Title: Verbal labels selectively bias brain responses to high-energy foods.
Authors: Toepel U, Ohla K, Hudry J, le Coutre J, Murray MM
Journal: NeuroImage
Year: 2014 Feb 15
Volume: 87
Pages: 154-63
DOI: 10.1016/j.neuroimage.2013.10.038

Verbal labels selectively bias brain responses to high-energy foods

Ulrike Toepel[1], Kathrin Ohla[2,3], Julie Hudry[2], Johannes le Coutre[2,4], Micah M. Murray[1,5]

The Functional Electrical Neuroimaging Laboratory,
[1]Department of Clinical Neurosciences and Department of Radiology,
Vaudois University Hospital Center and University of Lausanne, Switzerland

[2] Nestlé Research Center, Vers-chez-les-Blanc, Lausanne, Switzerland

[3]German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany

[4]The University of Tokyo, Organization for Interdisciplinary Research Projects, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

[5]Electroencephalography Brain Mapping Core, Center for Biomedical Imaging (CIBM) of Lausanne and Geneva, Switzerland

Corresponding author:

Dr. Ulrike Toepel

Functional Electrical Neuroimaging Lab

Departments of Clinical Neurosciences and Radiology

Centre Hospitalier Universitaire Vaudois (CHUV)

Hôpital Nestlé, 5 Avenue Pierre Decker

CH-1011 Lausanne, Switzerland

Ulrike.Toepel@chuv.ch

Manuscript information

Number of text pages:	13
Number of tables:	0
Number of figures:	5 (+ 3 supplementary figures)

Abstract

The influence of external factors on food preferences and choices is poorly understood. Knowing which and how food-external cues impact the sensory processing and cognitive valuation of food would provide a strong benefit toward a more integrative understanding of food intake behavior and potential means of interfering with deviant eating patterns to avoid detrimental health consequences for individuals on the long run. We investigated whether written labels with positive and negative (as opposed to 'neutral') valence differentially modulate the spatio-temporal brain dynamics in response to the subsequent viewing of high- and low-energetic food images. Electrical neuroimaging analyses were applied to visual evoked potentials (VEPs) from 20 normal-weight participants. VEPs and source estimations in response to high- and low- energy foods were differentially affected by the valence of preceding word labels over the ~260-300ms post-stimulus period. These effects were only observed when high-energy foods were preceded by labels with positive valence. Neural sources in occipital, as well as posterior frontal, insular and cingulate regions were down-regulated. These findings favor cognitive-affective influences especially on the visual responses to high-energetic food cues, potentially indicating decreases in cognitive control and goal-adaptive behavior. Inverse correlations between insular activity and effectiveness in food classification further indicate that this down-regulation directly impacts food-related behavior.

Keywords

Electrical Neuroimaging; ERP; VEP; Food; Emotion, Label

1. Introduction

Before eating, foods are valued according to their visual, olfactory and expected reward properties and ultimately selected for ingestion or not. For instance, the energy content (viz. calories or fat) of visually presented foods is automatically processed in the brain through a network encompassing visual as well as reward- and choice- related areas (Killgore et al. 2003; Stoeckel et al. 2008; Toepel et al. 2009). Yet, food-external information influences food preferences and choices and related brain response patterns as well, e.g. price tags (Knutson et al. 2007; Plassmann et al. 2008) and affect conveyed by faces (Winkielman et al. 2005). Verbal labels also substantially impact food sensation and hedonics (de Araujo et al. 2005; Grabenhorst et al. 2008; Linder et al. 2010; Ng et al. 2011). However, this interplay varies not only as a function of the emotional valence of a label (e.g. whether the label conveys positive or negative information), but also on the underlying sensory properties of a stimulus (i.e. whether an aversive or appetitive olfactory, gustatory or visual cue is perceived).

In a functional magnetic resonance imaging (fMRI) study, Ng and colleagues (2011) compared brain activation patterns between normal- and over- weight women while they received (or anticipated the receipt of) identical milkshake drinks that were differentially labeled as 'low-fat' or 'regular' (high-fat). When the identical sensory stimulation was accompanied either by the high-fat as opposed to the low-fat label, overweight women showed higher activity in ventral prefrontal somatosensory and reward-related brain regions (in contrast to normal-weight women). The authors suggested that these findings might indicate a 'perceived' lack of reward in overweight that is likely to be compensated by increased food intake. Another fMRI study investigated the influence of bio-organic labeling on visual food valuation and choices (Linder et al. 2010), i.e. employing a label that conveys positive information. For this purpose, study participants were presented with a range of food items that were either accompanied by a bio-organic label or by a rather neutral label. The study showed elevated activation in cortical (dorsolateral prefrontal cortex) and subcortical (striatum) brain regions when foods with the positive as opposed to the neutral label were perceived indicating the impact of labeling on food-related reward valuation and choice-making.

Furthermore, Grabenhorst and colleagues (2008) showed that the pleasantness of a flavor stimulus could be increased by a positive as compared with a neutral label; this modulation being accompanied by increased activation in the medial orbitofrontal cortex. Similarly, a study by de Araujo et al. (2005) indicated that the unpleasantness of an aversive odor could be decreased by a positive descriptor, as compared with a negative descriptor, with concomitant increases of neural activity in anterior cingulate and medial orbitofrontal cortices. A similar effect, that is the reduction of perceived unpleasantness, was also shown in the study by Nitschke et al. (2006). They primed the delivery of an aversive bitter taste with a negative label and found that the negative label reduced the perceived unpleasantness of the taste. This behavioral effect was accompanied by reduced activity in the insula.

Taken together, several studies indicate that verbal-emotional labeling impacts the perception and valuation of food cues. Hemodynamic imaging studies have furthermore shown that behavioral

modulations like altered pleasantness ratings induced by labeling are associated with changes in neural activation, e.g. in ventral prefrontal brain regions. Yet, evidence regarding the time course of labeling-induced modulations in food perception is still lacking. However, determining whether early signs of food discrimination are already influenced by food-external information might prove to be helpful to interfere with food valuation processes in the context of future therapeutic approaches to eating disorders.

One study has so far investigated the association of event-related potentials (ERPs) and pleasantness ratings. Identical gustatory stimuli were preceded by either a high-fat or low-fat pictorial food cue (Ohla et al. 2012). The identical gustatory incentives were rated as more pleasant when preceded by the image of a high-fat as opposed to a low-fat food. The pleasantness ratings correlated positively with source activity in the ventral prefrontal cortex at ~180ms after taste onset and correlated negatively with insular activations observed at ~350ms. These findings highlight that food perception and valuation processes as well as the accompanying brain activity in reward-related brain areas are implicitly modulated by external cues at early latencies.

Here, we investigated the influence of emotional labeling on the spatio-temporal brain dynamics accompanying the visual categorization of high- and low-energetic foods (in terms of fat content; Toepel et al. 2009). For this purpose, the viewing of each food image was preceded by the viewing of a word label with positive, negative or neutral emotional valence. We recorded VEPs while normal-weighted participants viewed the label-food combinations. As we could previously show that energetic properties impact the spatio-temporal brain dynamics of visual food discrimination (Toepel et al. 2009) and several studies revealed that labeling can influence the sensory processing and valuation of foods, we assumed that emotional labeling would differentially alter the responses to high- and low-energy foods.

2. Materials and Methods

2.1. Stimuli: Emotional labels

We collected >100 French attributes related to daily food intake from dictionaries and the internet and asked 40 participants (17 males; mean±s.e.m. age 26±0.67yrs.) to judge them for emotional valence on a 1-7 point Likert scale (1= very negative, 7= very positive). Among these attributes, 75 were judged as positive (mean±s.e.m. rating = 6.27±0.15), neutral (4.03±0.21) or negative (1.75±0.15), i.e. 25 for each emotional label. All participants indicated in addition that they were well familiar with the food attributes.

Further, 18 different volunteers (10 males; mean±s.e.m. age = 25.2±0.59yrs) judged the final attribute selection on the 1-9 point Self-Assessment-Manikin scale (SAM; Bradley & Lang 1994) for valence and arousal. Thereby, the attributes previously classified as negative were judged more negative (mean= 2.12, s.e.m.±0.30) in valence than the neutral (mean= 3.88, s.e.m.±0.16; t_{24}= 4.97, p≤ 0.001) and the positive labels (mean= 5.63, s.e.m.±0.37; t_{24}= 9.51, p≤ 0.001). The positive labels were accordingly judged as more positive in valence than neutral labels (t_{24}= 4.62, p≤ 0.001). In terms of arousal measures, the

negative (mean= 4.59, s.e.m.±0.20; t_{24}= 2.61, p≤ 0.001) and positive (mean= 4.35, s.e.m.±0.16; t_{24}= 5.07, p≤ 0.001) labels were judged as more arousing than the neutral ones (mean= 3.28, s.e.m.±0.12). Arousal judgments for the negative vs. positive labels did not differ. Examples of labels with positive valence are "appétissant" (appetizing), "sain" (healthy) or "frais" (fresh). Labels with negative valence were e.g. "avarié" (decayed), "dégoûtant" (disgusting) or "toxique" (toxic). Neutral valence label were e.g. "chauffé" (heated), "mou" (soft) or "coupé" (cut).

