cluster-level uncorrected for multiple comparisons (with a voxel-level cutoff of  $p < 0.001$ ). Brain regions were defined anatomically using the SPM Anatomy Toolbox (Eickhoff et al., 2005) for those regions that have been cytoarchitecturally mapped, and the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) for the remaining regions. Functional activations are shown using the Connectome Workbench software (<http://www.humanconnectome.org/software/connectome-workbench.html>).

## 2.2. Results

### 2.2.1. Behavioral results

The mean accuracy was 97.6% ( $\pm 0.3$ ). The repeated-measures ANOVA with factors *stimuli* (HD, LD, OBJ) and *quantity* (80 kcal/SQ, 160 kcal/LQ) on accuracy scores did not reveal any significant effect due mostly to the ceiling effect and to the low variability in performance. No significant results were also found in the one-way ANOVA with the factor *stimuli* (HD, LD, OBJ) on accuracy scores for the fixed amount quantity due similarly to ceiling effect and low variability in performance.

### 2.2.2. fMRI results

Significant clusters of activated voxels are reported in Table 1. To identify brain regions involved in processing of food images, HD and LD foods together were contrasted against OBJ. The brain regions that showed higher activity in response to food stimuli compared to OBJ included the extrastriate and striate cortex bilaterally (primarily involving V3 and V4, but also V1 and V2), the left orbitofrontal cortex (OFC), and right posterior insula (see Fig. 2). At a different threshold ( $p < 0.001$  at the cluster-level uncorrected for multiple comparisons) also the right OFC and the right parietal operculum showed increased activity in response to food images compared with OBJ.

In order to investigate the pattern of activity in response to differences in the energy density and energy content of the different foods, beta estimates from the peak voxels of each of the brain regions responsive to food images were extracted and analyzed in an ANOVA including the factor *stimuli* (HD/LD) and *quantity* (80 kcal/160 kcal). Results are shown in Table 2.

We analyzed separately the fixed amount quantity (corresponding to 250 gr of food or one object). In this condition HD and LD foods differ not only in their energy density but also in the overall energy content. The brain regions that showed higher activity in response to food stimuli compared to OBJ comprised a cluster localized in the occipital cortex, including the striate and extrastriate cortex bilaterally (V1, V2, V3 and V4; see Fig. 3). In order to investigate the pattern of activity in response

**Table 1**

Brain regions showing significant relative increases of BOLD response during the one-back task associated with each comparison of interest.

Region	Side	MNI coordinates			voxels	T score
		x	y	z		
<b>Food (HD + LD) &gt; OBJ</b>						
Lingual gyrus/V3	R	22	-88	-10	1747	8.16
Calcarine gyrus/V3	R	26	-94	2	s.c.	7.93
Lateral occipital complex/V4	L	-20	-96	0	1581	7.64
Inferior occipital gyrus/V3	L	-20	-94	-12	s.c.	7.33
Orbitofrontal cortex	L	-28	34	-16	199	5.42
Posterior insula	R	40	-4	4	182	4.73
Orbitofrontal cortex*	R	30	36	-14	72	4.22
Parietal operculum*	R	38	-12	22	79	3.88
<b>FA: Food (HD + LD) &gt; OBJ</b>						
Superior occipital gyrus/V1	L	-10	-98	4	5672	8.13
Calcarine gyrus/V3	R	14	-92	12	s.c.	7.39

Note: HD: high energy-dense foods; LD: low energy-dense foods; OBJ: food-related objects; FA: fixed amount; L: left; R: right; s.c.: same cluster; \* significant at  $p < 0.001$  uncorrected.

to HD and LD foods, beta estimates from the peak voxel of each hemifield of the cluster of brain activity responsive to food images were extracted and analyzed using a paired-samples *t*-test. The beta values of the peak voxel of the left occipital region (MNI: 10 -98 4) located in V1 showed higher values in response to HD than LD foods ( $t_{(24)} = 2.6$ ,  $p = 0.016$ ). The same pattern was shown in the beta values of the peak voxel of the right occipital region (MNI: 14-92 12) located in V3 ( $t_{(24)} = 2.1$ ,  $p = 0.048$ ).

## 3. Go/No-Go task

### 3.1. Experimental methods

Methods and procedure were the same as in the one-back task unless otherwise specified.

