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Hungry Brains: A Meta-Analytical Review of Brain Activation Imaging Studies On Food Perception and Appetite in Obese Individuals

Devoto F.[1,2], Zapparoli L.[1], Bonandrini R.[3], Berlingeri M.[4], Ferrulli A.[5], Luzi L.[5], Banfi G.[1,6], Paulesu E.[1,3]

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1. *fMRI Unit, IRCSS Galeazzi, Milan, Italy*
2. *Department of Psychology and PhD Program in Neuroscience of the School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy*
3. *Department of Psychology and NeuroMi - Milan Centre for Neuroscience, University of Milano-Bicocca, Milan, Italy*
4. *DISTUM, Department of Humanistic Studies, University of Urbino Carlo Bo, Urbino, Italy*
5. *IRCCS Policlinico San Donato, Milano, Italy*
6. *University Vita e Salute San Raffaele, Milano, Italy*

Corresponding author:

Eraldo Paulesu

E-mail: eraldo.paulesu@unimib.it

List of abbreviations:

ALE, Activation Likelihood Estimation; **BMI**, Body Mass Index; **BOLD**, Blood Oxygenation Level Dependent; BP, Binding Potential; **CCA**, Cluster Composition Analysis; **CL**, Cluster; **dlPFC**, Dorsolateral Prefrontal Cortex; **fMRI**, Functional Magnetic Resonance Imaging; **HC**, Hierarchical Clustering; **HW**, Healthy Weight; **OB**, Obese; **OP**, Observed Probability; **PET**, Positron Emission Tomography; **PFC**, Prefrontal Cortex; **PL**, Prior Likelihood; **R-DVM**, Refined Dynamic Vulnerability Model; **SN**, Substantia Nigra; **VTA**, Ventral Tegmental Area.

1. Introduction

Obesity has become a major health concern. A recent study on different European countries estimated that 47.6% o adults are overweight or even obese[1]; furthermore, pediatric obesity is also increased at alarming rates, thus representing a substantial medical and economic burden[2]. To minimize the economic and health consequences of this condition, different approaches have been employed; however, most treatments, from physical activity and lifestyle interventions to bariatric surgery[3], often result in only a transient weight loss[4]. Despite the causes of overweight and obesity may appear straightforward (i.e., an individual's intake of food exceeds the homeostatic energy needs), the mechanisms underlying the overeating behavior remain largely mysterious. Indeed, eating is a complex and multisensory experience that calls into play different interrelating factors, at either the peripheral (homeostatic) level, with the long-term and circadian fluctuations of signaling molecules (e.g., ghrelin, insulin, leptin; see[5] for a review), and central (neurocognitive) level. The hypothalamus and reticular formation, represent, of course, the interface between the humoral and the neurocognitive levels[6,7]. With that said, it follows that any treatment or approach to the study of the normal and pathological eating behavior "cannot remain brainless", to use the wording of Schmidt and Campbell[8].

In the last 30 years, neuroimaging techniques including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have offered system-level tools for the study of neurocognition, leading an increasing number of neuroscientists to study the neurofunctional mechanisms underlying eating behavior in healthy weight (HW) subjects, and their altered functioning in the obese (OB) population using receptor binding or activation protocols (reviews in [9,10]). The studies based on activation techniques, the focus of this article, are now sufficiently numerous and diverse to justify an attempt at a quantitative review of the cumulative evidence.

In the present manuscript, we reassess the available task-based imaging activation evidence using a quantitative meta-analytical approach. This is not the first meta-analysis on the subject, yet, as the reader

shall see, for the first time we explicitly assess the mutual relationship between three factors that may interact in giving rise to specific brain activation patterns: (1) weight status (lean versus obese) (2) sensory modality of food-related stimulation and (3) satiation state at the time of testing. The data available about the aforementioned variables have been taken as benchmarks for the discussion of the main neurocognitive theories of obesity and overeating (see[10] for a detailed, paper by paper, review).

In what follows we first introduce, briefly, the main theories on neural vulnerability factors associated with obesity; second, as individual imaging studies represent the "raw data" for the present meta-analysis, we rather summarize evidence derived by previous meta-analyses and we spell-out the methodological and historical justifications for the present new meta-analysis.

How and why we may become overweight or even obese? Neurocognitive theories of long-term phenomena.

As extensively discussed elsewhere[10], there are several theories that try to give neurocognitive explanations of the development of obesity. These all, one way or the other, associate the dysregulation of food intake with alterations within either the reward system or the cognitive control system. Initial evidence[11-14] permits to combine these theories with the genetic makeup that determines the expression of greater dopamine signaling capacity. This is associated with the TaqIA (rs1800497) polymorphism: subjects with A2/A2 genotype seem to have 30–40% more dopamine D2 receptors[15,16].

The theories focusing on the *reward system* and its anatomical underpinnings - the ventral tegmental area, the ventral striatum, the orbitofrontal cortex and the insula - postulate that subjects become obese because of their permanently increased reward signaling for food-related stimuli (food taste of food intake or food-related cues). For example, the **Reward Surfeit Theory of Obesity**[17,18] suggests that subjects would keep overeating because this gives them a strong permanent reward during the intake of high-calorie, palatable food.

A refinement of this theory can be found in the **Incentive Sensitization Theory of Obesity**[19,20] which anchors the migration of reward responses from taste-related experiences triggered by anticipatory visual cues, to modifications within (a) the *reward system* (manifested in the terms of a down-regulation after repeated cue-reward associations), (b) the *habit related system*: obese would show an up-regulation in the long run that is driven by visual cues. This theory echoes similar concepts from the domain of drug abuse and chronic addiction (see for example [21,22]). Instrumental in the making of these modifications within the reward system would be variations in dopaminergic and endorphin neurotransmission[19,23,24].

On the contrary, the **Reward Deficit Theory of Obesity** posits that obese people keep overeating because "they would never get satisfied enough by their eating", their reward system being less sensitive to dopaminergic signals[25]. Based on initial evidence that blocking D2 dopaminergic receptors leads to obesity[26], the theory has been put into question by the evidence that atypical neuroleptics (with less effect on D2 receptors) have a greater obesogenic effects than haloperidol[27]. A U-shaped response of the ventral striatum to too high or too low levels of dopamine in obese may still keep the theories mentioned so far under the same conceptual umbrella.

In a different vein, an **Inhibitory Control Deficit Theory**[28] calls into play higher-level control functions: these would be not as good in obese patients who would over-react to food-related cues, a behavior related to a more general trait of impulsivity. Consistent with this concept, obese patients would be more prone to temporal discounting phenomena, thus preferring short-term food rewards over the long-term ones[29-31]. However, while the supposed inhibitory control deficit does correlate with a general impulsiveness[32], to date only few neuroimaging studies have shown a relationship between lower activity in inhibitory regions during a delay-discounting task and future weight gain[33,34]: this makes it impossible to draw firm conclusions about the role of inhibitory control regions in overeating.

Other two theories try to achieve an integration of these different neurocognitive accounts of obesity, the **Dynamic Vulnerability Model of Obesity (DVM, [35,36])** and its refined form, the **R-DVM**[10]. The

refined form of the theory brings together, in a sequential fashion, the most solid aspects of those discussed before conceding that the predisposition to obesity starts with a hyper-responsivity of the reward system to taste which in turn leads to overeating also in combination with genetic factors related to dopamine signaling[11,12,37].

This hyper-responsivity to taste is thought to contribute to greater cue-reward learning and faster habituation to food of the reward system (reinforcer satiation), both of which have been shown to predict overeating independently[38]. Enhanced cue-reward learning is believed to trigger incentive motivational processes in subjects exposed to food cues, as suggested by the comparison of brain activity in HW and OB individuals exposed to food pictures[13,39,40].

Stice and Yokum[10] also propose that a bias for immediate reward is a further factor behind overeating and weight gain, as immediate reward bias predicts weight gain in children[41,42] even over a 30-year follow-up[43]. Finally, the R-DVM predicts that the repeated overeating, leading to weight gain, contributes to the blunted responses of the reward system to palatable high-calorie food intake. It is worthy to note that the R-DVM is based on evidence coming from prospective studies on the neurofunctional predictors of weight gain. Yet, it is not clear whether the neurofunctional predictors of weight gain map into the brain abnormalities associated with chronic obesity.

Hungry brains: how satiety interacts with food-related behavior in obese and healthy weight individuals.

If anything, one missing link between obesity and brain mechanisms in the aforementioned models is the one related to short-term circadian regulatory phenomena, as those implied by the varying levels of satiety during the day[5], and how the sense of satiety interacts with the factors mentioned so far[44-48] in obesity or in lean weight subjects.