2.2. Stimuli: Food images

Fifty high-energy and 50 low-energy food images (by means of fat content; cf. Toepel et al. 2009) were presented to 24 participants (12 female; mean±s.e.m. age= 27.7±1.32yrs; mean±s.e.m. BMI= 22.13±0.45). The low-level visual features of all food images (i.e. luminosity), and between food image classes (i.e. spatial frequencies) had been adapted (Knebel et al. 2008). All photographs measured 300x300 pixels, which corresponded to ~6° visual angle on the computer monitor and were taken using an identical background from an identical top-view angle. Participants were asked to judge the food images on a 1-9 point SAM scale (Bradley & Lang 1994) for valence and arousal. In terms of valence ratings, high-energy foods (mean±s.e.m. = 5.19±0.10) and low-energy foods (5.26±0.11) did not differ significantly (t_{49} ≤ 1). Also, there were no significant differences obtained in the arousal ratings between high-energy foods (4.08±0.11) and low-energy foods (3.89±0.11).

2.3. Participants in the EEG study

Twenty (11 female) normal-weighted volunteers, aged 18-32 years (mean±s.e.m. = 24.1±0.97yrs; mean BMI±s.e.m. = 22.07±0.59), participated in the study. Nineteen of these participants were right-handed, and one was ambidextrous according to the Edinburgh Handedness Inventory (Oldfield 1971). None of the participants had current or prior neurological or psychiatric illnesses or self-reported eating disorders. All participants had normal or corrected-to-normal vision. All of the EEG recording sessions started between 13:00 and 14:00h to control for circadian modulations of hunger. Further, participants were instructed (and also themselves reported) to have eaten lunch before the recording sessions. All participants provided written, informed consent to the procedures, which were approved by the Ethics Committee of the Faculty of Biology and Medicine of the University of Lausanne and the Vaudois University Hospital Center (CHUV).

2.4. Procedure of the EEG study

Participants completed 600 trials via a 21" CRT monitor that they viewed within an electrically shielded and sound attenuated booth. Each trial started with a central fixation cross, followed by the visual presentation of either an emotionally positive, negative or neutral food label for 500ms. Following a variable inter-stimulus-interval (ISI) of 200-500ms, participants were presented with either an image of an

energy-dense high-fat food or an energy-sparse low-fat food for 500ms in pseudo-randomized order (Figure 1a). Subjects were asked to indicate by button-press on a response box using the index finger whether they thought that the preceding food item had depicted a food that is high or low in fat content. Responses were allowed during the presentation of the food image and 500ms after image offset. This behavioral task served to drive participants' attention away from the verbal label for which no task instruction was given. Stimulus presentation and response recordings were controlled by E-Prime (Psychology Software Tools Inc., Pittsburgh, USA; www.pstnet.com/eprime). Emotional labels and food images were combined in a way that no food image was coupled more than once with the same verbal attribute. Overall, subjects thus performed 100 trials per condition; i.e. high-fat food images preceded either a positive (henceforth: HiFat-Pos), negative (HiFat-Neg) or neutral (HiFat-Neu) attribute as well as low-fat food images preceded either by a positive (LoFat-Pos), negative (LoFat-Neg) or neutral (LoFat-Neu) label.

- Figure 1 about here -

2.5. Electroencephalography (EEG) acquisition and preprocessing

Continuous EEG was acquired at 512Hz though a 160-channel Biosemi ActiveTwo system (Biosemi, Amsterdam, The Netherlands) referenced to a ground circuitry (common mode sense and driven right leg electrodes or CMS-DRL). This circuitry functions as a feedback loop driving the average potential across the montage as close as possible to the amplifier zero. Details of this circuitry, including a diagram can be found on the Biosemi website (http://www.biosemi.com/pics/zero_ref1_big.gif). The electrode montage is displayed in Supplementary Figure 1. All data pre-processing steps and VEP averaging were done using the CarTool software (http://sites.google.com/site/fbmlab/cartool; Brunet et al. 2011). All statistical analyses were conducted using the Statistical Toolbox for Electrical Neuroimaging (STEN) developed by Jean-François Knebel (www.unil.ch/fenl/Sten). To calculate VEPs, epochs of EEG from 98ms pre- to 488ms post food image onset (i.e. 50 data points before and 250 data points after stimulus onset) were separately averaged for each image category and each participant. In addition to an automatic ±80µV artifact rejection criterion, EEG epochs containing eye blinks or other noise transients were removed by trial-to-trial inspection of the data. Data were band-pass filtered during single-subject averaging (0.01-40Hz) and baseline-corrected using the 98ms pre-stimulus period. Data from artifact electrodes of each participant were interpolated using 3-D splines (Perrin et al. 1987), and EEG epochs were averaged as a function of image category and preceding emotional label. During group-averaging, data were recalculated against the average reference. The average number of accepted VEP epochs ranged from 97.1 (s.e.m. ±1.74) to 98.05 (s.e.m. ±1.32) per condition.

2.6. EEG Analyses and source estimation

As in prior work (Toepel et al. 2009, 2012; Lietti et al. 2012) we applied analyses to global and local measures of the electric field at the scalp. These so-called electrical neuroimaging analyses allow differentiating effects caused by modulations in the VEP strength from alterations in VEP topography (Murray et al. 2008; Michel et al. 2004; Michel and Murray 2012). Temporal autocorrelation in the analyses of the VEPs on the head surface was controlled for by considering only effects exceeding the statistical threshold of $p \leq 0.05$ for more than 15 contiguous data sampling points (i.e. ~30ms; Guthrie and Buchwald 1991). Voltage waveform VEP analyses further included a spatial extent criterion of a minimum of at least 8 sensors (i.e. 5% of the electrode montage) for each time sample considered significant.

2.6.1. VEP analyses

The main goal of our analyses was to identify differential effects of verbal labeling on the brain responses to either food category. We first computed an electrode- and time- wise 2x3 ANOVA on the VEP waveform data at each of the 160 electrodes including the factors of food image category (HiFat vs. LoFat) and preceding label (positive, negative and neutral). The dynamics of the obtained interaction between food category and label are presented as the number of significant electrodes as a function of time. We also assessed modulations in the global strength of the VEPs using a time-wise 2x3 ANOVA on Global Field Power (GFP; Lehmann and Skrandies 1980; Koenig and Melie-Garcia 2010).

Moreover, a sample-wise 2x3 topographic ANOVA (TANOVA) on global VEP dissimilarity (Lehmann and Skrandies 1980) via a non-parametric randomization procedure (5000 randomizations per sampling point) served to identify statistical differences in the electric field configuration between the label-food-combinations (Koenig et al. 2008, Koenig et al., 2011; Murray et al. 2008). To identify stable periods of VEP topography over the post-image interval that potentially differed across experimental conditions, we submitted the group-average VEPs to a common topographic cluster (i.e. map) analysis based on a hierarchical clustering algorithm (Murray et al. 2008). The optimal number of stable clusters (i.e. the minimal number of maps that accounts for the greatest variance of the dataset) was determined using a modified Krzanowski-Lai criterion (Murray et al. 2008). Periods over which differential topographic maps were observed in the group-average VEPs were tested by comparing each of these maps with the moment-by-moment scalp topography of an individual's VEP from each condition. For this fitting procedure, each time point of each single subject VEP was labeled according to the map it best correlated with spatially (Murray et al. 2008). The dependent measure was map presence in milliseconds. These values were submitted to a repeated measures ANOVA with the factors of image category, verbal label and topographic map. The fitted map that predominated over a period of stable clustering best described the VEP over the time interval. The topographic clustering in conjunction with the analysis of global dissimilarity is a method for identifying time intervals over which the underlying neural source configurations of the VEPs differed (Lehmann 1987).

Whenever interactions between the factors of food image category (HiFat vs. LoFat) and verbal label (positive, negative and neutral) were obtained in the 2x3 ANOVAs we then conducted focused 1-way ANOVAs for each image category and when appropriate (i.e. when a significant main effect was observed) we then conducted paired t-tests between specific pairs of conditions. We would emphasize, however, that the time period analyzed in any such focused ANOVAs and paired t-tests was limited to that exhibiting a significant interaction. In these post-hoc analyses, similar statistical criteria as on the 2x3 ANOVA were applied (i.e. $p \leq 0.05$ for more than 15 contiguous data sampling points; spatial extent of >8 sensors for VEP waveform analyses).