#### 3.1.1. Stimuli and experimental paradigm

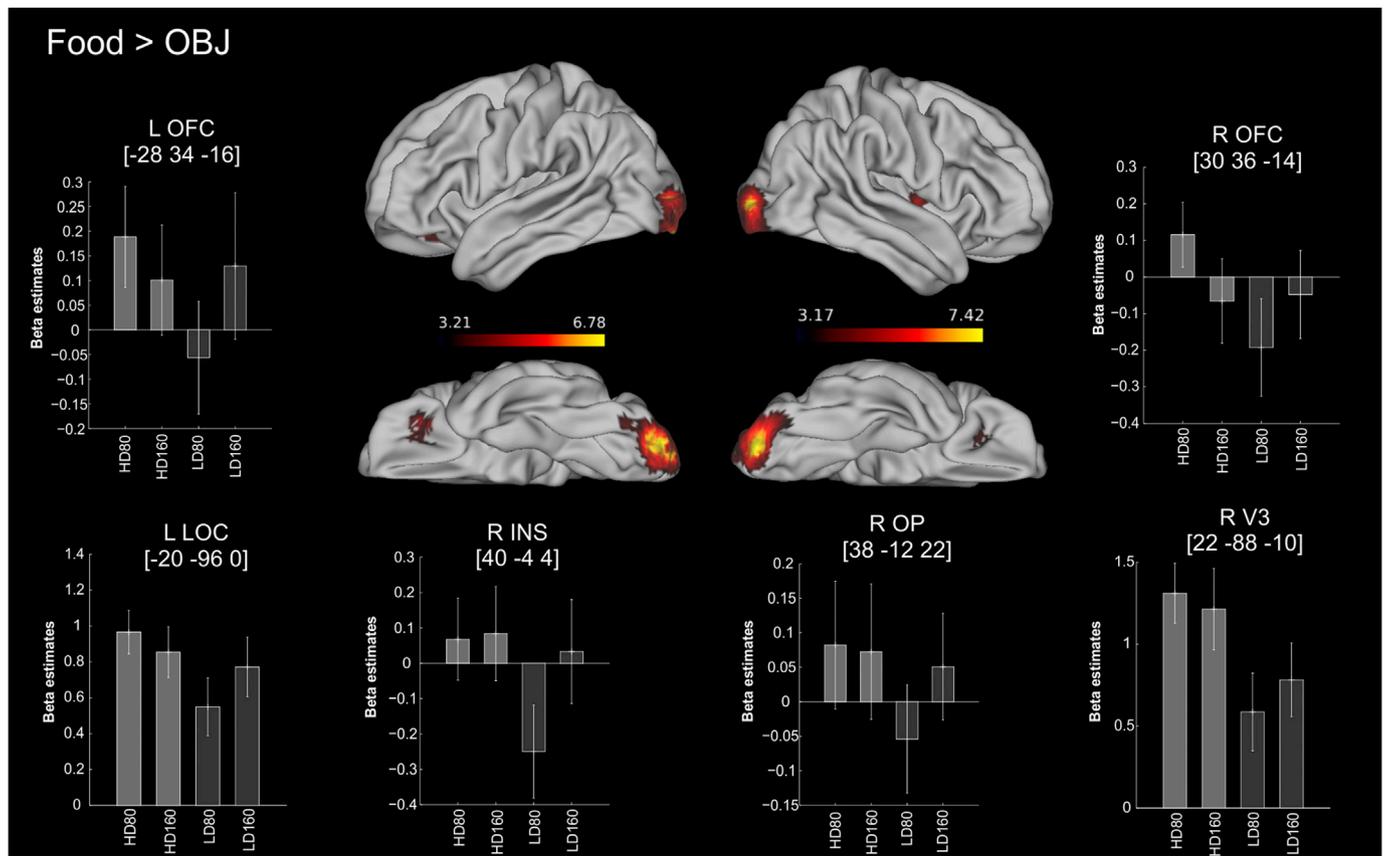
During the Go/No-Go task, participants saw 14 high energy-dense (HD) and 14 low energy-dense (LD) food items and 52 pictures of food-related objects (OBJ; i.e., kitchen utensils) from the same database used in the one-back task (Feroni et al. in prep). A table with the complete list of food stimuli and their energy densities is provided in the Supplementary materials (Table S4). Each HD and LD food stimulus was shown in two portion sizes of 80 and 160 kcal as previously described. The food-related objects were presented in a small and a large quantity (26 objects per quantity). Stimuli were selected in order to match as much as possible the stimulus types based on different dimensions of the stimuli (validated in Feroni et al. in prep) such as arousal, familiarity, valence, and on some perceptual factors (i.e., spatial frequency, percentage of red/green/blue color, size, brightness, normalized complexity). We additionally tested for differences in the hedonic pleasure associated with the food items (i.e. how pleasurable would be to eat the food in the picture). Results of these analyses are showed in the Supplementary materials (S2.1, Table S5, and S2.2).

On every trial of the Go/No-Go task, participants saw a fixation cross on a white background for a jittered timing ranging from 800 to 1200 ms, in incremental steps of 100 ms. The fixation was followed by a picture of one type of food or of an object for 500 ms on a white background followed by a jittered inter-trial interval (i.e. white background alone) ranging from 2600 to 3800 ms, in incremental steps of 300 ms. Participants' task was to press a button if the picture displayed an object (Go trials) or withhold their response if the picture displayed a food (No-Go trials). On each one of two run (see one-back task, 'MRI data acquisition' section), participants performed a total number of 170 trials: 56 trials in which foods were presented (35% of the experimental trials, No-Go condition), 104 trials (65% of the experimental trials, Go condition) in which food-related objects were presented (repeating the OBJ items two times), and 10 null events, in which a white background on the screen replaced the stimuli. The order of the stimuli was randomized. Participants performed two runs of the Go/No-Go task for a total of 340 trials and a total duration of about 14 min. They were instructed to react as fast as possible to the stimuli, as Go responses executed after the offset of the image, i.e., slower than 500 ms, were considered misses. Both the time pressure and the different proportion of Go and No-Go trials (65% vs. 35%) were used to create a strong tendency to respond.