Indeed, despite the growing evidence pointing to altered brain responses to hunger and satiety in OB individuals, the effect of the motivational state on the neural responses to food has not been fully considered by all the neurocognitive models of obesity: yet, it is reasonable to hypothesize that an impaired sense of satiety may contribute to the maintenance (or to the worsening) of the obese weight status. The incentive sensitization theory is the only model that implemented the satiety state as a modulator of the reward system reactivity[19]. In its transposition to computational models[49], hunger is expected to multiply the incentive salience process, boosting "liking" and "wanting" reactions to food intake and associated cues. On the contrary, satiety is expected to blunt hedonic reactions to food consumption and anticipation, leading to diminished "liking" and "wanting" reactions and to down-regulated activity of the mesocorticolimbic system in response to food intake and food cues.

Cross-sectional studies comparing HW and OB individuals during fasting (i.e., hunger state) and fed (i.e., satiety state) conditions suggest that OB show persistent brain activations to food intake and to food cues even after eating to satiety. For example, PET studies using measures of regional cerebral blood flow reported increased neuronal activity in the prefrontal cortex (PFC) and decreased activity in limbic, paralimbic and striatal regions in OB compared to HW individuals during the feeding to satiety of a liquid meal[45,46].

There is also evidence that OB, compared to HW individuals, exhibit greater activation of the hypothalamus and the dorsolateral PFC (dlPFC)[48], in addition to greater responses of striatal, medial and superior frontal regions in response to food images in a satiety condition[47]. Altogether, previous studies suggest that OB individuals suggest a persistent brain activation in response to food even in a condition of satiety, which highlights the on-going motivational and reward processes in the absence of homeostatic energy needs[50]. On the other hand, hunger has been associated with increased activation of regions involved in reward, motivation (insula, hypothalamus, striatum, orbitofrontal cortex) and memory (hippocampus, amygdala) in HW individuals exposed to simple tastes[51], whereas higher self-reported

impaired satiety was associated with reduced responses of the dlPFC in response to food images in OB individuals[50]. So far, neuroimaging studies have provided evidence suggesting that the appetitive and motivational states exert a different influence on the neurofunctional responses to food in HW and OB individuals, thus suggesting an impaired central satiety signaling. Despite not being directly associated with future weight gain in previous studies, we believe that an impaired central satiety signaling might have a role in overeating and/or in the maintenance of the unhealthy weight.

To summarize the two preceding sections, as it should be clear by now, there are multiple theories on the neurocognitive underpinnings of obesity, in its making and in its maintenance over time. Besides the testing in animal models, a substantial part of the evidence taken in support to each and every theory rests, at least in part, on functional neuroimaging activation data. Given the complexity of the matter at stake, no single experiment has had the potential to address all the relevant issues with a single paradigm. However, to date there have been no less than twenty functional imaging brain activation studies, to make a conservative estimate, that have attacked these issues from a variety of perspectives. This is a suitable situation to address, using meta-analytical techniques, the available functional imaging evidence and assess the relative explanatory power of the "three factors" cited at the beginning of this introduction. This leads us inevitably to a short summary of previous meta-analysis of imaging data on obesity. As we will argue, these previous meta-analyses, while valuable in their own right, did not fully exploit the available data and this justifies our effort.

Previous meta-analyses on functional imaging in obesity

In an effort to summarize the results of the above-mentioned studies, an increasing number of quantitative meta-analyses have been published. Meta-analyses have the ambition, at the very least, to find highly reproducible results across different studies.

Some authors have focused on the neural responses to taste[52] and to food images[53,54] in HW subjects, while others focused on the aberrant neural responses of OB individuals to visual food cues[55-57]. In a nutshell, in response to food cues, OB subjects show hyper-activations in limbic and frontal regions, whereas most convergent hypo-activations were found in the left dlPFC and in the left insula[55]: this finding was replicated by the meta-analysis of Kennedy and Dimitropoulos[56] who also explored the role of the satiety state on the neural responses to food cues, showing that OB individuals exhibit persistent activity to food images in striatal and frontal regions, despite their satiety state[56].

Another evidence for impaired central satiety signaling in OB individuals has been provided by Pursey and colleagues[58] who performed a series of ALE meta-analyses to explore the role of satiety in response to the exposure to visual food cues and the changes in the neurofunctional activations after weight loss. They found that OB individuals have persistent activation of gustatory, limbic and reward-related striatal regions to food cues, even after a meal[58]. Moreover, the most convergent decrease of activity in response to food cues, after weight loss, was found in the right medial/superior frontal gyrus, in addition to the left superior temporal gyrus, thalamus, cingulate gyrus and right precentral gyrus.

All these previous meta-analyses on imaging data from obese populations were based on the use of the ALE technique[59,60], whose ease of use has been instrumental for the appearance of an increasingly vast meta-analytical literature. However, meta-analyses based on ALE (GingerALE[59]) are limited by the need of testing regional functional anatomical effects from highly homogeneous studies permitting, at the most, the evaluation of the neurofunctional differences (e.g., Task A > Task B) and commonalities (e.g., conjunction effect of Task A & Task B) between two classes of studies. The software cannot test more complex factorial models, the level of analysis needed for a complex neurocognitive scenario like the one behind overeating and the eventual manifestation and maintenance of obesity.

Aims of the study

Our study was motivated, on the one hand, from the conjecture that there is sufficient empirical evidence from several different brain activation studies on obesity to define a replicable underlying dysfunctional anatomy and, on the other hand, from the desire of testing the different neurocognitive theories of obesity in the light of the three factors discussed before: body weight, sensory modality of food-related stimulation and satiety. By design, we limited ourselves to evidence coming from fMRI/PET activation studies on adults in two fixed states, obese or lean[1]. To the best of our knowledge, this is the first meta-analytical attempt to summarize the previous neuroimaging literature in light of the principal neurocognitive theories of overeating and obesity while classifying the available data according to a factorial design suitable for reflecting both anticipatory (e.g., visual) and consummatory (i.e., gustatory) processing of food stimuli. With this respect, Table 1 shows to what extent the three factors and their interactions were tested by previous meta-analyses on the topic.

[TABLE 1]

To this aim, we re-assessed the previous activation literature by using a recent meta-analytical technique, which provides reproducible results using hierarchical clustering (HC), the optimized algorithm of Cattinelli et al.[61] implemented in a meta-analytical suite called CluB (Clustering the Brain)[2]:

[1] By design, we did not include in our meta-analysis data coming from PET molecular imaging studies mapping neurotransmitter receptor density of displacement. It is not clear to what extent this information is biologically consistent with that carried by changes in BOLD signal or regional cerebral blood flow. We felt methodologically not acceptable to bias the identification of brain clusters using information derived from multiple heterogeneous sources. Furthermore, PET studies based on ligand work are typically analyzed using regions of interest, an approach not suited for quantitative meta-analyses typically based on stereotactic coordinates, as in our case.

[2] The CluB software can be found here https://goo.gl/rB2DQx.

CluB identifies clusters of regional effects from a starting data-set but it also permits a *post-hoc* statistical assessment of the association of a given cluster with a factor or indeed the interactions between factors. In fact, the theories summarized above have different predictions on the neurofunctional responses to food in function of the sensory modality of stimulus presentation and of the weight status, something that was not assessed in previous meta-analyses. We also speculated on how and whether an impaired central satiety signaling may interact with the factors above.

Predictions

At variance with what can be done in a fresh empirical experiment in which the variables under examination are controlled by the experimenter, meta-analyses are more observational in nature. Yet, our factorial approach permitted, at the very least, to test to what extent various neurocognitive theories on overeating are justified by the available imaging literature (for the application of the same logic in a different domain see[62]).

As it can be appreciated by the inspection of Table 2, where models are somewhat arranged in order of complexity, simple theories compete with each other (e.g., reward surfeit and reward deficit theories); other theories can be integrated together more easily (e.g., the inhibitory control theory can be added to any other theory), while the R-DVM, with its integration of the most robust aspects of other theories, represents the most complex and dynamic scenario, providing predictions for both anticipatory (e.g., visual food cues) and consummatory (e.g., actual receipt of taste in the mouth) brain responses to food. Indeed, throughout the manuscript, we will refer to the "visual" and "gustatory" levels of the "sensory modality" factor as reflecting *anticipatory* and *consummatory* brain responses to food, respectively, in accordance with previous neurocognitive theories.

Despite not committing ourselves to any of the aforementioned models from the outset – we consider these not to be necessarily mutually exclusive - and despite the limitations of meta-analyses as far as the

[TABLE 2]

possibility of making strong predictions, we had a series of educated guesses in mind at least about what theory would be supported by a given finding[3] (see Table 2).

Starting from a very easy one, the **Reward Surfeit Theory**[63] suggests that a predisposing factor to excessive food intake in some individuals is the fact that food ingestion has a particular rewarding value. Thus, the main prediction of the Reward Surfeit Theory is that OB individuals display higher activation of the reward system in response to food intake.