2.6.2. Source Estimations

Intracranial sources underlying the surface electric fields were estimated for each image category and preceding emotional label using the local auto-regressive average (LAURA) distributed linear inverse solution (Grave de Peralta et al. 2001; Grave de Peralta Menendez et al. 2004). The version of LAURA used here employs a realistic head model with 3005 solution points arranged within the gray matter of the Montreal Neurological Institute's (MNI) average brain. This implementation of LAURA was generated with the Spherical Model with Anatomical Constraints (SMAC; Spinelli et al. 2000). As an output, LAURA provides a current density value (in $\mu A/mm^3$) at each node. Prior basic and clinical research have documented and discussed in detail the spatial accuracy of this inverse solution, which are on the order of the grid size of the solution points (here ~6x6x6mm, Gonzalez Andino et al. 2005a,b; Grave de Peralta Menendez et al. 2004 and Michel et al. 2004). The time period for which intracranial sources were estimated and statistically compared as a function of emotional label was defined by the results of the abovementioned VEP analyses. Statistics on the source estimations was performed by first averaging the VEP data over the time interval exhibiting a 2x3 interaction at the level of analyses of the electric field at the scalp in order to generate a single data point for each participant to increase the signal-to-noise ratio for source estimations. The inverse solution (20 participants x 2 image categories x 3 label types) was then estimated for each of the 3005 nodes of the solution point matrix. A 2x3 ANOVA at each source node was then performed first to assess which sources nodes revealed an interaction between image category and emotional label. In the event of a significant interaction, we then performed focused 1-way ANOVAs for each image category and, when appropriate, post-hoc t-tests between specific pairs of conditions.

Only effects with p-values ≤ 0.05 and present in at least 15 contiguous nodes were considered significant. This spatial criterion was determined using the AlphaSim program (http://afni.nihm.nih.gov) as similarly applied in other studies from our group (Knebel and Murray 2012; Thelen et al. 2012; Toepel et al. 2012). The source nodes showing significant effects were rendered on the MNI brain for visualization with Talairach and Tournoux (1988) coordinates of maximal differences indicated.

Additional Pearson correlation analyses between neural activity patterns and food classification behavior (i.e. into high- or low-fat containing items) were performed on individuals' responses and focused

on those nodes of the solution point matrix (and their six immediate neighbors) that had revealed the maximal statistical differences between conditions. Only values exceeding the statistical threshold of r(18)= ±0.45; p≤ 0.05 (two-tailed) were considered significant.

3. Results

3.1. Behavior

Food image classification accuracy and reaction times are displayed in Figure 1b. These data were submitted to a 2x3 ANOVA using within-subject factors of category (HiFat, LoFat) and verbal label (positive, negative or neutral) and revealed a significant main effect of food category ($F_{1,19}$= 5.59; p≤ 0.05; η_p^2= 0.23). LoFat foods were in general categorized more often as belonging to the appropriate food category (LoFat-Pos= 83.92% [s.e.m. ± 2.5]; LoFat-Neg= 83.91% [s.e.m. ± 2.13]; LoFat-Neu= 81.75% [s.e.m. ± 2.56]) than HiFat foods (HiFat-Pos= 75.23% [s.e.m. ± 2.17]; HiFat-Neg= 74.14% [s.e.m. ± 2.18]; HiFat-Neu= 75.38% [s.e.m. ± 2.43]).

There was no interaction between food category and emotional label ($F_{1,19}$= 1.61; p= 0.2; η_p^2= 0.08), indicating that verbal labels did not differentially influence the behavioral scores to the classification of both food categories. There was no main effect of verbal label ($F_{1,19}$= 0.23; p= 0.76; η_p^2= 0.01). The 2x3 ANOVA on reaction times to correctly classified food images revealed no main effects or interaction.

- Figure 2 about here -

3.2. VEP voltage waveform analyses

An exemplar VEP waveform is shown in Figure 2a, and the prototypical peaks can be observed. The time-point-wise 2x3 ANOVA on VEPs at the level of individual electrodes revealed a significant food image category × verbal label interaction between 246-369ms post-image onset (Figure 2b) that was distributed over posterior and right-lateral electrodes. Focused 1-way ANOVAs for each image category were therefore conducted. The results of these ANOVAs are shown in Figure 2c for responses to HiFat food images, exhibiting a significant effect of verbal label over the same time window as the interaction obtained by the higher-level ANOVA. Responses to LoFat food images showed no significant differences (data not shown). Finally, paired t-tests were conducted between responses to HiFat food images preceded by different types of verbal labels (Figure 2d and 2e). These analyses indicated that responses to HiFat images preceded by positive verbal labels differed from responses to HiFat images preceded by either negative or neutral verbal labels over a similar time interval as evinced by the ANOVAs. The responses to HiFat images preceded by negative vs. neutral labels did not reliably differ. We would remind the reader, however, that analyses of voltage waveforms are reference-dependent (discussed in Murray et al., 2008; Tzovara et al., 2012). Consequently, our interpretations are based instead on reference-independent global measures of the electric field at the scalp.

- Figure 3 about here -

3.3. GFP waveform analyses

The time-point-wise 2x3 ANOVA of GFP waveforms (as displayed Figure 3a) likewise identified a significant interaction between food image category and verbal label over the 263-371ms post-stimulus period (Figure 3b), which overlaps that observed for voltage waveforms. Focused 1-way ANOVAs for each food image category were therefore conducted, and only the HiFat food images exhibited an effect of verbal label, which extended over the same time window as the interaction obtained by the higher-level ANOVA (Figure 3c). GFP responses to LoFat food images did not exhibit an effect of verbal label (results not shown). Paired t-tests between responses to HiFat food images preceded by different types of verbal labels (Figure 3d and 3e) identified GFP modulations between HiFat images preceded by positive verbal labels and both, HiFat images preceded by negative or neutral verbal labels. While the responses to HiFat images preceded by positive vs. neutral labels differed also over the 263-371ms post-stimulus period, shorter lasting differences were observed when comparing the responses to HiFat foods preceded by positive vs. negative labels (i.e. 263-297ms). Responses to to HiFat images preceded by negative vs. neutral labels did not reliably differ. The amplitude of responses to HiFat food images preceded by positive labels was overall lower than those to all other viewing conditions over the time interval that revealed statistical differences.

3.4. Global dissimilarity analyses

Analyses of global dissimilarity tested for topographic differences and identified a significant interaction between factors of food image category and verbal label over the 225-363ms post-stimulus period (Figure 4a). Focused analyses for each food image category were therefore conducted. The topography of responses to LoFat images failed to exhibit a main effect of preceding verbal label on global dissimilarity. By contrast, the topography of responses to HiFat images exhibited a main effect of preceding verbal label starting over the 225-363ms post-stimulus period (Figure 4b). Paired contrasts revealed that these topographic differences were largely due to responses to HiFat food images preceded by positive verbal labels which differed topographically with respect to both HiFat images preceded by neutral verbal labels (Figure 4c) as well as negative verbal labels (Figure 4d). These last two conditions did not significantly differ topographically.

- Figure 4 about here -

3.5. Topographic cluster analysis

The collective topographic cluster analysis on all viewing conditions computed to obtain time intervals of stable VEP configurations identified 9 distinct topographies (template maps) that overall explained 98.33% of the variance in the collective dataset across conditions. The map topographies were similar between conditions over most of the post-stimulus period, except for the interval from 258-310ms that yielded two differing template map topographies at the group-average VEP level (visualized as Map A and B in Supplementary Figure 2). To validate whether the obtained template VEP maps differentially characterized participants' responses to the food viewing conditions, we computed the spatial correlation of the template maps A and B with the single-subject VEPs at each time point over the 258-310ms interval. The output of this fitting procedure is the topographic map presence in milliseconds (see Methods section) which was subjected to a 2x3x2 ANOVA. The analysis revealed a significant 3-way interaction between food image category, verbal label and template map ($F_{(2,38)}$= 3.66; p≤ 0.05; η_p^2= 0.16). Focused ANOVAs were conducted as a function of food image category. For LoFat images, there was no main effect or interaction (p>0.28). For HiFat images, on the other hand, a main effect of verbal label was observed ($F_{(2,18)}$= 4.16; p≤ 0.04; η_p^2= 0.32). Paired t-tests indicated that this was due to the predominance of map A in response to HiFat images preceded by positive verbal labels and the predominance of map B in response to HiFat food images preceded by either a negative (t(19)=2.35; p=0.029; η_p^2= 0.23) or neutral ($t_{(19)}$= 2.96; p≤ 0.01; η_p^2= 0.32) verbal labels (the latter of which did not significantly differ). These results in turn served as the rationale for signal-averaging over time prior to source estimations and analyses thereof that are described in the following section.

3.6. Distributed source estimations

Neural sources and their modulation as a function of the viewed image category and the preceding verbal label were estimated over the time interval of stable topographic VEP clustering, i.e. 258-310ms. In line with the analyses of the electric field at the scalp, we first computed a 2x3 ANOVA with the factors of food image category (HiFat and LoFat) and verbal labels (positive, negative and neutral) across the 3005 nodes comprising the solution points (see Materials and Methods). The analyses revealed an interaction between these factors in the left posterior dorsal frontal cortex (pdFC; Max: -21, -27, 58) and the posterior cingulate cortex (PCC; Max: 3, -41, 23). Supplementary Figure 3a illustrates the observed interaction on the MNI average brain. Focused ANOVAs across all solution points (i.e. unrestrained by the interaction term) were conducted for each image category separately. Responses to HiFat food images exhibited a main effect of preceding verbal label within the posterior dorsal frontal cortex, posterior cingulate cortex, as well as occipital cortex (Supplementary Figure 3b). No main effect was observed for responses to LoFat images.