Prior to the main task, participants completed a short practice of two blocks of 20 images different from those shown in the experimental session, i.e., 6 images of foods, 12 images of food-related objects, and 2 null-events.

#### 3.1.2. Behavioral data analysis

In order to evaluate participants' response inhibition in response to the four different food groups, a *d*'-prime (*d'*; discrimination performance) score was computed for each participant for each of the four groups of foods (HD80, HD160, LD80, LD160) by subtracting the *z*-transformed false alarm rate from the *z*-transformed hit rate using the



**Fig. 2.** fMRI results for the one-back task. Regions significantly activated in response to food stimuli (HD + LD) compared with OBJ. Bar graphs depict mean beta estimates (and SEM) from the peak voxel of each cluster of activation. Colorbar limits represent 2% to 98% percentile of the T values projected and interpolated on the surface. MNI coordinates are shown in parenthesis. OFC: orbitofrontal cortex; LOC: lateral occipital complex; INS: insula; OP: parietal operculum.

**Table 2**

Results of the *stimuli* (HD/LD) and *quantity* (80 kcal/160 kcal) ANOVAs on the parameter estimates from the contrast of food against objects.

Brain region	MNI coordinates	Main effect of quantity	Main effect of stimuli	Interaction quantity x stimuli
R Lingual gyrus (V3)	22 -88 -10	p = 0.44	p = 0.0008 HD > LD	p = 0.39
L LOC (V4)	-20 -96 0	p = 0.55	p = 0.002 HD > LD	p = 0.14
L OFC	-28 34 -16	p = 0.60	p = 0.12 HD > LD	p = 0.27
R Insula	40 -4 4	p = 0.14	p = 0.06 HD > LD	p = 0.24
R OFC	30 36 -14	p = 0.87	p = 0.03 HD > LD	p = 0.16
R OP	38 -12 22	p = 0.57	p = 0.37	p = 0.36

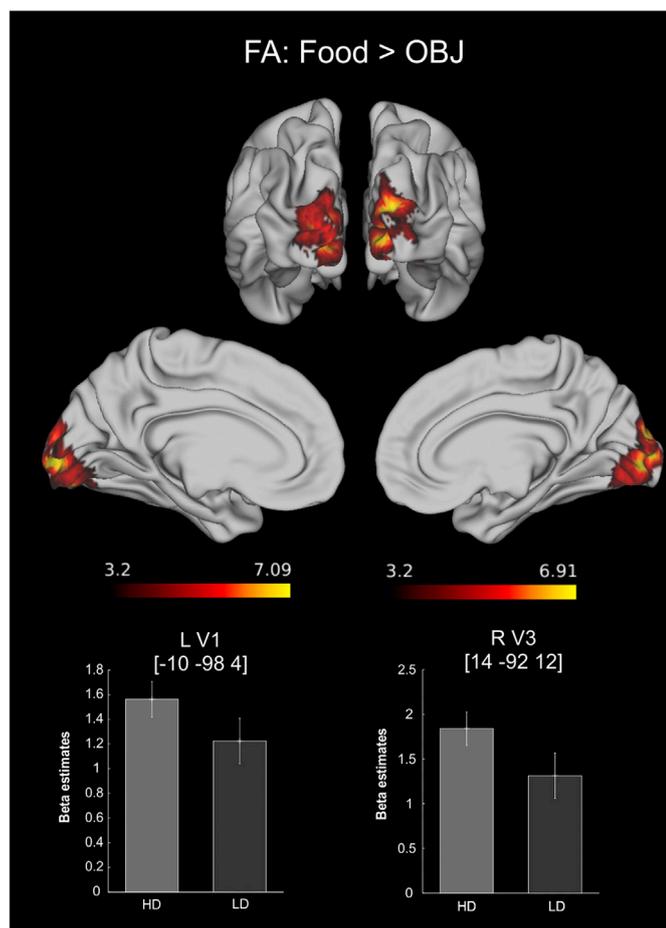
Note: HD: high energy-dense foods; LD: low energy-dense foods; LOC: lateral occipital complex; OFC: orbitofrontal cortex; OP: parietal operculum; L: left; R: right.

loglinear approach (Stanislaw and Todorov, 1999). Being that all food items were No-Go stimuli, we considered false alarms whenever participants mistakenly pressed the button in response to a food item, and hits when participants correctly withheld their response. Comparisons between  $d'$  scores were performed with a repeated-measures ANOVA with within subject factors *stimuli* (HD, LD) and *quantity* (80 kcal, 160 kcal). With the aim of comparing our data with previously published evidence (Batterink et al., 2010), we performed a second ANOVA adding the BMI value of each participant as a continuous covariate on  $d'$  scores.