On the other hand, the **Incentive Sensitization Theory**[19,20] would be supported if there were evidence that obese individuals, who have undergone repetitive pairings of visual cues with the hedonic sequelae of food ingestion, had shown greater involvement of regions involved in salience attribution (e.g., insula, amygdala, hippocampal complex) and reward processing (midbrain, striatum, orbitofrontal cortex) in response to visual food cues[13,39,40,47,48,57].

Further, a down-regulation of dopamine-mediated reward regions in OB, in agreement with studies on overfeeding in animal models of obesity[18,64-67] and some neuroimaging studies in humans[16,25,26,68], would be in line with the idea that, rather than being an initial vulnerability factor to overeating, the down-regulation of the dopaminergic reward system is the main consequence of weight gain[69], in accordance with the **Reward Deficit Theory**[25,26]**.**

Finally, the **Inhibitory Control Deficit Theory**[28,70] emphasizes the role of the neural circuits underlying the inhibition of inappropriate behavior and pathological temporal discounting[34], mainly

[3] It has to be pointed out that the nominal report from several sources of the involvement of a given anatomical structure in a given process does not guarantee by itself that the findings, once the stereotactic coordinates are used, will converge. anatomically in a meta-analysis. This is particularly true the less specific it is the anatomical definition originally used (e.g., prefrontal cortex; insular cortex).

involving the PFC and particularly its dorsolateral subdivisions. On the basis of this theory, we would expect that HW individuals had exhibited greater activations of the dlPFC compared to OB during the perception of food images, to suggest a limited inhibitory processing in the OB population.

All these models but the incentive sensitization theory have not taken into great account the role of circadian fluctuation of satiation and hunger on overeating. Yet, the demonstration of a strong effect of the level of hunger and its interaction with the various systems would call for a further refinement of some of the models discussed.

Having spelled out the main benchmarks for the different theories considered and the ensuing educated guesses, what counts here is that we did put ourselves in a sufficiently good position to test them and to provide quantitative answers to the issues described.

2. Materials and Methods

Our meta-analytical approach involves a series of analytical steps starting from the identification of the raw data (data collection and data preparation), followed by hierarchical clustering and statistical inferences on the clusters which comprise a cluster composition analysis and a validation of the spatial relevance of each cluster. These procedures are described in detail below.

2.1. Data collection and preparation

We identified neuroimaging studies exploring the neural correlates of the processing of food stimuli (presented in either the visual-anticipatory or gustatory-consummatory modality) in HW and OB individuals across different motivational states using the following procedures.

First, we entered the following queries in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/): "obesity and fMRI", "obesity and PET" "obesity and functional magnetic resonance imaging", "obesity and positron-emission tomography" and "obesity and neuroimaging". The initial set of studies included 7391 papers, updated to February 2017 (Figure S1 in Supplementary Materials).

Second, after removal of duplicates, we ran a preliminary selection based on the titles and abstracts of the papers, through which we excluded the studies that did not match the following criteria:

- Data reported using stereotactic coordinates (either MNI or Talairach atlases);
- Activation protocol on food-related stimuli limited to passive visual (i.e., reflecting the anticipation and not the actual food intake) or gustatory (i.e., reflecting the actual taste/food in the mouth) stimulation (only simple effects related to stimuli or between-group comparisons for the factor obesity were considered). For example, studies employing delay-discounting tasks[33,34] or requiring explicit inhibitory processes[71,72], not reflecting simple anticipatory processing, have been excluded.

- For studies contrasting or collapsing together different sensory modalities or satiety states, we considered only foci coming from contrasts derived from stimulation in a single sensory modality (visual or gustatory) and satiety state (foci coming from contrasts in which fasting and fed conditions were merged[73,74] have been excluded);
- Adult subjects;
- Populations involved: either obese subjects, or healthy weight, or both;
- For studies with obese subjects, we considered only populations with BMI above or equal to 30 (World Health Organization, 2000);
- For comparative studies of obese versus control subjects, we considered only studies that employed a standard BMI cut-off to dichotomize groups (i.e., we did not consider correlation studies);
- Whole brain analyses (no region-of-interest analyses);
- For studies assessing the effects of hormonal or drug treatments, we considered only studies that reported foci belonging to the pre-treatment condition; these were used for the analysis.

This selection, initially primarily based on titles and then on abstracts, yielded to the identification of 37 papers candidates for the meta-analysis (Figure S1).

Third, we made a further selection by inspecting the entire manuscripts and applying the aforementioned inclusion criteria in detail.

The final dataset included 22 papers[39,44,47,57,75-92], 70 contrasts and 660 activation foci (see Table S1 in the Supplementary Materials for a detailed description of the paradigms).

To arrange the dataset for the subsequent Cluster Composition Analysis (CCA), each focus was classified according to the three factors of interest: group (HW vs. OB), sensory modality (visual vs. gustatory) and satiety (fasting vs. fed). Further, all the Talairach coordinates were converted to MNI

space through the Talairach to MNI (SPM) transformation implemented in GingerALE[59,60], version 2.3.6. Ten out of 660 foci were excluded from the dataset because they fell outside even from the less conservative brain boundary mask of the GingerALE software.

In the end, the dataset was based on 556 participants, 329 HW, and 227 OB (mean BMI = 22.4 vs. 35.6; mean age = 32.6 vs. 36.9 years), with an average of 8.6 hours of fasting for the fasting condition. Subjects in the fed condition were by default those who just have had a meal.

2.2. Hierarchical Clustering Analysis and Cluster Composition Analysis.

To identify anatomically coherent regional effects, we first performed a HC analysis using the unique-solution clustering algorithm developed by Cattinelli et al.[61]. This method, implemented in a suite of MATLAB (2014a MathWorks) and C++ scripts called CluB (Clustering the Brain), takes into account the squared Euclidian distance between each couple of foci included in the dataset. The clusters with minimal dissimilarity are recursively merged using Ward's criterion[93], to minimize the intra-cluster variability and maximizing the between-cluster sum of squares[61]. To impose a suitable a priori spatial resolution of our analyses, we set to be 5 mm the maximum mean spatial variance within each cluster in the three directions. The centroid coordinates of each resulting cluster were then labeled according to the Automatic Anatomic Labelling (AAL)[94] and then controlled by visual inspection on the MRIcron[94] visualization software.

The output of the HC analysis was then entered as an input for the subsequent CCA. This procedure allows a post-hoc statistical exploration of each cluster by computing, within each cluster, the proportion of foci belonging to different levels of a variable of interest. Such proportion is then compared with a target proportion, which, in our case, is extracted from the overall distribution of foci classified according to our factors of interest in the whole dataset (Prior Likelihood, PL). First, we ran a CCA to explore the main effects of group, sensory modality, and satiety. This composition analysis was done by running a

binomial test on the proportion of foci associated with each level of the three factors within each cluster. For example, if a cluster X had a cardinality of N = 20 and included 15 foci associated with the level "HW" of the "group" factor, CluB computes the proportion 15/20 (i.e., 0.75) and compares it with the theoretical proportion computed over the entire dataset (e.g., PL_{HW} = 377/650 = .58). Hence, (a) the Prior Likelihood represents the probability of success under the null hypothesis and (b) a significant binomial test ($p < .05$) indicates that the proportion of activation peaks included in that specific part of the brain is higher than the proportion computed all over the brain. Afterwards, to test for interaction effects (sensory modality-by-satiety, group-by-sensory modality, and group-by-satiety), we performed a series of Fisher's exact tests[95] on the empirical peak-distribution within each cluster. Finally, with the aim to interpret the directionality of the second-level interactions, we employed the following method: for each cell of the 2 x 2 crosstab, we calculated the ratio between the proportion of observed foci and the total number of foci within the cluster (OP, observed probability). Then, we divided this value for the proportion of foci belonging to the same factors considering the entire dataset (PL, prior likelihood). This computation (i.e., OP/PL) results in an index that indicates the degree to which the distribution of activation peaks belonging to a specific combination of factors within a cluster exceeds the expected probability. Values greater than one indicate a higher probability for the cluster to be specific for that particular combination of factors. Despite not being associated with a formal statistical test, the same procedure was applied to explore, descriptively, eventual three-way interaction effects (i.e., group-by-sensory modality-by-satiety interactions).

To limit the impact of any given study on our inferences, we considered for further discussion only clusters with at least 3 contributing studies; moreover, we discarded those clusters with cardinality (i.e., number of peaks) inferior to the 25th percentile (< 3) of the total cardinality of clusters.

2.3. Validation of the spatial relevance of each cluster using the ALE procedure

As the HC procedure does not provide a statistical test of the spatial significance of the resulting clusters, this can be compensated for by searching for spatial convergence between the clustering solution and the results of an Activation Likelihood Estimate (ALE)-based meta-analysis on the same overall dataset (see, for example [62]). For the spatial cross-validation ALE we employed the Turkeltaub Non-Additive method[60], with the general statistical threshold set to $p < 0.05$ FDR corrected. For the small subcortical structures, we accepted as significant also clusters converging on a ALE map thresholded at the slightly more liberal $p < 0.001$ uncorrected threshold. The resulting maps were overlapped with the HC map with the "intersection" function in the software MRIcron (https://www.nitrc.org/projects/mricron). Only the clusters that fell in this intersection map were then taken into account for further analyses (the cluster composition analysis) and discussion.