Separate post-hoc paired t-tests comparing source estimations to HiFat food images preceded by negative vs. neutral, positive vs. negative as well as positive vs. neutral labeling were performed across all solution points (i.e. unrestrained by the interaction term) and revealed significant differences between the responses to HiFat viewing preceded by positive as opposed to neutral labeling. Figure 4 illustrates that

neural activity was reduced when participants viewed images of HiFat foods preceded by positive (as opposed to neutral) labeling on the border between the posterior dorsal frontal cortex (pdFC; Max: -21, -27, 64) and the postcentral gyrus, the posterior cingulate cortex (PCC; Max: -3, -22, 29), the right posterior insula (INS; Max: 35, -16, 20) and the occipital cortex (OC; Max: 21, -88, -2). An additional correlation analysis further demonstrated an inverse relationship between source activity within the insula in response to HiFat foods preceded by a positive verbal label and reaction times during the classification task to the same images (Figure 5). No other brain region modulated as a function of preceding label (or food category) revealed such associations. The paired t-test comparing source estimations for HiFat food images preceded by positive vs. negative verbal labels revealed a single significant cluster within the posterior dorsal frontal cortex (Supplementary Figure 3c). No significant differences were observed between source estimations to HiFat food images preceded by negative vs. neutral verbal labels.

Insert Figure 5 about here

4. Discussion

In our present study, we show implicit and differential influences of verbal-emotional labeling on the spatio-temporal brain dynamics of food categorization. Results revealed substantial differences in head-surface VEP responses and neural source activity induced by verbal labeling when high-energy foods, but not when low-energy foods were viewed. In particular, these differences were observed when high-energy foods were preceded by positive (in contrast to neutral) verbal labels, and reflected as decreases of the electrophysiological measures, i.e. in local VEP amplitude (Figure 2a), in global response strength (GFP; Figure 3a), in topographic map appearance (of the otherwise predominant template map B; Supplementary Figure 2), as well as diminished neural activity in several brain regions (Figure 5 and Supplementary Figure 3c). These modulations occurred as early as 250ms after food image onset while participants completed a food classification task independent from verbal labeling. In contrast, participants' performance did not indicate a differential impact of verbal label type on the behavioral classification of high- vs. low-energy foods.

Implicit influences of emotions on spatio-temporal brain markers have thus far been investigated in the context of face categorization. Negative (as opposed to neutral or positive) facial expressions were shown to induce elevated responses ~100-170ms (Blau et al. 2007; Hung et al. 2010; Jiang et al. 2009). Studies employing emotional interference paradigms, i.e. judgments on the script color of emotional words, have further shown modulated VEP amplitudes starting ~200ms (Franken et al. 2009). Also, decreased responses starting at ~300ms were observed when participants watched complex scenes with pleasant and unpleasant (vs. neutral) content while being engaged in an emotion-disregarding behavioral task (Hajcak et al. 2006). That is, the implicit evaluation of stimuli in terms of emotional content

substantially interferes with the sensory processing and the explicit evaluation of stimulus attributes. Moreover, emotions have also been reported to influence attention and, by extension, the spatio-temporal brain dynamics of inhibitory control between 200-500ms after stimulus onset (Albert et al. 2010; Wang et al. 2011). Since differential responses to high-energy food images preceded by positive as compared to neutral and negative labels have been observed, but not when comparing the latter two, our findings are unlikely due to a general effect of arousal.

As previously emphasized, the current study revealed downregulated brain responses to high-energy food images preceded by a verbal label with positive valence in the posterior dorsal frontal cortex, the posterior cingulate and right insula, as well as in the occipital cortex. Functional neuroimaging studies have associated activity in these areas (and further fronto-striatal-limbic and posterior regions) to cognitive influences on the sensory processing and reward valuation of stimuli, e.g. by pricing information (Knutson et al. 2007; Plassmann et al. 2008), but also to emotion-cognition interference and inhibitory processes therein (Goldstein et al. 2007; Ochsner & Gross 2005). For example, the study of Knutson and colleagues (2007) showed that striatal, prefrontal and insular activity patterns are predictive of subsequent product choices. In addition, the study also showed that in particular cingulate activity is modulated as a function of conflicts between courses of action (i.e. favoring a product or dismissing it). In direct relation to cognitive-affective influences on food valuation, participants in a recent study were asked to actively downregulate food cravings (Hutcherson et al. 2012). In this study, most prominent response decreases were observed in the dorsolateral prefrontal cortex, but likewise in the posterior insula, the postcentral gyrus and the posterior cingulate. These findings were taken as evidence for the modulation of (reward) values attributed to food that is imposed by cognitive-regulatory mechanisms.

Taken together, electrophysiological and hemodynamic imaging have previously revealed substantial influences of cognitive-emotional regulation on the perception of biologically salient and rewarding objects and goods. In light of the present study, selectively decreased responses to high-energetic food cues when preceded by labels with positive emotional valence thus indicate an implicit valence- and reward-specific interplay of regulatory processes on food cue perception that becomes effective within ~250ms after stimulus onset. Moreover, correlations between neural activity and food classification performance showed an inverse relationship between insular activity and reaction times when positively labeled high-energetic food cues had been viewed, indicating a distinct behavioral impact of food labeling.

Such results comply with assumptions on the interplay of emotionally-driven regulatory strategies and processes of cognitive control (Ochsner and Gross 2005), highlighting how implicit attention to emotional features might impact stimulus appraisal and cognitive control. Moreover, the brain network found to be modulated has been linked to stimulus salience and valuation (Linder et al. 2010; Menon and Uddin 2010), the exertion of cognitive and affective control in the context of decision-making (McClure et al. 2004; Hare et al. 2009) and behavioral adaptation (Pearson et al 2011). Thus, the present study reveals

that verbal labels bearing positive emotional valence impact the implicit valuation and categorization of visual food cues, specifically when high-energetic foods are viewed. Positive labels preceding high-energy food cues impose a down-regulation of brain regions implicated into cognitive control and behavioral adaptation. As especially the consumption of high-energy high-fat foods beyond energetic needs leads to overweight and detrimental health consequences on the long run, our results might indicate in extension that an implicit attribution of positive valence to “unhealthy” foods interferes with brain mechanisms of behavioral inhibition and goal-adaptive comportment. Whether or not such implicit emotional influences are also observed on preferences for individual foods and consumption decisions remains to be determined. Moreover, whether also other cognitive-emotionally significant stimuli, e.g. face expressions or colors, have similar or adverse impacts on food valuation and control mechanisms is an unexplored issue so far (but see Genschow et al. 2012). Further determining the influence of external cues on food valuation might yet prove to be useful in the context of recent and future attempts in cognitive-behavioral interventions to support weight management.

5. Acknowledgements

The Cartool software (http://sites.google.com/site/fbmlab/cartool) has been programmed by Denis Brunet from the Functional Brain Mapping Laboratory, Geneva. The STEN toolbox (http://www.unil.ch/fenl/Sten) has been programmed by Jean-François Knebel from the Functional Electrical Neuroimaging Laboratory, CHUV and University of Lausanne. Both software tool developments are supported by the EEG Brain Mapping Core of the Center for Biomedical Imaging (CIBM; www.cibm.ch) of Geneva and Lausanne. MMM is supported by the Swiss National Science Foundation (grant 310030B-133136). Ulrike Toepel is supported by an interdisciplinary research grant from the Faculty of Biology and Medicine of the University of Lausanne.

6. References

Albert, J., López-Martín, S., Carretié, L., 2010. Emotional context modulates response inhibition: neural and behavioral data. *Neuroimage* 49, 914-921.

Blau, V.C., Maurer, U., Tottenham, N., McCandliss, B.D., 2007. The face-specific N170 component is modulated by emotional facial expression. *Behav. Brain. Funct.* 23, 3:7.

Bradley, M. M., Lang, P. J., 1994. Measuring emotion: The Self-Assessment Manikin and the semantic differential. *J. Behav. Ther. Exp. Psychiatry* 25, 49-59.

Brunet, D, Murray, M.M., Michel, C.M., 2011. Spatiotemporal analysis of multichannel EEG: CARTOOL. *Comput. Intell. Neurosci.* 2011:813870.

de Araujo, I.E., Rolls, E.T., Velazco, M.I., Margot, C., Cayeux, I., 2005. Cognitive modulation of olfactory processing. *Neuron* 46, 671-679.

Franken, I.H., Gootjes, L., van Strien, J.W., 2009. Automatic processing of emotional words during an emotional Stroop task. *Neuroreport* 20, 776-781.