### 3.1.3. fMRI data analysis

Data were analyzed using a random-effects general linear model (GLM). Six regressors of interest were defined at the single-subject level by modeling the event sequence of each of the experimental conditions (the three types of stimuli – HD, LD, OBJ – in the two quantities – 80 kcal/SQ, 160 kcal/LQ). For each of these regressors, the size of each stimulus presented (as proportion of non-white to the total amount of pixels in the image) was added as parametric modulator. Error trials (late responses, false alarms and missing responses) were modeled separately. The spatial realignment parameters were added to the design matrix as conditions of no interest. Events were time locked to the onset of the stimulus and the resulting stimulus functions were convolved with a canonical hemodynamic response function (and its first-order temporal derivative, to account for small differences in the duration of the peak response). Data were high-pass filtered at 1/128 Hz to remove low frequency noise from the BOLD signal. For each subject, 12 condition-specific contrast images were created (for each trial type and its parametric modulator). The first-level individual images were then fed to a second-level flexible factorial design with a within-subjects factor with 12 levels, using a random effects analysis. All contrasts were thresholded at  $p < 0.05$  familywise error whole-brain corrected at the cluster-level (with a voxel-level cutoff of  $p < 0.001$ ).

In addition, we tested whether some of the regions that showed increased BOLD response at the group level in response to HD food stimuli in the one-back task were also involved in processing HD food stimuli during response inhibition. Those regions were the right orbitofrontal cortex (MNI coordinates [30 36–14]), the left orbitofrontal cortex (MNI coordinates [-28 34–14]) and the right posterior insula (MNI coordinates [40–4 4]). These regions have been also frequently reported in literature in response to food stimuli with high energy content. A small



**Fig. 3.** fMRI results for the one-back task. Regions significantly activated for the fixed amount quantity in response to food stimuli (HD + LD) compared with OBJ. Bar graphs depict mean beta estimates (and SEM) from the peak voxel of each cluster of activation. Colorbar limits represent 2% to 98% percentile of the T values projected and interpolated on the surface. MNI coordinates are shown in parenthesis.

volume correction (SVC) with a sphere of 12 mm radius was used on the coordinates extracted from the results of the one-back task. Results from this ROI analysis are reported at a significance level of  $p < 0.05$  FWE, corrected for the search volume.