3. Results

3.1. Hierarchical Clustering and Cluster Composition Analysis

The HC analysis returned 119 clusters, each composed by 3 to 16 peaks; mean standard deviation along the three axes was 4.98 mm (x-axis), 4.89 mm (y-axis) and 4.86 mm (z-axis). Of these, 38 were retained following the intersection analysis procedure with the ALE map. On average these clusters contained 8 foci (range: 3-16). The full list of clusters overlapping with the ALE map is available in the Supplementary Materials (Table S2). These clusters were then submitted to a cluster composition analysis (CCA) to test for association with group, stimulation modality and satiety.

The following group, modality or satiety associations imply a more frequent detection of an activation effect in the specified level for each factor (e.g., obese, visual-anticipatory modality, etc.).

3.2. Group-specific clusters

The binomial CCA performed to test whether each cluster was significantly associated with either group revealed that three clusters were significantly associated with HW individuals, that is clusters containing a significantly smaller number of peaks from obese individuals, and three with OB subjects, that is clusters containing more peaks from obese subjects (Table 3, Figure 1). The HW-specific clusters were located in the left midbrain (CL45), right thalamus (CL103) and right Rolandic operculum (CL113). As only two studies contributed to this cluster[76,80], CL113 will not be discussed further. The centroid coordinates of the OB-specific clusters were located in the left ventral striatum (VS, CL43), right superior frontal gyrus (CL23) and the left anterior insula/frontal operculum (CL116).

[TABLE 3 and FIGURE 1]

3.3. Sensory modality-specific clusters

There was one cluster, located in the left anterior insula/frontal operculum (CL116), that was also significantly associated with the visual modality, while six clusters were specific for the gustatory modality (Table 3, Figure 2): these were located in the right pallidum (CL29), right anterior insula (CL41), left ventral striatum (CL43), left postcentral gyrus/Rolandic operculum (CL101) and right thalamus (CL103).

[FIGURE 2]

3.4. Satiety-specific clusters

Only one cluster in the left posterior insula (CL104) was significantly associated with the fasting condition. Three clusters, located in the right superior frontal gyrus (CL23), right caudolateral orbitofrontal cortex (CL31) and in the right superior medial prefrontal cortex (CL72) were associated with the fed condition (Table 3, Figure 3).

[FIGURE 3]

3.5. Group-by-Sensory modality interaction

We identified one significant *group-by-sensory modality* interaction effect (Table 3, Figure 4), and it was located in the left ventral striatum (CL43). The inspection of the graph in Figure 4 (top right) shows that the VS was more likely to be engaged by OB individuals during gustatory stimulation.

3.6. Group-by-satiety interaction

No cluster displayed a significant interaction effect.

[FIGURE 4]

3.7. Sensory modality-by-satiety interaction

Only one cluster, located in the left caudate head/nucleus accumbens (CauH/NAc, CL99) displayed a significant interaction effect (Table 3, Figure 4). The inspection of the graph in the Figure 4 (top left) shows that the left CauH/NAc was more likely to be associated with gustatory stimulation in a fasting state and with the visual stimulation in a fed state.

3.8. Group-by-Sensory modality-by-Satiety effects

Given the numerosity of the peaks in the clusters commented below, a formal estimate of the significance of this level of interaction was not possible. Yet we thought it was interesting to illustrate the origin of the effects in CL43 and CL99, considering the factors "Satiety" and "Group", respectively. To this end we plotted the OP/PL ratio for each combination of the three factors (Figure 4, bottom row). The inspection of the graph in Figure 4 (bottom left) shows that the left CauH/NAc (CL99) were coming essentially from OB individuals during the visual stimulation in a fed state and during the gustatory stimulation in the fasted state. Similarly, the bottom graph in Figure 4 (bottom right) shows that the left ventral striatum (CL43) was determined by activations in OB individuals during gustatory stimulation in the fasting state.

4. Discussion

Before entering into the details of our observations, we wish to clear the discussion of our findings from a possible prejudice. Admittedly, our work was inspired by theories developed to explain substance abuse and one may be led to conclude that with the present findings we will root for a plain explanation of obesity as a case of food addiction. We are not doing so in any deterministic manner. We are well aware that the concept of obesity as a food addiction has been recently criticized on theoretical, empirical and even ethical considerations[96,97]. However, we believe that this does not lessen the potential value of showing that one or more theories, originally developed for explaining substance abuse may fit, as a whole or in part, the available activation imaging literature on obesity. As the literature treated here has not covered all possible aspects of the brain physiology in obesity (e.g., fMRI has little if anything to tell about neurotransmission) it follows that our evidence should not be treated as a strict case for the concept of obesity as caused by food addiction[4].

Having made clear our position with respect to the concept of food addiction, we now attempt to answer three questions on the dysfunctional anatomy associated with obesity, as described by functional imaging activation studies: (1) do the patterns of functional and dysfunctional anatomy converge anatomically in a replicable manner, surviving to a formal meta-analysis and can be specific for a particular modality of stimulus presentation (visual-anticipatory vs. gustatory-consummatory), satiety level (fasting vs. fed) and group (healthy weight vs. obese)? (2) Do the aforementioned patterns reflect the interactive effect of the three factors that we examined (BMI, sensory modality of stimulation and

[4] Another word of caution is needed here: brain activation data by no means can offer a complete picture of the complex phenomena under examination. Molecular brain imaging using PET and specific ligands are offering important complementary ways to address the neural bases of obesity. However, the available corpus of data from this literature in humans is more limited and dominated by "resting state" measures of receptor binding potentials and their relation with BMI: this set of data would not permit the testing of the neurocognitive hypotheses of obesity along a factorial design as it was possible for the activation data. For a comprehensive review of this literature we refer the reader to the article by Van Galen et al. (2017).

satiety), particularly for obese individuals? (3) Do these findings allow us to support in part or full a particular neurocognitive theory on the making and maintenance of obesity discussed in the introduction.

The first hypothesis is not as trivial as it might seem. Anatomical replications in functional neuroimaging are such if they go beyond the mere observation of recurrent anatomical names: indeed, a nominal reference to a given brain structure and the ensuing discussions are deprived of much value unless the precise stereotactic locations of a statistical effect are used and their convergence is submitted to a quantitative meta-analytical assessment[5].

Of course, the testing of the second and third hypotheses was the motivation of our efforts and the answers will be discussed in detail below. For clarity, the discussion will be broken down into questions reflecting or embedded within the effects tested (e.g., Is the reward system down-regulated in obese subjects?) or reflecting the interactions between factors (e.g., Is the tuning of the reward system modulated by the sensory modality of stimulation in obese subjects?). Following an incremental logic, the main effects of sensory modality and satiety will be presented first, followed by the discussion of the main effect of group. Then, we will discuss the interaction among the factors taken into consideration, with particular reference to the effects related to obese individuals. Finally, we will try to integrate our findings and spell-out the implications for the neurocognitive theories of obesity described in the introduction.

Hypothesis one: anatomical convergence of functional effects across studies

The combined clustering procedures identified two main classes of spatially significant clusters: the first is less interesting, as these spatially significant clusters were not associated with group, nor with sensory modality or level of satiety. There were 38 such clusters (Table S2 in Supplementary Materials).

[5] As argued before, the lack of PET ligand data reported with stereotactic coordinates makes it impossible a formal meta-analysis of ligand work with the PET/fMRI activation data.

Not surprisingly, this broad network of brain regions is compatible with both the exteroceptive (visual) and the interoceptive (gustatory, somatosensory) processing of food-related information, in keeping with the activation paradigms that generated such observations. These effects were also captured by previous meta-analyses[52-58,98].

Of greater interest was the second class of clusters, for which the post-hoc CCA revealed significant main effects and interactions between the factors under examination.

To what extent visual-anticipatory rather than gustatory-consummatory food-related stimulation elicit specific patterns of activation?

Visual modality. Among the clusters significantly associated with a specific sensory modality of food-related stimuli presentation, only one cluster was specific for the visual modality: the left anterior insula. As a right insular cluster was specific for gustatory stimuli (see below), these findings suggest *asymmetrical processing* of food-related stimuli for the insular cortex (Figure 2, in purple). Neurofunctional patterns of activation during food perception in different sensory modalities have been shown to overlap in the left insula, whereas olfactory and gustatory stimuli were found to elicit more bilaterally distributed responses[98]. Notably, in the latter study, exposure to food images selectively evoked responses in the left, rather than the right, insular cortex[98]. Our result hence dovetails with findings of previous independent[6] fMRI studies[99-104] supporting an asymmetrical information processing in the insular cortex in function of the sensory modality of stimulus presentation.