Genschow, O., Reutner, L., Wänke, M., 2012. The color red reduces snack food and soft drink intake. *Appetite* 58, 699-702.

Goldstein, M., Brendel, G., Tuescher, O., Pan, H., Epstein, J., Beutel, M., Yang, Y., Thomas, K., Levy, K., Silverman, M., Clarkin, J., Posner, M., Kernberg, O., Stern, E., Silbersweig, D., 2007. Neural substrates of the interaction of emotional stimulus processing and motor inhibitory control: an emotional linguistic go/no-go fMRI study. *Neuroimage* 36, 1026-1040.

Gonzalez Andino, S.L., Murray, M.M., Foxe, J.J., de Peralta Menendez, R.G., 2005a. How single-trial electrical neuroimaging contributes to multisensory research. *Exp. Brain Res*. 166, 298-304.

Gonzalez Andino, S.L., Michel, C.M., Thut, G., Landis, T., Grave de Peralta, R., 2005b. Prediction of response speed by anticipatory high-frequency (gamma band) oscillations in the human brain. *Hum. Brain Mapp.* 24, 50-58.

Grabenhorst, F., Rolls, E.T., Bilderbeck, A., 2008. How cognition modulates affective responses to taste and flavor: top-down influences on the orbitofrontal and pregenual cingulate cortices. Cereb. Cortex. 18, 1549-1559.

Grave de Peralta, R., Gonzalez Andino, S.L., Lantz, G., Michel, C.M., Landis, T., 2001. Noninvasive localization of electromagnetic epileptic activity: 1. Method descriptions and simulations. *Brain Topogr.* 14, 131-137.

Grave de Peralta Menendez, R., Murray, M.M., Michel, C.M., Martuzzi, R., Gonzalez Andino, S.L., 2004. Electrical neuroimaging based on biophysical constraints. *Neuroimage* 21, 527-539.

Guthrie, D., Buchwald, J.S., 1991. Significance testing of difference potentials. *Psychophysiology* 28, 240-244.

Hajcak, G., Moser, J.S., Simons, R.F., 2006. Attending to affect: appraisal strategies modulate the electrocortical response to arousing pictures. *Emotion* 6, 517-522.

Hare, T.A., Camerer, C.F., Rangel, A., 2009. Self-control in decision-making involves modulation of the vmPFC valuation system. *Science* 324, 646-648.

Hung, Y., Smith, M.L., Bayle, D.J., Mills, T., Cheyne, D., Taylor, M.J., 2010. Unattended emotional faces elicit early lateralized amygdala-frontal and fusiform activations. *Neuroimage* 50, 727-733.

Hutcherson, C.A., Plassmann, H., Gross, J.J., Rangel, A., 2012. Cognitive Regulation during Decision Making Shifts Behavioral Control between Ventromedial and Dorsolateral Prefrontal Value Systems. *J. Neurosci.* 32, 13543-13554.

Jiang, Y., Shannon, R.W., Vizueta, N., Bernat, E.M., Patrick, C.J., He, S., 2009. Dynamics of processing invisible faces in the brain: automatic neural encoding of facial expression information. *Neuroimage* 44, 1171-1177.

Killgore, W.D., Young, A.D., Femia, L.A., Bogorodzki, P., Rogowska, J., Yurgelun-Todd, D.A., 2003. Cortical and limbic activation during viewing of high- versus low-calorie foods. *Neuroimage*, 19, 1381-1394.

Knebel, J.F., Toepel, U., Hudry, J., Le Coutre, J., Murray, M.M., 2008. Methods for generating controlled image sets in cognitive neuroscience research. *Brain Topogr.* 20, 284-290.

Knebel, J.F., Murray, M.M., 2012. Towards a resolution of conflicting models of illusory contour processing in humans. *Neuroimage* 59, 2808-2817.

Knutson, B., Rick, S., Wimmer, G.E., Prelec, D., Loewenstein, G., 2007. Neural predictors of purchases. *Neuron* 53, 147-56.

Koenig, T., Melie-García, L., Stein, M., Strik, W., Lehmann, C., 2008. Establishing correlations of scalp field maps with other experimental variables using covariance analysis and resampling methods. *Clin. Neurophysiol.* 119, 1262-1270.

Koenig, T., Melie-García, L., 2010. A method to determine the presence of averaged event-related fields using randomization tests. *Brain Topogr.* 23, 233-242.

Koenig, T., Kottlow, M., Stein, M., Melie-García, L., 2011. Ragu: a free tool for the analysis of EEG and MEG event-related scalp field data using global randomization statistics. *Comput Intell Neurosci*, 938925.

Lehmann, D., Skrandies, W., 1980. Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalogr. Clin. Neurophysiol.* 48, 609-621.

Lehmann, D., 1987. Principles of spatial analysis. In: Gevins, A.S., Reymond, A. (Eds.), *Handbook of electroencephalography and clinical neurophysiology. Methods of Analysis of Brain Electrical and Magnetic Signals, vol. 1* (pp. 309-354). Amsterdam: Elsevier.

Lietti, C.V., Murray, M.M., Hudry, J., le Coutre, J., Toepel, U., 2012. The role of energetic value in dynamic brain response adaptation during repeated food image viewing. *Appetite* 58, 11-18.

Linder, N.S., Uhl, G., Fliessbach, K., Trautner, P., Elger, C.E., Weber, B., 2010. Organic labeling influences food valuation and choice. *Neuroimage* 53, 215-220.

McClure, S.M., Laibson, D.I., Loewenstein, G., Cohen, J.D., 2004. Separate neural systems value immediate and delayed monetary rewards. *Science* 306, 503-507.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct.* 214, 655-667.

Michel, C.M., Murray, M.M., Lantz, G., Gonzalez, S., Spinelli, L., Grave de Peralta, R., 2004. EEG source imaging. *Clin. Neurophysiol.*115, 2195-2222.

Michel, C.M., Murray, M.M., 2012. Towards the utilization of EEG as a brain imaging tool. *Neuroimage* 61, 371-385.

Murray, M.M., Brunet, D., Michel, C.M., 2008. Topographic ERP Analyses: A Step-by-Step Tutorial Review. *Brain Topogr.* 20, 249-264.

Ng, J., Stice, E., Yokum, S., Bohon, C., 2011. An fMRI study of obesity, food reward, and perceived caloric density. Does a low-fat label make food less appealing? *Appetite* 57, 65-72.

Nitschke, J.B., Dixon, G.E., Sarinopoulos, I., Short, S.J., Cohen, J.D., Smith, E.E., Kosslyn, S.M., Rose, R.M., Davidson, R.J., 2006. Altering expectancy dampens neural response to aversive taste in primary taste cortex. *Nat Neurosci.* 9, 435-442.

Ochsner, K.N., Gross, J.J., 2005. The cognitive control of emotion. *Trends Cogn Sci.* 9, 242-249.

Ohla, K., Toepel, U., le Coutre, J., Hudry, J., 2012. Visual-gustatory interaction: orbitofrontal and insular cortices mediate the effect of high-calorie visual food cues on taste pleasantness. *PLoS One* 7, e32434.

Oldfield, R.C., 1971. The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia* 9, 97–113.

Pearson, J.M., Heilbronner, S.R., Barack, D.L., Hayden, B.Y., Platt, M.L., 2011. Posterior cingulate cortex: adapting behavior to a changing world. *Trends Cogn. Sci.* 15, 143-151.

Perrin, F., Pernier, J., Bertrand, O., Giard, M.H., Echallier, J.F., 1987. Mapping of scalp potentials by surface spline interpolation. *Electroencephalogr. Clin. Neurophysiol.* 66, 75-81.

Plassmann, H., O'Doherty, J., Shiv, B., Rangel, A., 2008. Marketing actions can modulate neural representations of experienced pleasantness. *Proc. Natl. Acad. Sci. U. S. A.* 105, 1050-1054.

Stoeckel, L.E., Weller, R.E., Cook 3rd, E.W., Twieg, D.B., Knowlton, R.C., Cox, J.E., 2008. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage* 41, 636-647.

Talairach, J., Tournoux, P., 1988. *Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System - an Approach to Cerebral Imaging*. New York: Thieme Medical Publishers.

Thelen, A., Cappe, C., Murray, M.M., 2012. Electrical neuroimaging of memory discrimination based on single-trial multisensory learning. *Neuroimage* 62, 1478-1488.

Toepel, U., Knebel, J.F., Hudry, J., Le Coutre, J., Murray, M.M., 2009. The brain tracks the energetic value in food images. *Neuroimage* 44, 967-974.

Toepel, U., Knebel, J.-F., Hudry, J., Le Coutre, J., Murray, M.M., 2012. Gender and Weight Shape Brain Dynamics during Food Viewing. *PLoS One* 7, e36778.

Tzovara, A., Murray, M.M., Michel, C.M., De Lucia, M. 2012, A tutorial review of electrical neuroimaging from group-average to single-trial event-related potentials. *Dev Neuropsychol*. 37, 518-544.