### 3.2. Results

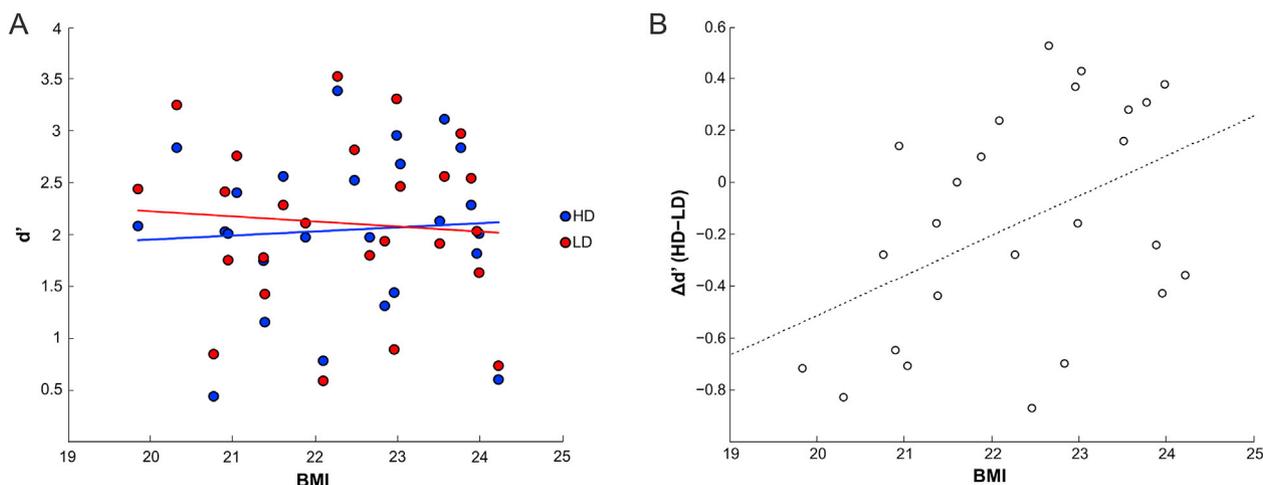
#### 3.2.1. Behavioral results

The repeated-measures ANOVA with factors *stimuli* (HD, LD) and *quantity* (80 kcal, 160 kcal) on  $d'$  scores did not reveal any significant effects. In addition, we performed a second ANOVA with the same factors and including the BMI of each of the participants as covariate. This analysis revealed a main effect of *stimuli* ( $F(1,23) = 6.3$ ,  $p = 0.02$ , partial  $\eta^2 = 0.21$ ) with better response inhibition towards LD foods ( $2.2 \pm 0.18$ ; mean  $\pm$  SEM) compared with HD foods ( $2.04 \pm 0.16$ ; mean  $\pm$  SEM). There was also a significant interaction *stimuli*  $\times$  BMI ( $F(1,23) = 5.77$ ,  $p = 0.025$ , partial  $\eta^2 = 0.20$ ), showing that response inhibition was modulated by BMI. As shown in Fig. 4A,  $d'$  scores for HD foods were higher with higher BMIs, whereas  $d'$  scores for LD foods were lower with higher BMIs. To further investigate this effect, since the focus of the study was the understanding of the difference in inhibition performance towards HD and LD foods, we additionally calculated the difference in  $d'$  between HD and LD foods ( $\Delta d'$ ) and we correlated it with participants' BMI. We found a significant positive correlation between the  $\Delta d'$  and BMI ( $r = 0.45$ ,  $p = 0.025$ , see Fig. 4B) suggesting that the lower the BMI the bigger was the difference in response inhibition towards LD and HD foods. Participants with lower BMI showed better inhibition towards LD foods than HD foods, whereas participants with higher BMI did not show such difference or they showed an inverted pattern, with better response inhibition towards HD foods. No other effects were significant. Our result cannot be explained by the score at the Restraint scale, as no correlation was found between restrained eating score and BMI ( $r = -0.24$ ,  $p = 0.24$ ) or between restrained eating score and  $\Delta d'$  ( $r = -0.18$ ,  $p = 0.38$ ).

#### 3.2.2. fMRI results

Significant clusters of activated voxels are reported in Table 3.

We contrasted HD and LD foods to look for brain regions responsive to differences in energy density in the context of response inhibition, as both types of food were No-Go conditions. Both contrasts were masked (exclusive masking at  $p < 0.05$ ) with the corresponding contrast for the parametric modulator of size (sHD > sLD or sLD > sHD), to control for the effect of the different size of foods. The contrast HD > LD (Fig. 5A) revealed the involvement of the lateral occipital complex bilaterally, and a separate cluster of activated voxels involving the lateral occipital cortex and the right fusiform gyrus. Additionally, we performed a small volume correction testing for activity in the left and right orbitofrontal cortex and in the right posterior insula, using the coordinates from the results of the one-back task. Results revealed a significant involvement of the right orbitofrontal cortex ( $p < 0.05$  SVFWE, MNI coordinates [22 36–12], T



**Fig. 4.** Behavioral results for the Go/No-Go task. A) Significant interaction *stimuli*  $\times$  BMI. B) Significant positive correlation between participants' BMI and the difference in response inhibition ( $\Delta d'$ ) towards HD and LD foods. Negative  $\Delta d'$  score indicates better response inhibition towards LD than HD foods, whereas a positive  $\Delta d'$  score indicates better response inhibition towards HD than LD foods.

**Table 3**  
Brain regions showing significant relative increases of BOLD response during the Go/No-Go task associated with each comparison of interest.

Region	Side	MNI coordinates			voxels	T score
		x	y	x		
<b>HD &gt; LD</b>						
Lateral occipital complex/V4	R	58	-64	-10	180	4.76
Lateral occipital complex/V4	L	-30	-90	-4	268	4.62
Lateral occipital complex/V4	R	32	-90	-4	199	4.3
Orbitofrontal cortex*	R	22	36	-12	35	3.98
<b>LD &gt; HD</b>						
Lingual gyrus/V3	L	-12	-78	-12	3408	7.40
Lingual gyrus/V3	R	12	-78	-10	s.c.	6.08
<b>160 kcal &gt; 80 kcal</b>						
Calcarine gyrus/V1	R	8	-90	6	2765	5.45
Cuneus/V2	R	12	-92	14	s.c.	5.31

Note: HD: high energy-dense foods; LD: low energy-dense foods; L: left; R: right; s.c.: same cluster; \* significant with small volume correction.