Gustatory modality. The majority of the clusters was specifically associated with the gustatory modality (Figure 2, in blue), revealing a network of brain regions typically involved in reward (ventral striatum)[19,105] and sensory processing (right thalamus, right insula, postcentral gyrus/Rolandic operculum) of gustatory stimuli, much as it was found in a previous meta-analysis on the topic[52].

[6] The fMRI studies cited are independent in that the data of those studies did not enter in our meta-analysis.

Common or distinct neural substrates of hunger and satiety?

Perceiving food cues or tastes when hungry or sated elicits *distinct* patterns of neurofunctional activation.

Satiety. We found that three clusters were significantly associated with the fed condition, in the prefrontal cortex: the right SFG, the right caudo-lateral OFC, the superior medial PFC (Figure 3, in dark purple). The prefrontal cortex plays an important role in several higher-order processes such as attention control[106], working memory and decision-making[107], and its over-activation in OB seems a consistent result across meta-analyses and imaging studies on satiety[45,46,56,58]. More specifically, this result may be in keeping with the role of the prefrontal cortex in meal termination[108,109].

Hunger. On the contrary, only the left middle insular cortex was specific for the fasting (i.e., hunger) condition, in a region posterior to the one involved in visual perception of food (Figure 3, in green). This portion of the insular cortex has been linked to the subjective experience of several types of *cravings*, such as craving for food[110,111], for substances of abuse such as cocaine[112,113] and even for air[114]; more importantly, lesions to the insula disrupt addiction to cigarettes smoking[115,116], thus suggesting that the region plays a pivotal role in craving and in addiction-like behaviors.

As discussed below, the sensory modality of stimulus presentation and the satiety state interact in a meaningful way, revealing distinct dysfunctional brain responses in obese individuals.

Is the reward-system up- or down-regulated in obese individuals?

As much as this can be reflected by measures of the BOLD response, our results suggest that the reward-system of obese individuals may be *both up-* (Figure 1, in cyan) *and down-regulated* (Figure 1, in red), in its distinct anatomical subdivisions. Overall, we confirm one of the most frequently reported findings in imaging studies and meta-analyses on food perception in OB individuals: the higher

recruitment of regions involved in reward and motivation (dorsal and ventral striatum), salience (insula and superior frontal gyrus) and gustatory processing (anterior insula) in response to food-related stimulation[55,56,58]. Indeed, most of the clusters associated with HW or OB individuals were also specific for a given sensory modality or satiety condition, thus suggesting that OB individuals show hyper-activation of areas that usually respond to the visual or the gustatory sensory modality (anterior insula/frontal operculum and ventral striatum, respectively), or when satiated (right superior frontal gyrus). In particular, persistent PFC activations in response to food in OB individuals have been linked to the deployment of attentional resources by a taste input[117] or increased inhibitory efforts to contrast striatal and limbic hyper-activations[45,46]. This latter hypothesis is particularly intriguing, because it would frame the striatal and PFC association with obesity under the same conceptual umbrella.

However, in obese individuals, we also identified less frequent activation of the thalamus and the midbrain, in a region compatible with the dopaminergic nuclei: the ventral tegmental area (VTA) and the substantia nigra (SN). Hypoactivation of the midbrain in humans has gone largely unnoticed by previous functional imaging studies and meta-analyses on the topic, despite the quite compelling evidence pointing to dysregulation of VTA activity in animal models of obesity[18,65-67].

Given the nature of the signal submitted to meta-analysis (focal changes of the BOLD response) any discussion on the possible mechanisms behind the brainstem signals remains a matter of educated guesses at best. However, it has been recently found that cafeteria diet[7] induced obese mice have increased D2 receptors auto-inhibition of the VTA dopaminergic neurons[64], while obesity was found to decrease the excitability of GABAergic neurons in the VTA[65]. Accordingly, it is tempting to hypothesize that a down-regulation of the VTA, particularly as this may involve GABAergic neurons, may lead to a disinhibition

[7] Consisting of bacon, potato chips, cheesecake, cookies, breakfast cereals, marshmallows, and chocolate candies.

of ventral striatal activity in response to food. Furthermore, the increased response to food in the ventral striatum and a reduced VTA response might represent the two sides of the same coin of a dysregulated reward system.

Hypothesis two: are there anatomo-(dys)functional interactions between BMI, sensory modality and satiety?

We expected that the interaction between the sensory modality of food presentation (visual-anticipatory vs. gustatory-consummatory) and the satiety state (hungry vs. sated) would unveil specific patterns of dysfunctional responses to food in obese individuals, thus favoring a quantitative assessment of the current neurocognitive theories of obesity. To test our second hypothesis, we first explored the directionality of the significant two-way interactions in the VS and the CauH/NAc; second, we looked for a further modulation of the satiety state and the BMI status in the VS and CauH/NAc, by exploring the origin of what may represent a higher level interaction.

Beyond the main effects of group and sensory modality, the left VS showed a significant **Group-by-Sensory modality interaction**. The post-hoc analysis of the interaction showed that, in obese individuals, there are more convergent activations in the gustatory versus the visual sensory modality, whereas in healthy weight subjects there is no difference between sensory modalities (Figure 4, top right). A further inspection of the cluster composition revealed that the more frequent response to taste was mainly driven by studies in the fasting condition, thus suggesting more potent reward-related responses to taste in fasting obese individuals (Figure 4, bottom right). With this respect, as the duration of fasting time for healthy weight and obese individuals was identical, one may hypothesize that fasting could be perceived more threatening to an obese organism, that is used to higher availability of short-term and long-term energy resources, compared with a normal weight organism. Accordingly, more frequent

activation of regions involved in the motivational/hedonic aspects of food perception such as the ventral striatum, might represent the way of the obese organism to defend the new status of positive energy balance[118], reinforcing the action of eating (noteworthy, the interaction involves the gustatory – consummatory – rather than the visual – anticipatory – sensory modality). Also, one may hypothesize a stronger response to hunger-related peripheral signals (e.g., ghrelin).

The **Sensory modality -by- Satiety effect** observed in the CauH/NAc points to another dysfunctional interaction that might account for overeating: a persistent over-reaction to visual food cues in regions typically involved in reward and motivation[47]. As shown by the inspection of the plot in Figure 4 (top left), satiety seems to modulate in opposite directions the neurofunctional response to food in the CauH/NAc, in function of the sensory modality of stimuli presentation. Given that the specificity for the gustatory stimulation during fasting strongly resembled the effect that we observed in the left VS, we further explored the composition of the cluster with respect to the BMI group (healthy weight vs. obese), to assess whether the effect was mainly driven by obesity. The inspection of the plot in Figure 4 (bottom left) suggests that obese individuals show more frequent activation of the left CauH/NAc in the gustatory stimulation condition during fasting and for visual food stimuli when fed.

Taken as a whole, our results suggest the following conclusions: (i) the tuning of the reward system, in obese individuals, interacts with the sensory modality and the level of satiety; (ii) the way they interact is compatible with enhanced reward processing to taste (particularly when fasting) and with continued reward processing in response to anticipatory visual food cues even when well fed; (iii) current neurocognitive theories are not mutually exclusive, but might tap onto different aspects or timing (onset vs. maintenance) of obesity. This is what we discuss next.

Hypothesis three: do the available data permit to identify a best fitting neurocognitive theory of obesity?

In Table 2 we tried to summarize the benchmarks that one could take in favor of any given neurocognitive theory of obesity. Among the theories there are some that clearly did not stand up as winners in our analyses: for example, the Inhibitory Control Deficit Theory of obesity[28,70] did not receive any support as we did not see reduced frontal lobe activity in obese subjects. As much as anyone who tried to be in a diet knows how much cognitive effort is needed to stick to the dietetic regimen, and to suppress undesirable food eating, it is possible that the lack of support to an Inhibitory Control Deficit Theory might be a by-product of the fact that the hypothesis has been tested only occasionally or indirectly[8]. Indeed, evidence suggests that obese compared to healthy weight individuals show altered activity of inhibitory control regions during Go/No-Go tasks[72] and during delay-discounting tasks[33,34] involving food stimuli, and this alteration is related to weight-loss maintenance[33] and future weight gain[34]. However, since the neural activation during those tasks could not be attributed to simple anticipatory processing, we had to exclude them by our meta-analysis (please refer to inclusion criteria in the Methods section). More importantly, our predictions for the **Inhibitory Control Deficit Theory** mainly stemmed by previous meta-analytical[55,56,58] and preliminary fMRI evidence suggesting that obese individuals show less recruitment of brain regions associated with inhibitory control in response to the mere exposure to food-related stimuli[119,120]. As the simple exposure to anticipatory food cues might not be sufficient to detect a deficient activity in inhibitory control regions, specific paradigms are needed to further explore the Inhibitory Control Deficit account, particularly if this has to be framed in the context of an altered predisposition to temporally discounted rewards[34,41].