Wang, Y., Yang, J., Yuan, J., Fu, A., Meng, X., Li, H., 2011. The impact of emotion valence on brain processing of behavioral inhibitory control: spatiotemporal dynamics. *Neurosci. Lett.* 502, 112-116.

Winkielman, P., Berridge, K.C., Wilbarger, J.L., 2005. Unconscious affective reactions to masked happy versus angry faces influence consumption behavior and judgments of value. *Pers. Soc. Psychol. Bull.* 31, 121-135.

Figure captions

Figure 1. a. Timeline of an experimental trial, illustrating the experimental condition in which the image of a high-fat food is preceded by a label with positive valence. b. Behavioral data obtained on the food classification task (mean±s.e.m. indicated).

Figure 2. VEP voltage waveform measures and analyses. a. Exemplar group-average VEP waveforms at a parieto-occipital midline electrode (POz). Results of the 2x3 ANOVA on VEP waveforms with the factors food image category (HiFat and LoFat) and emotional label (positive, negative and neutral) revealing significant interactions between both factors at the electrode level between ~250-360ms after food image onset (panel b). Focused ANOVAs (panel c) and paired t-tests (panels d and e) confirmed effects were due to modulations of responses to HiFat food images preceded by differing verbal labels, in particular positive labels. In panels b-e results are displayed as the number of electrodes exhibiting a significant modulation as a function of time.

Figure 3. Global Field Power waveforms and analyses. a. Mean global field power waveforms. Results of the 2x3 ANOVA on GFP with the factors food image category (HiFat and LoFat) and emotional label (positive, negative and neutral) revealing significant interactions between both factors between ~270-360ms after food image onset (panel b). The focused ANOVA identified a main effect of preceding verbal label for HiFat food images (panel c). Paired t-tests identified significant differences driven by responses to HiFat food images preceded by positive verbal labels, especially when compared to neutral label precedence (d-e).

Figure 4. Global Dissimilarity analyses. a. The results of the 2x3 interaction between factors of food image category and preceding verbal label identified modulations over the 225-363ms post-stimulus period. Focused topographic ANOVAs (TANOVAs) identified topographic differences for HiFat food images as a function of the preceding verbal label over this same time period (panel b). These differences were explainable by distinct responses to HiFat food images preceded by positive verbal labels (panels c and d). In all panels data are shown as 1 minus p-value as a function of time.

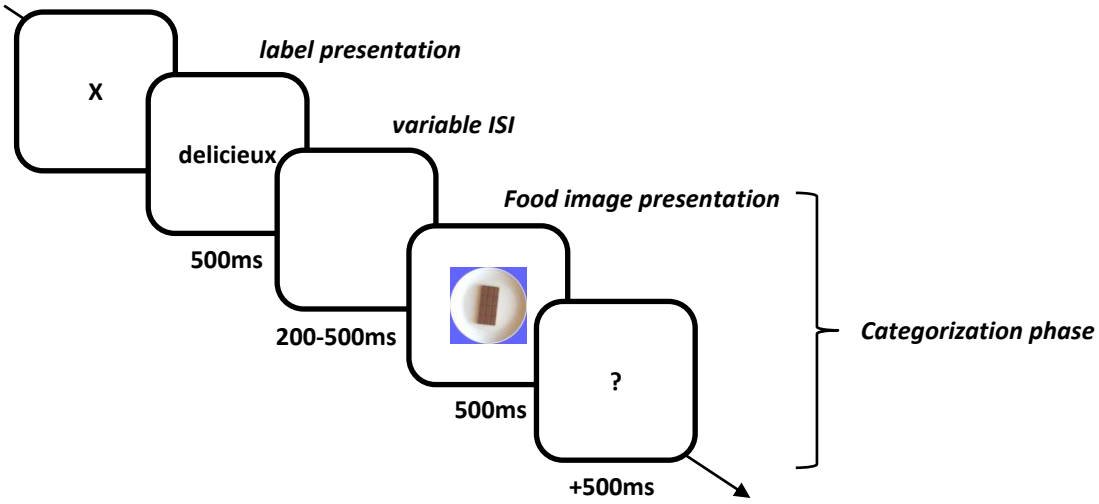
Figure 5. Results of neural source estimation analyses on the stable VEP clustering period from 258-301ms. The figure displays the results of the paired t-test between responses to HiFat food images preceded by positive vs. neutral verbal labels. The inset displays the negative correlation between individuals' neural source activity in the insula and reaction times on the behavioral food classification task.

Supplementary Figure 1. Illustration of the 160-channel electrode montage. The electrodes are shown from a top view with the left hemiscalp on the left and anterior scalp locations upwards.

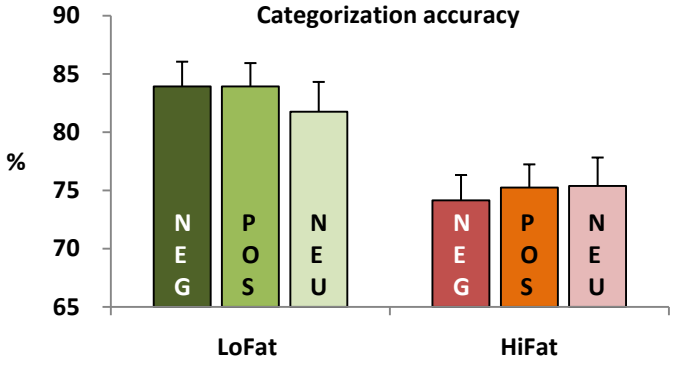
Supplementary Figure 2. Results of the fitting analysis applied using template maps from the topographic clustering analysis.

Supplementary Figure 3. Analyses of source estimations.

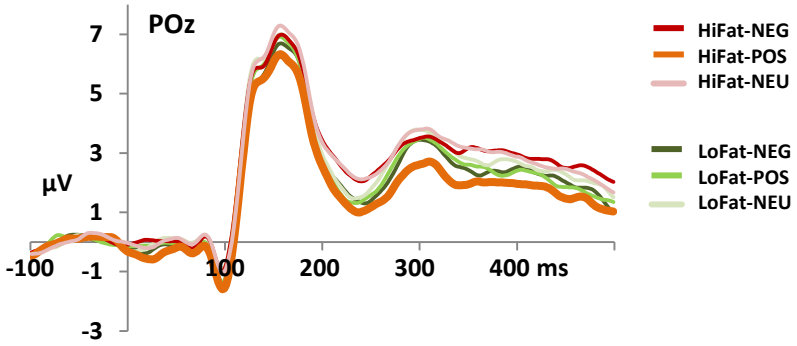
a. Trial structure



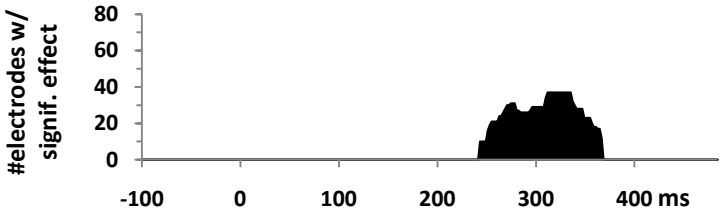
b. Behavioral data



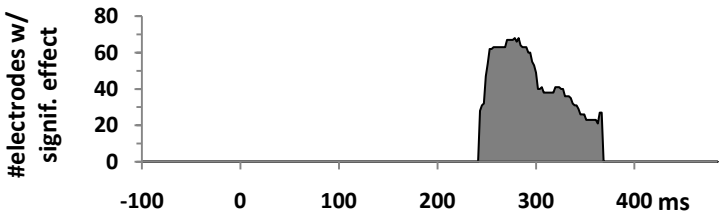
a. Exemplar VEP waveforms



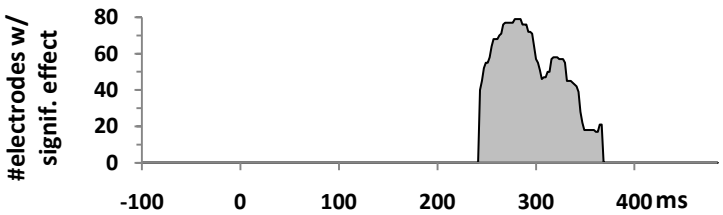
b. 2x3 ANOVA results (food category x verbal label interaction)



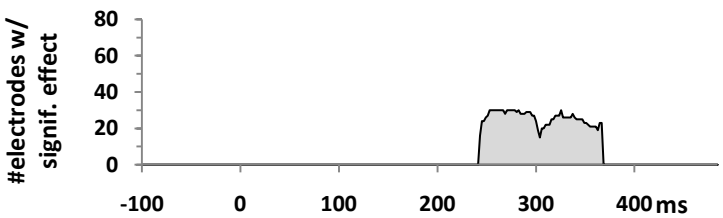
c. 1-way ANOVA results for the HiFat food category