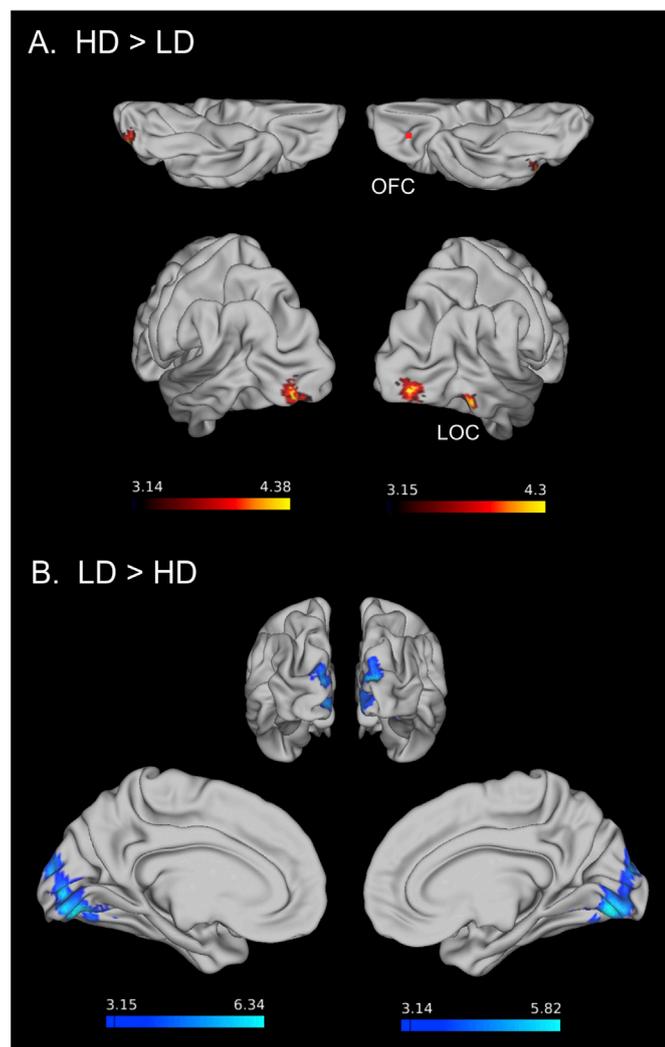
score = 3.98), showing increased BOLD activity in response to HD food stimuli, compared with LD food stimuli. Concerning the contrast LD > HD (Fig. 5B), significant activations were restricted to the occipital cortex, involving the striate and extrastriate cortex bilaterally (primarily involving V1, but extending also to V2 and V3).

To identify brain regions involved in the difference in the energy content (within the No-Go condition), we contrasted the food items that contained 160 kcal with the ones that contained 80 kcal. The regions that showed higher BOLD response in response to food items containing 160 kcal compared to 80 kcal (see Fig. 6) were localized in the occipital lobe, including the striate and extrastriate cortex bilaterally (mainly V1 and V2, extending to V3), and bilateral cerebellum. We found no significant regions with higher activity for 80 kcal compared with 160 kcal food stimuli.

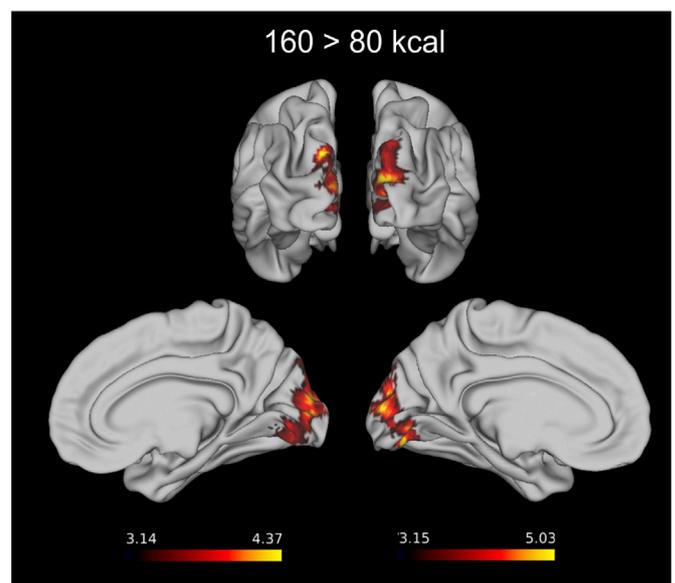
We tested also for interactions between energy density and energy content and found that neither of them ([80 kcal: HD - LD] - [160 kcal: HD - LD]) and [80 kcal: LD - HD] - [160 kcal: LD - HD]) led to any significant activation. Thus differences in energy density for the two quantities are not associated with differential neural processing.

#### 4. Discussion

The present study investigates the neural correlates of visual food processing and response inhibition towards food in an fMRI study using two different cognitive tasks with the same group of normal-weight participants. The main aim of the study was to test whether and how the energy density and the energy content of foods contribute to the pattern of brain responses during visual processing of food and response inhibition. To the best of our knowledge, this study isolated for the first time the neural correlates of the differences in the energy density of foods, when controlling for energy content. In order to do this, we used images depicting foods varying in their energy density (HD, LD) but with a constant energy content across HD and LD foods (80 or 160 kcal). By controlling for the actual energy content of the amount of food shown, it is possible to determine whether the regions previously associated with activity in response to high-energy foods (Killgore et al., 2003; Beaver et al., 2006; Batterink et al., 2010; Frank et al., 2010) are responsive to the energy density or to differences in the actual energy content. Indeed, our brain can simply prefer foods with a higher energy content, as an



**Fig. 5.** fMRI results for the Go/No-Go task. (A) Regions significantly activated in response to HD food stimuli compared with LD are shown from red to yellow. (B) Regions significantly activated in response to LD food stimuli compared with HD are shown from blue to light blue. Colorbar limits represent 2% to 98% percentile of the T values projected and interpolated on the surface. OFC: orbitofrontal cortex; LOC: lateral occipital complex.