[8] One possible benchmark would have been a reduced prefrontal activation when viewing food-related cues in a fed state. However, a group by feeding state interaction was not observed in the prefrontal cortex.

If deciding on the less fitting explanations was perhaps an easy task, deciding on a best fitting theory may be more complicated. This is why in what follows we take an Occam's razor-like approach[9] and exclude the need of more theories if one can explain most of the results.

We start by comparing the **Reward Surfeit Theory** and **Reward Deficit Theory**. The former is supported by the fact that obese individuals showed more frequent activation in regions involved in reward and motivation (ventral and dorsal striatum) in response to taste, in particular when fasting. The latter would find support by the less frequent activation of the brainstem in a region compatible with the dopaminergic nuclei of the midbrain and in agreement with animal models[64,65,67] pointing to a blunted reward system activity in chronic obesity. However, as discussed, if the brainstem down-regulation in obesity was involving specific populations of VTA GABAergic neurons this may lead to a dysregulated and increased response of the ventral striatum. As this would make the data still compatible with the **Reward Surfeit Theory**, we abandon the **Reward Deficit Theory** and retain the **Reward Surfeit Theory** for further discussion.

The next theory to be compared with the **Reward Surfeit Theory** is the **Incentive Sensitization Theory**. This is clearly more articulated and dynamic than the former: by assuming repeated pairings between visual anticipatory cues with the hedonic impact of food consumption, the theory is supported by the evidence of an enhanced response for visual food cues in regions usually involved in salience and reward. Accordingly, we retain the **Incentive Sensitization Theory** as the provisional best fit of the data of our meta-analysis. In fact, our data show that obese individuals, after their prolonged period of overeating, exhibit hyper-responsivity of regions involved in gustatory and salience processing (insula), reward and motivation (nucleus accumbens, caudate head) in response to food cues, which witnesses the process of incentive sensitization to anticipatory visual cues. Nonetheless, the composition of the cluster

[9] Strictly speaking, the Occam's razor approach posits that one should prefer simpler over more articulated explanations. Here we favour best fitting explanations.

in the CauH/NAc suggests that OB individuals exhibit persistent reward and motivational processing in response to food images, as if the incentive salience of food cues could override the peripheral signals of satiety, motivating the eating behavior in absence of homeostatic energy needs. Furthermore, the theory accommodates the impact of physiological body signals like hunger. According to Berridge and colleagues[19] "normal hunger acts as a physiological "drive" signal to magnify the incentive "wanting" and hedonic "liking" triggered by tasty foods and their associated cues whereas satiety dampens the multiplicative impact of cues and foods" (Figure 1, page 32). Therefore, the interaction of hunger with a sensitized reward system would lead to powerful activity of the mesocorticolimbic circuitry in response to visual food cues and to food consumption, which could be also interpreted in favor of a **Reward Surfeit Theory** of obesity.

However, we add that while satiety should normally dampen the impact of food cues, it seems to do so to a lesser extent in obese patients. In the data meta-analyzed here the level of satiety seems to have a different impact on the functional brain patterns of obese subjects in response to food cues or to tastes. The differential response observed in reward areas (more frequent activations for visual cues even in a satiated state in obese) sets the rationale for new empirical studies in which these factors are explicitly manipulated and modeled. In addition, the more frequent activations in reward-areas for obese individuals in response to taste while starving suggests the fact that fasting is a particularly powerful signal for obese, their hyperactivation in such condition representing, perhaps, the result of a greater reward value of food as in classical animal experiments in which animals are exposed to unpredicted rewards[121,122]. To summarize, we believe that our data confirm that any complete theory of eating behavior in obesity should incorporate the differential weight that the level of satiety has for obese subjects. The combination of different levels of satiation with cognitive control task in lean and obese subjects may also revitalize the **Inhibitory Control Deficit Theory** in a more context dependent manner.

Obesity in its making and the vulnerability factors for obesity

There is one other aspect in which ***Incentive Sensitization Theory*** seems not sufficiently explicit: the making of obesity and the connection if its making with vulnerability factors leading certain individuals to have a greater likelihood of becoming obese. These are aspects that our meta-analysis was unable to capture as the studies on obese individuals submitted to meta-analysis were cross-sectional. There is one candidate theory in the literature that that tries to integrate diachronically an initial reward surfeit followed by enhanced value to food related cues and the blunting of the hedonic system, particularly when subjects are exposed to high-calories foods. This is the Refined Dynamic Vulnerability Model[10]. Much of the model is based on considerations derived from longitudinal studies (an aspect not considered here because there are no such studies in the selected imaging literature) and from observations to the response to high-calories food intake. This last aspect was also impossible to assess with the present meta-analysis as a mere 7% of the total gustatory foci came from studies employing high-calorie liquid meals[44,91], whereas the remaining foci came from studies employing pure tastes as gustatory stimuli[44,80,91,123].

Implications for brain-centered treatments of obesity

Having shown that the **Incentive Sensitization Theory** is a likely candidate to provide a neurocognitive explanation of obesity, at least in its steady adult state, it is natural to wonder to what extent this has been or could be conceptually useful to plan therapeutic interventions. Unfortunately, the available evidence of a translation of these principles into clinical practice is limited. The long-lasting temporal characteristics of sensitization suggest that the suppression of the relevance of food cues and their interaction with the level of satiation might be a particularly difficult route to pursue. Clearly this is one area where cognitive behavioral therapy may have an impact.

As far as a more directly brain based approach, neurostimulation and neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current magnetic stimulation (tDCS), have been tested in obesity and eating disorders (for a review see [9]). So far, all the studies employing these techniques have targeted the prefrontal cortex[124-131] providing mixed results. As shown by our quantitative meta-analysis and by a recent review of Stice and colleagues[10], the evidence in support of an inhibitory control deficit explanation behind overeating and obesity is scarce.

One other approach could be to target brain regions involved in salience (insula), reward and motivation (nucleus accumbens and caudate nucleus) as these appear more frequently active in obese individuals exposed to food pictures. Given the role of the insular cortex in the subjective feeling of craving[111] and in nicotine addiction[132] and the recent advances in neurostimulation techniques in reaching deep cortical structures[133], the insular cortex stands out as a promising target for future neurostimulation treatments of overeating and obesity, something that is being tested in clinical trials at the moment.

Finally there has been a recent revival of neuro-pharmacological interventions in obesity beyond amphetamine-like drugs: for example, a combination of naltrexone, an opioid antagonist, and bupropion, an antidepressant, which inhibit dopamine and norepinephrine reuptake seems effective in appetite suppression and weight loss promotion by acting on both the hypothalamus and the ventral tegmental area (review in [134]).

Whether these interventions, in isolation or combined, could reverse the incentive sensitization of the reward system to food and its cues, promoting weight loss and long term healthier eating, remains to be seen and demonstrated explicitly. If so, this would provide a further support to the **Incentive Sensitization Theory.**

Strengths, limitations and future directions

We believe that our meta-analysis represents a step ahead in the attempt to provide an integrated picture of the available imaging evidence on obesity and food related behavior. By adopting a factorial approach, we tried to test the major neurocognitive theories in the field while also taking into account the modulatory role of the motivational state of the participants, to consider satiety specific effects or interactions. We combined the ALE method[59], which reveals the brain regions with most convergent activation across the whole dataset, with hierarchical clustering[61] and *post-hoc* statistical characterization of the clusters concerning the factors of interest. An undoubted advantage of this approach was the possibility to include a heterogeneous set of studies without renouncing to a functional characterization of the meta-analytic clusters. This approach has unveiled previously unnoticed results (e.g., the effect of satiety).

Yet our work has some limitations. We already commented upon the issue of considering obesity as the end point of an addiction to food. We are not rooting for this hypothesis in any deterministic and simplistic manner: we are only showing that many aspects of one theory are supported by the existing activation imaging literature. Future studies will help to decide on whether the concept of food addiction should be abandoned or retained. For the time being, we remark that there are intriguing similarities between the two domains of substance abuse and excessive food intake in already obese subjects.

Further limitations. We cannot exclude that the disproportion between male and female participants of the reviewed studies may have left some effects overlooked. Indeed, there is evidence of gender-specific differences in the brain responses towards food[79,80]. Similarly, it was impossible to take into account data associated with altered levels of appetitive hormones in OB individuals. This is an important issue as altered hormone levels are known to influence the neural responses to food stimuli (see[5] for a review). Not least, the evaluation of the highest order interactions remained at a descriptive level by observation

of which of eight possible levels was pulling in the direction of the higher-level interaction (the group by modality by satiety interactions). While more data are needed to attach a significance to such higher order effects, at the very least, our evidence provides the rationale for future experiments in which body weight, stimulation modality and satiety are manipulated in a controlled manner.