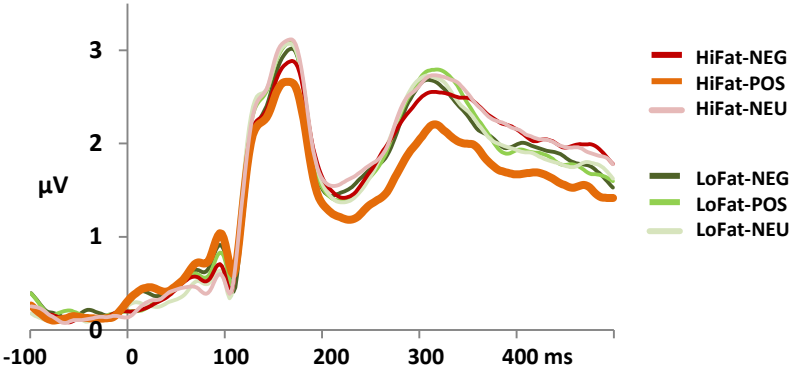
d. Paired t-test results for the HiFat food category (POS vs. NEU)



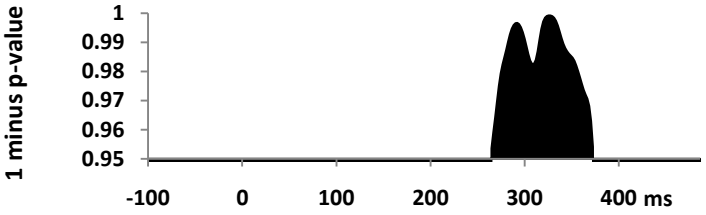
e. Paired t-test results for the HiFat food category (POS vs. NEG)



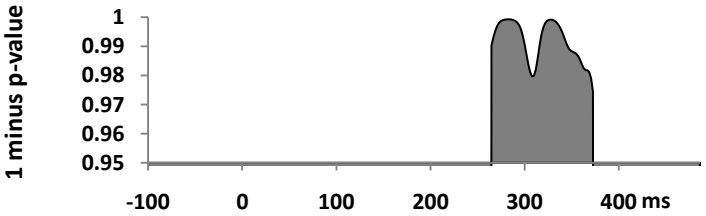
a. Global Field Power waveform



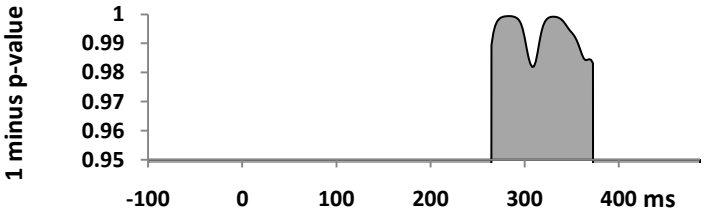
b. 2x3 ANOVA results (food category x verbal label interaction)



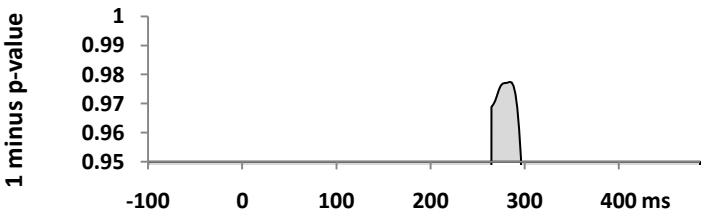
c. 1-way ANOVA results for the HiFat food category



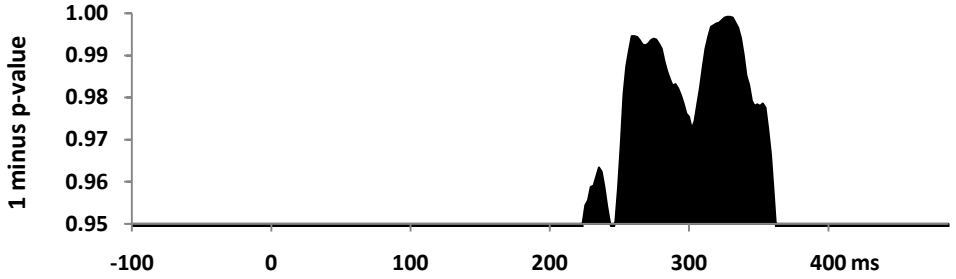
d. Paired t-test results for the HiFat food category (POS vs. NEU)



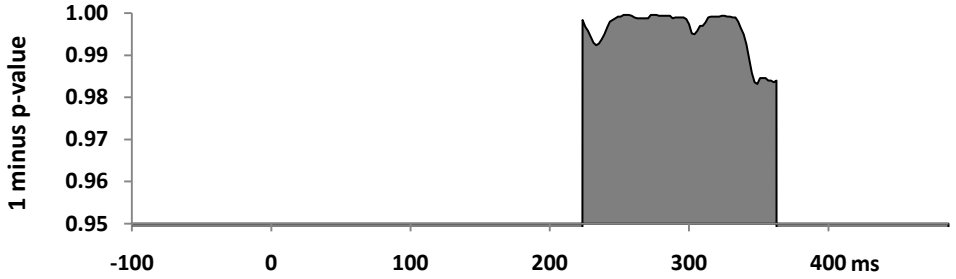
e. Paired t-test results for the HiFat food category (POS vs. NEG)



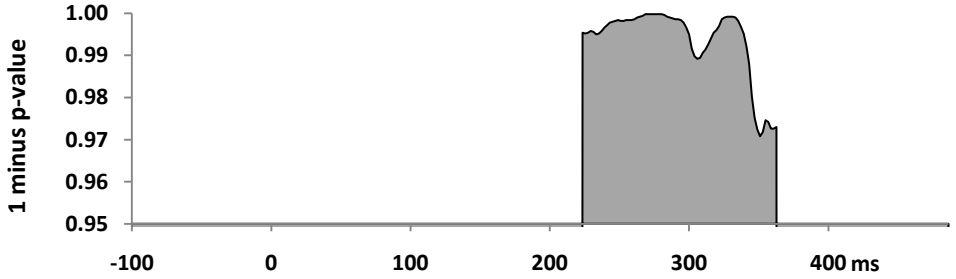
a. Global Dissimilarity: 2x3 TANOVA results (food category x verbal label interaction)



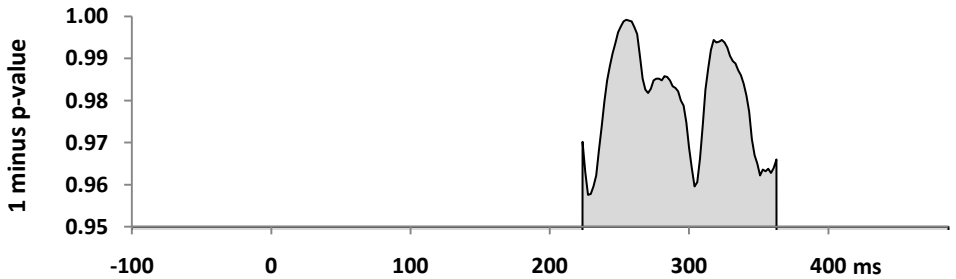
b. Global Dissimilarity: 1-way TANOVA results for the HiFat food category



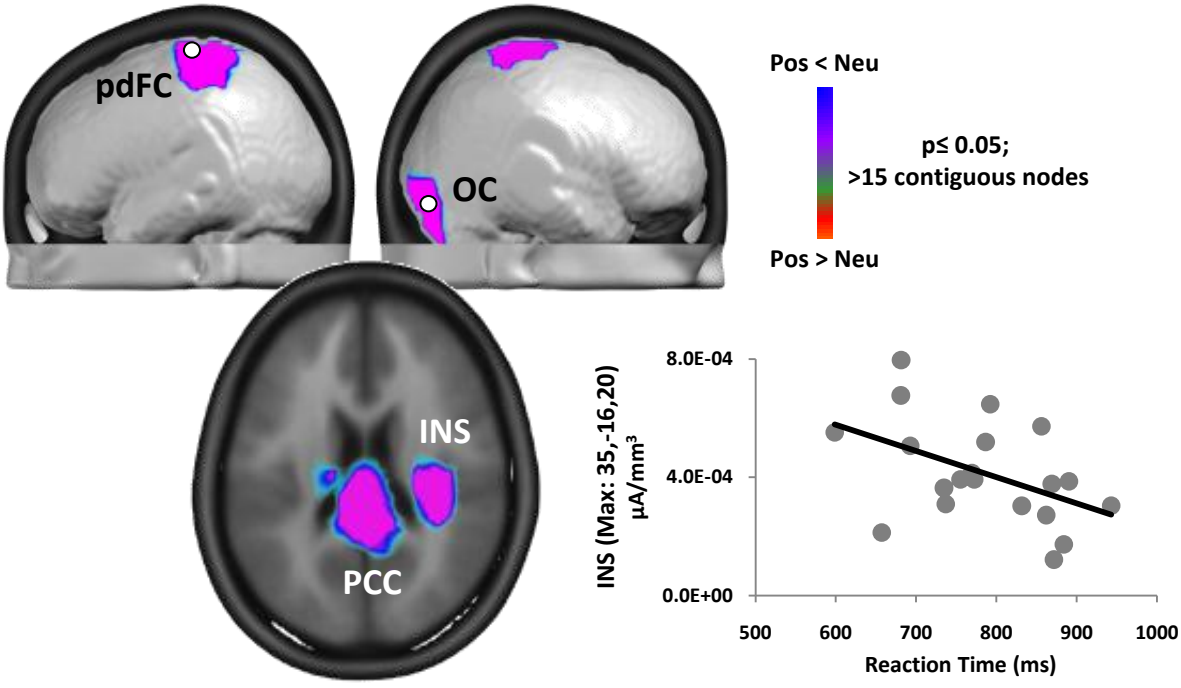
c. TANOVA results for the HiFat food category (POS vs. NEU)