**Fig. 6.** fMRI results for the Go/No-Go task. Regions significantly activated for food stimuli containing 160 kcal compared with foods containing 80 kcal are shown. Colorbar limits represent 2% to 98% percentile of the T values projected and interpolated on the surface.

evolutionary strategy for survival, or it might prefer foods with a higher energy density, even when they contain the same number of calories as less-dense foods (see e.g., [Wrangham et al., 1999](#)). This latter process can reflect either a minimization of the energy needed for feeding, or an effect of memory and past experience that drives our attention towards more rewarding high energy-dense foods, even when they are not associated with higher energy intake ([Drewnowski, 1998](#); [Rolls, 2007](#)). Throughout the two present tasks, brain regions involved in preferential visual processing, reward and sensory experience showed differential BOLD activity depending on the energy density of the foods, with higher activity in response to HD foods (compared with LD foods).

#### 4.1. Neural signatures of energy density during visual perception of food

We used a one-back task to investigate the differences in brain activity in response to HD and LD foods during visual processing.

We performed a contrast between foods (HD and LD) and OBJ to reveal the brain network responsive to the visual perception of food items. The regions that showed higher activity in response to food stimuli were located in the extrastriate occipital cortex, lateral occipital complex, orbitofrontal cortex bilaterally, right insula and parietal operculum. However, not all of these regions showed a differential level of activation depending on the energy density of the foods. In particular, the extrastriate and lateral occipital cortices, the right orbitofrontal cortex and (at trend level) the right posterior insula are the regions that showed higher BOLD activity when processing HD foods (compared with LD ones).

HD food items elicited higher BOLD response than LD food items in the lateral occipital complex, a visual region involved in the ventral stream dedicated to object recognition ([Grill-Spector et al., 1999](#); [Larsson and Heeger, 2006](#)). The lateral occipital complex, together with the adjacent fusiform gyrus, are regions consistently responsive to food stimuli in general ([van der Laan et al., 2011](#); [Huerta et al., 2014](#)), but also specifically to high-energy foods ([Toepel et al., 2009](#)). We hypothesized that HD foods might favor a preferential visual processing and the deployment of more attentional resources, as this region seems to be sensible to attentional modulation ([Murray and Wojciulik, 2004](#); [Murray and He, 2006](#)). However, the ratings of the stimuli used (Supplementary Materials, [Table S2](#)) revealed a difference in the complexity of the stimuli, higher in the HD than in the LD food items, and in the size of the stimuli, with bigger items for LD than HD foods. Therefore, for the one-back task we cannot completely rule out a possible contribution of these two perceptual features to the differential activity of the lateral occipital complex in response to HD and LD food stimuli.

The medial orbitofrontal cortex was another region whose activity was enhanced in response to food stimuli, with differences between HD and LD foods only in the right hemisphere. The orbitofrontal cortex is a region important for monitoring the rewarding value of stimuli ([Kringelbach and Rolls, 2004](#)), including food ([Rolls, 2000](#)). This brain region has been previously found to be activated in response to food stimuli ([Small et al., 2001](#); [Wang et al., 2004](#); [Simmons et al., 2005](#); [Porubská et al., 2006](#)), in particular to high-energy foods ([Stoeckel et al., 2008](#); [Frank et al., 2010](#)).

We found higher activity of the posterior right insula when food items were presented, and a tendency towards a preferential activation in response to HD food stimuli, compared with LD ones. The right insula showed consistently enhanced BOLD activity in response to taste and odor foods cues ([Small et al., 2001](#); [Huerta et al., 2014](#)), but also to food images ([Wang et al., 2004](#); [Simmons et al., 2005](#); [Porubská et al., 2006](#)). Previous evidence ([van der Laan et al., 2011](#); [Huerta et al., 2014](#)) also found the activation of the left insula in response to high-energy food stimuli. In addition, both orbitofrontal cortex and insula are brain regions whose activity seems to be dependent on motivational factors such as the level of hunger ([Small et al., 2001](#); [Wang et al., 2004](#); [Porubská et al., 2006](#)).

In the one-back task we included in the stimulus set also items with a fixed amount of food (250 g). The contrast between the fixed amount of

food vs. objects (i.e. only one object per stimulus) revealed a bilateral cluster involving mainly V1 and V2, but also V3, V4. The analysis of the beta values extracted from the local maxima of the clusters of activation (in left V1 and right V3) showed higher activity in response to HD than LD food stimuli. In this set of stimuli, we did not find higher BOLD activity in response to food items in other brain regions usually associated with food processing. The fixed amount condition was analyzed separately from the other two quantities (where the energy content was matched), as the fixed amount of 250 g made HD food items differ from LD ones not only in their energy density, but also in their energy content and volume. Indeed, the amount of food shown is systematically bigger for LD than for HD foods, and in many cases the portion goes beyond what is normally eaten. This represents a possible confound in our results, as previous studies showed that people are able to track and choose the “ideal” portion size of foods ([Brunstrom et al., 2010](#); [Toepel et al., 2015](#)) that is not necessarily the largest available. Therefore, we do report the results but we withhold from providing an extensive and conclusive interpretation of them.