One other issue that remains unaddressed here is the importance of subjective "liking" and "wanting" ratings of food stimuli in (i) shaping the neurofunctional responses to food and (ii) providing support to a neurocognitive theory over the other as assessed by our meta-analysis. The Reward Surfeit Hypothesis implies that the highly hedonic experience of food ingestion may prompt for future overeating, suggesting that people who overeat will show enhanced "liking" reactions to food intake. On the contrary, the Incentive Sensitization Theory focuses on the "wanting" reactions elicited by food cues, suggesting that overeating is triggered by excessive "wanting" that can be accompanied by normal "liking" of food stimuli. As shown in Supplementary Table S1, only half of the studies included in our meta-analysis collected and reported subjective ratings for the stimuli employed. More importantly, the ratings required to the participants are quite heterogeneous across studies, each focusing on a slightly different quality of the stimuli (e.g., pleasantness of the image, palatability or liking of a food). Despite not being a limitation of our meta-analysis per se, the lack of such data has made it impossible to assess how good is the fitting of the theories considered in the light of "liking" and "wanting" components of reward processing: this remains an issue for future studies.

Finally, as we reviewed data comparing adult OB and HW, we cannot draw any conclusion about the temporal and causal dynamics of the phenomena described. Inevitably, given the cross-sectional nature of the studies included in our meta-analysis, our results cannot but provide a relatively "static" picture of the neurofunctional correlates of food perception in obese versus healthy weight individuals, making it impossible to disentangle causes from consequences in chronic overeating over the brain patterns described.

Furthermore, it would be tempting to try and connect the relative less frequent activation of the midbrain in obese individuals and their striatal hyper-responsivity for taste and food cues. However, this is impossible at this stage with the present data and it remains to be empirically tested whether i) the midbrain down-regulation is causally linked to disinhibited striatal activity and ii) whether it is associated with overeating before the individuals become obese. With this respect, we remark that the genetic make-up linked to higher or lower dopamine signalling capacity seems crucial in determining increased versus decreased striatal activity in response to food[11-14,37,135]. The field is much in need of prospective studies examining the differences (and similarities) between the neurofunctional predictors of overeating in HW and OB individuals and whether a differential response to satiety or hunger may represent a vulnerability factor with respect to future weight gain. To the best of our knowledge, we are not aware of any prospective study that explored whether, and how, "hungry" or "insatiable" brains can predict future overeating and weight gain, something left for future studies.

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	Visual-Anticipatory Food Cues		**Gustatory-Consummatory Food Cues**	
	Fasting	*Fed*	*Fasting*	*Fed*
Healthy Weight	• Pursey et al. 2014 • Huerta et al. 2014 • Kennedy & Dimitropoulos 2014 • Tang et al. 2012 • van der Laan et al. 2011 • van Meer et al. 2015	• Pursey et al. 2014 • Kennedy & Dimitropoulos 2014 • van der Laan et al. 2011	• Huerta et al. 2014 • Veldhuizen et al. 2011	• Yeung et al. 2016 (participants with mixed weight status)
Obese	• Pursey et al. 2014 • Kennedy & Dimitropoulos 2014	• Pursey et al. 2014 • Kennedy & Dimitropoulos 2014		• Yeung et al. 2016 (participants with mixed weight status)

Table 1 | Overview of meta-analytical studies on visual-anticipatory and gustatory-consummatory perception of food in healthy weight and obese individuals varying in satiety state.

	Reward Surfeit Theory	Reward Deficit Theory	Incentive Sensitization Theory	Inhibitory Control Deficit Theory	Refined – Dynamic Vulnerability Model
Anticipatory Food Cues			↑ **Hyper**-activity of brain regions involved in salience attribution (insula, amygdala, parahippocampal gyrus, hippocampus) and reward (midbrain, striatum, OFC)	↓ **Hypo**-activity of regions involved in inhibitory control (vmPFC, dlPFC)	↑ **Hyper**-activity of brain regions involved in salience attribution (insula, amygdala, parahippocampal gyrus, hippocampus) and reward (midbrain, striatum, OFC)
Consummatory Food Intake	↑ **Hyper**-activity of the reward circuitry (midbrain, striatum, Insula, OFC)	↓ **Hypo**-activity of the reward circuitry (midbrain, striatum, Insula, OFC)			↓ **Hypo**-activity of the reward circuitry (midbrain, striatum, Insula, OFC)

Table 2 | Anatomo-functional predictions of the main neurocognitive theories on the development and maintenance of obesity. The R-DVM is not explicitly tested in this meta-analysis based on cross-sectional studies in adult obese subjects.

		Left Hemisphere			Right Hemisphere				Group-specific		Sensory modality-specific		Satiety-specific		Group-by-Sensory modality interaction	Group-by-Satiety interaction	Sensory modality-by-Satiety interaction
Anatomical Label	**Cluster ID**	**X (sd)**	**Y (sd)**	**Z (sd)**	**X (sd)**	**Y (sd)**	**Z (sd)**	**Total Foci**	**HW**	**OB**	**Visual - Anticipatory**	**Gustatory - Consummatory**	**Fasting**	**Fed**			
Superior Frontal Gyrus	23				22 (3.5)	25 (3.8)	51 (6.1)	4	1	**0.031**	0.199	1	0.997	**0.044**	1	1	1
Globus Pallidus	29				14 (4.5)	6 (6.2)	-1 (5)	15	0.737	0.453	0.992	**0.03**	0.098	0.983	0.093	1	1
Orbitofrontal Cortex	31				34 (6.2)	30 (2.6)	-15 (4.4)	12	0.804	0.389	0.396	0.817	0.989	**0.043**	0.516	0.608	1
Insula	41				38 (3.9)	18 (4.9)	-3 (4)	14	0.636	0.575	1	**0.001**	0.779	0.432	0.225	0.244	0.221
Ventral Striatum	43	-19 (4)	5 (5.8)	-9 (3.5)				11	0.999	**0.009**	1	**0.001**	0.051	1	**0.002**	1	1
Midbrain (ventral tegmental area/substantia nigra)	45	-5 (3.8)	-15 (2.1)	-4 (6.2)				9	**0.007**	1	0.653	0.62	0.088	1	1	1	1
Superior Medial Frontal Cortex	72				2 (2.1)	59 (3.8)	21 (8.3)	6	0.792	0.497	0.353	0.911	0.996	**0.031**	1	0.097	1
Caudate Head/Nucleus Accumbens	99	-7 (5.5)	14 (8.6)	-9 (6.4)				8	0.937	0.206	0.981	0.087	0.903	0.289	0.505	1	**0.031**
Postcentral Gyrus/Rolandic Operculum	101	-50 (7)	-16 (4.4)	18 (4.3)				7	0.883	0.329	0.993	**0.045**	0.478	0.849	1	1	1
Thalamus	103				14 (4.1)	-14 (3.4)	0 (5.5)	9	**0.007**	1	0.999	**0.008**	0.637	0.667	1	1	0.107
Posterior Insula	104	-39 (4)	-4 (5.6)	6 (5.4)				16	0.92	0.183	0.168	0.94	**0.013**	1	1	1	1
Anterior Insula/Frontal Operculum	116	-38 (5.7)	13 (6.4)	-19 (7.2)				10	0.997	**0.017**	**0.018**	1	0.565	0.725	1	0.509	1

Table 3 | Results of the Cluster Composition Analysis. For each cluster we report: the centroid coordinates in the MNI stereotaxic space; the standard deviation (sd) of the Euclidean distance from the centroid along the three axes; the number of foci falling within the cluster; the p values associated with the binomial and Fisher's tests. Significant main and interaction effects are shown in bold. HW, healthy weight; OB, obese.

Figure Captions

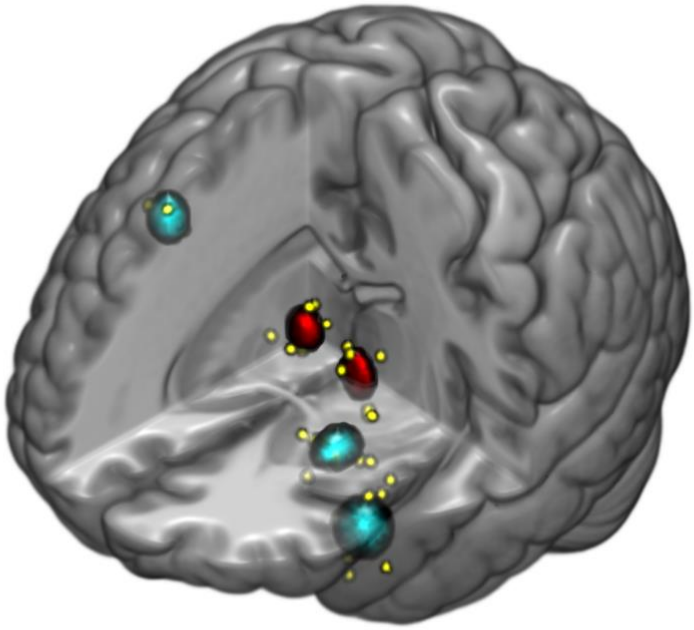

Figure 1 | Distribution of clusters showing a significant main effect of group. Clusters associated with obese individuals are depicted in cyan, whereas clusters specific for healthy weight subjects are depicted in red. Yellow dots represent the cloud of peaks that generated the cluster.