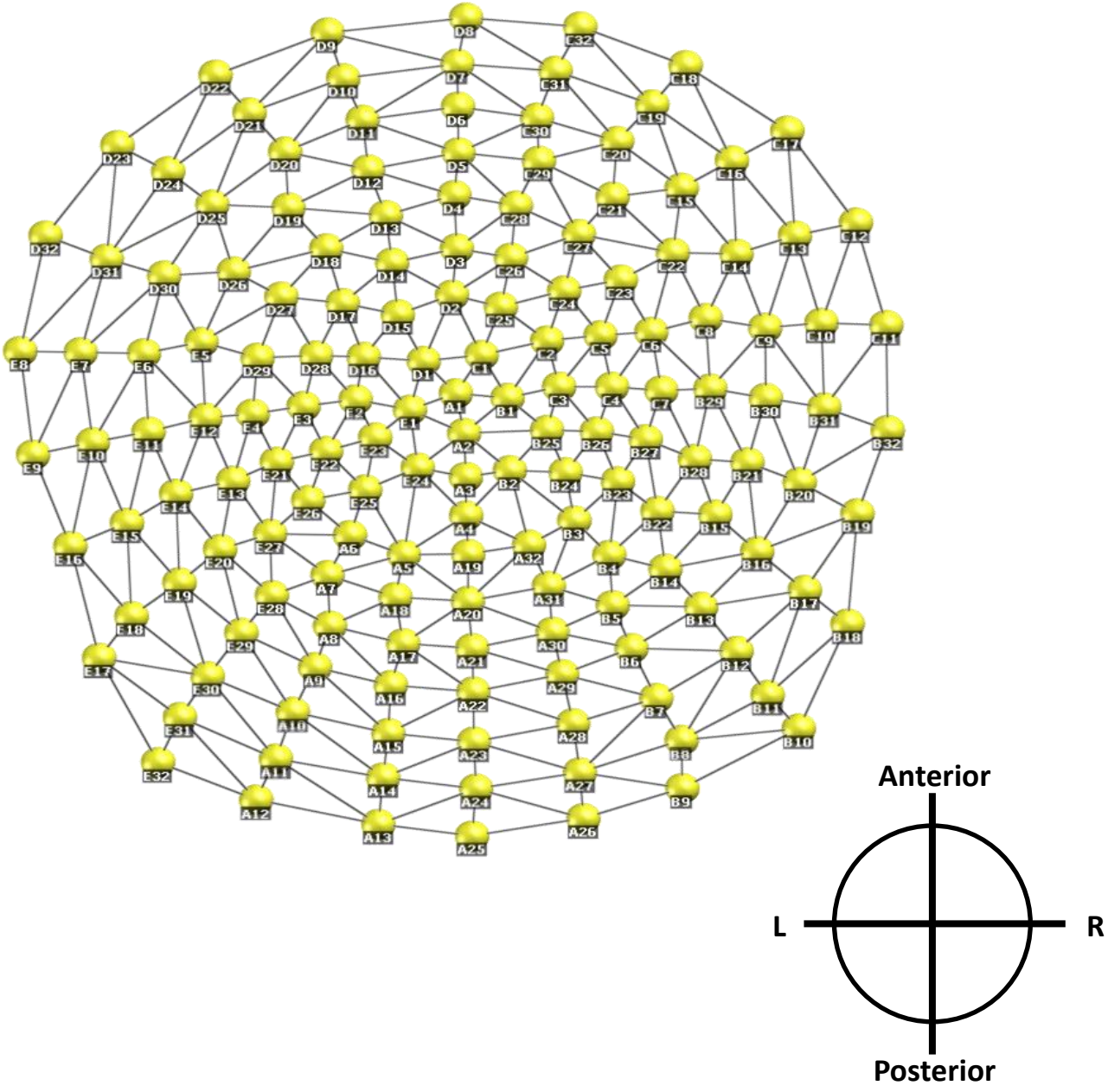
d. TANOVA results for the HiFat food category (POS vs. NEG)



HiFat images preceded by positive vs. neutral verbal labels

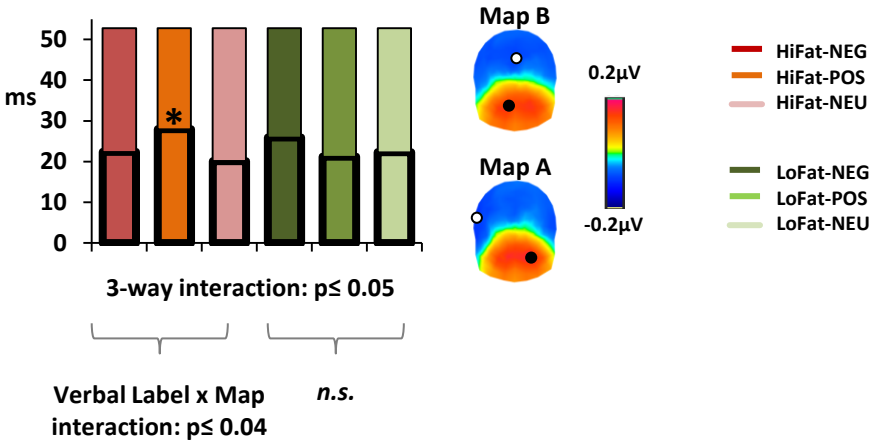


z = 20



Supplementary Figure 1: Electrode montage

a. Template maps and fitting results over the 258-310ms post-stimulus interval

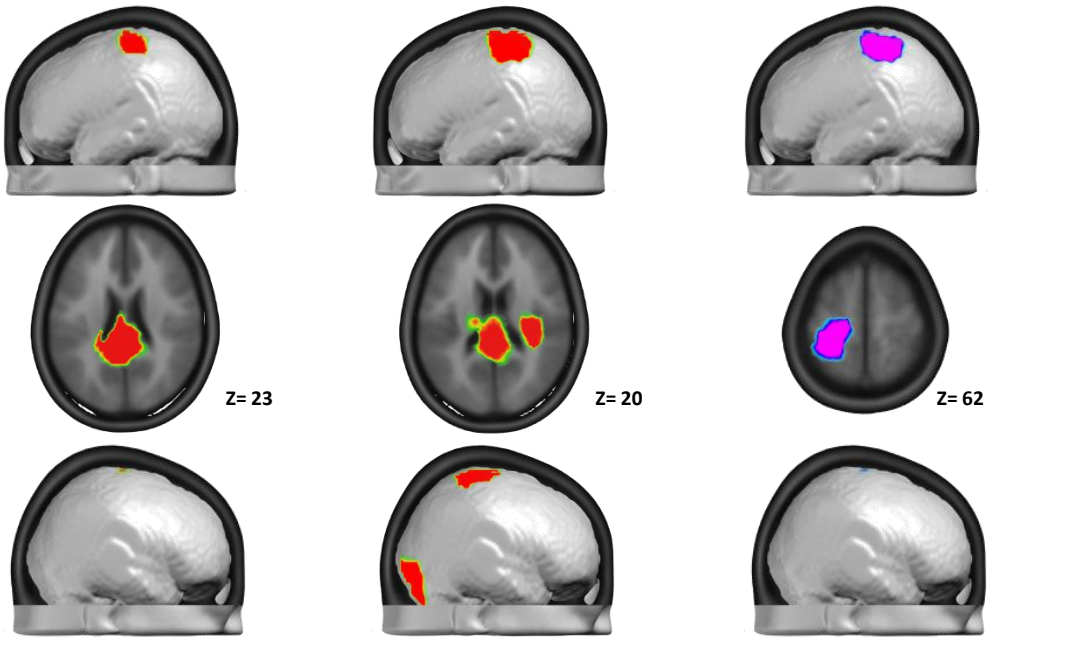


Supplementary Figure 2: Topographic cluster analysis and fitting results

a. 2x3 ANOVA:
Food category x verbal label interaction (258-310ms)

b. 1-way ANOVA:
HiFat food images

c. Paired t-test:
HiFat food images preceded by POS vs. NEG verbal labels



***p*<0.05; >15 contiguous nodes**

POS < NEG **NEG < POS**

Supplementary Figure 3