Food-related kitchen objects were used as control stimuli in both experiments to provide an accurate control of the semantic context that does not differ between the stimuli. As previous research ([Toepel et al., 2009](#); [Toepel et al., 2012](#)), we aimed at controlling for generic food-associations, excluding the regions of the brain that would respond not only to food, but also to food-related items. In this way it is possible to identify brain activations that are uniquely associated with food. However, we are aware of the risk associated with such a strict control. Using objects usually associated with foods, we might have missed those brain regions whose activity is indeed associated with processing of food items, but also triggered by semantically-related objects (for review on the distinction between food and food-related object processing see [Aiello et al., 2018b](#); [Rumiati et al., 2016](#); [Rumiati and Foroni, 2016](#); [Vignando et al., 2018](#)).

#### 4.2. Behavioral and neural signatures of calorie density during response inhibition towards food

We used a Go/No-Go task to investigate the differences in brain regions involved in visual processing of HD and LD food items when response inhibition towards food was required. Participants always responded to food-related objects while having to withhold their response when food stimuli were presented.

When controlling for BMI, participants' behavioral performance showed more efficient inhibition towards LD than HD foods. In addition, response inhibition performance of participants with lower BMIs (within normal-weight range) tended to be better in response to LD than HD foods, whereas participants with higher BMIs (within normal-weight range) tended to show more effective inhibition when HD foods were presented. Growing evidence suggests that high BMIs also correlates with dysfunctional inhibitory processes towards food (e.g., [Aiello et al., 2018a](#); see [Lavagnino et al., 2016](#) for a review), suggesting that BMI is likely to be an important factor in modulating the processes of response inhibition towards food. [Batterink et al. \(2010\)](#) reported a positive correlation between BMI and false positives using a similar Go/No-Go task in which high-energy foods were used as No-Go stimuli and low-energy foods as Go stimuli. In this study a group of adolescent girls with a BMI ranging from normal-weight to obese were tested. The present results are in line with the literature, in that they suggest a relationship between BMI and inhibition performance. However, these results should be interpreted with caution, as all participants were within normal-weight BMI limits, with a relatively small variation in BMI compared with previous studies in which also overweight and obese participants were included. The inclusion of only normal-weight participants in our sample was motivated by the aim of studying the cognitive processes underlying normal food processing as it is assumed to occur in healthy individuals. As all participants were normal-weight, the present results can be generalized only to this population.

Concerning imaging results, we found the involvement of the lateral occipital cortex bilaterally and a separate cluster located the right lateral occipital cortex, including also part of the fusiform gyrus, when inhibition towards HD foods (compared with LD) was required. The HD and LD food images used in the Go/No-Go task did not differ in complexity, strengthening the hypothesis that HD foods elicit preferential visual processing, possibly triggering attentional mechanisms, as previously mentioned. Similar attentional mechanisms seems to be at work when processing manufactured (compared to natural) foods (Foroni et al., 2016b). Future dedicated studies on attentional effects triggered by food items would be advisable to further investigate this hypothesis. In addition, the ROI analysis also revealed the involvement of the right orbitofrontal cortex. These regions seems to be therefore important for the processing of differences in the energy density when an inhibitory response is needed. Both brain regions showed also higher BOLD activity in response to HD food stimuli in the one-back task, suggesting a consistency in their functional role, even when different tasks are applied. Response inhibition towards LD food stimuli (compared with HD) was associated with higher BOLD activity in a bilateral cluster in the occipital lobe, mainly involving primary and secondary visual cortices, but extending also to V3 and V4. The different pattern of occipital activations in response to HD and LD food stimuli is informative as for the visual processing triggered by the two types of stimuli. LD foods tended to be larger than HD foods (indeed, with a lower energy density more quantity of food is needed to reach the same number of kcal), probably favoring a higher response of primary and secondary visual cortices, even with the inclusion of the parametric modulation by size of the stimuli.

Previous studies investigating inhibitory processes in obese and binge eating disorders (Batterink et al., 2010; Kishinevsky et al., 2012; Weygandt et al., 2013; Hege et al., 2014) highlighted the role of the dorsolateral and ventromedial prefrontal cortex, and their functional connectivity, as critical regions contributing to inhibitory control towards food. The activity of these regions is often altered in obese individuals or individuals with eating disorders. In the present study however, HD and LD foods were both presented as No-Go stimuli (i.e. both requiring response inhibition), and the two types of foods were contrasted to each other, revealing not the classical regions often associated with response inhibition, but instead regions involved in coding the energy density information of foods within the context of inhibition.

## 5. Conclusions

In one fMRI study, we used a one-back and a Go/No-Go task to identify the brain regions that showed higher BOLD response to HD foods compared with LD foods, even when the two set of food stimuli did not differ in their energy content, but only in their energy density. The pattern of brain activity was consistent across the two tasks examined, brain regions involved in reward and attentional modulation showed differential activity depending on the energy density of the foods, with higher activity in response to HD than LD foods. The present work clarified previously reported results and provides new insights on how our brain processes food in different behavioral contexts and on the role of the food energy density in such processing.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.neuroimage.2018.09.017>.

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