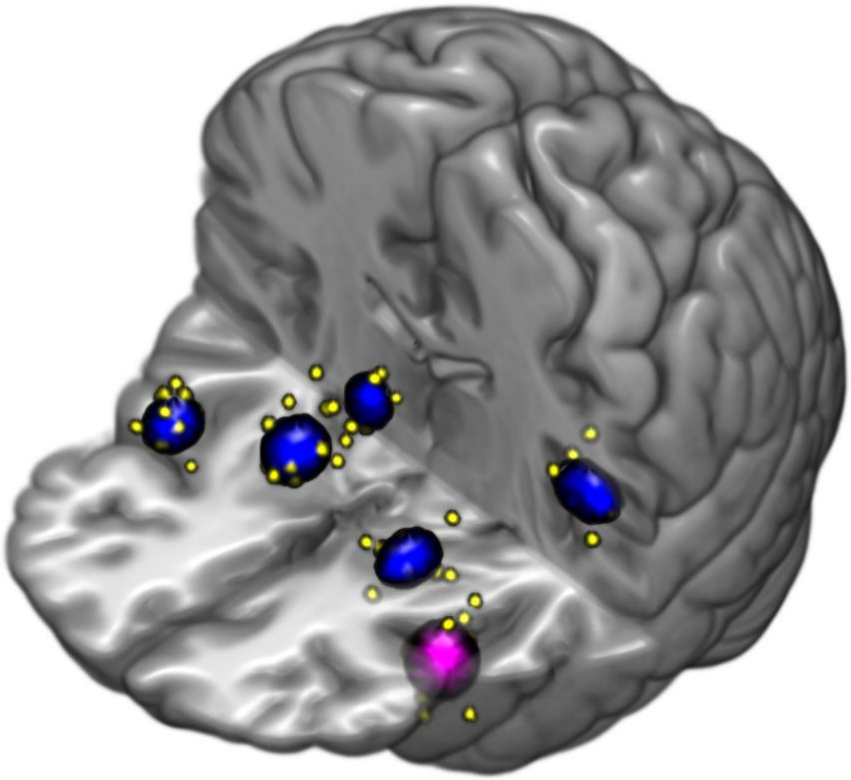

Figure 2 | Distribution of clusters showing a significant main effect of sensory modality. The cluster associated with the visual modality is depicted in purple, whereas clusters specific for the gustatory modality are depicted in blue. Yellow dots represent the cloud of peaks that generated the cluster.

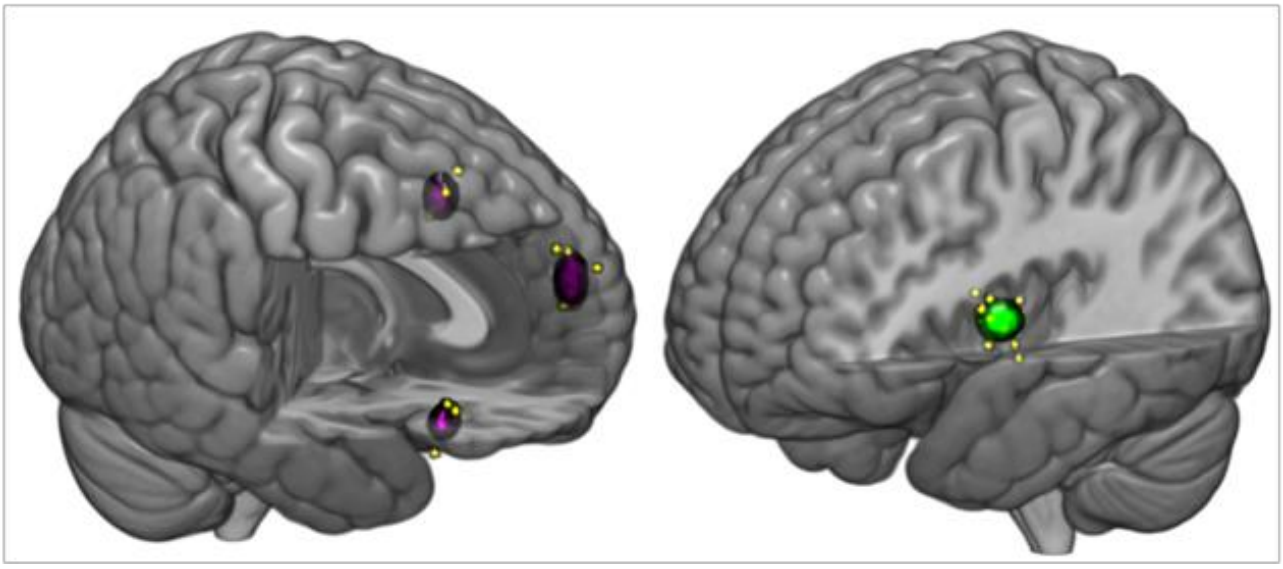

Figure 3 | Distribution of clusters showing a significant main effect of satiety state. Clusters associated with the fed condition are depicted in dark purple, whereas the cluster specific for the fasting state is depicted in green. Yellow dots represent the cloud of peaks that generated the cluster.

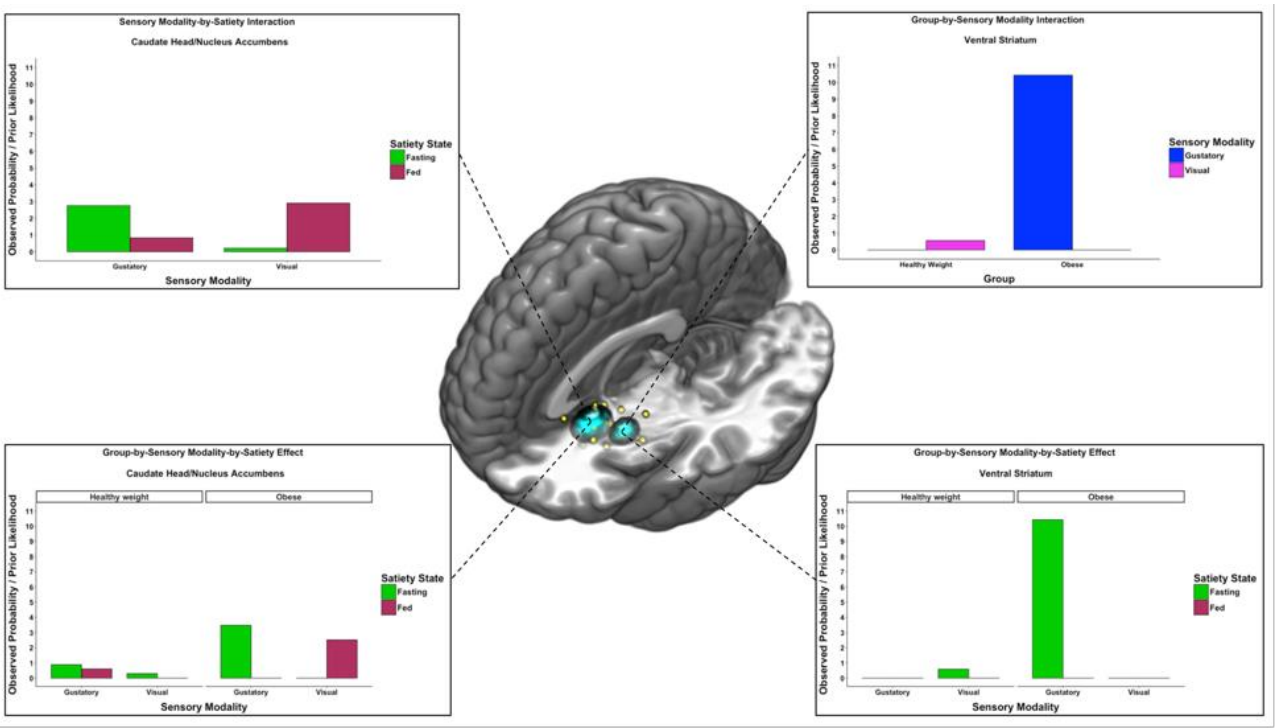

Figure 4 | Distribution of clusters showing a significant interaction effect. Yellow dots represent the cloud of peaks that generated the cluster. *Top:* bar plot for the significant group-by-sensory modality interaction in the left ventral striatum (top right) and for the significant sensory modality-by-satiety interaction in the left caudate head/nucleus accumbens (top left). *Bottom:* bar plot for further visual inspection of group-by-sensory modality-by-satiety interactions in the left ventral striatum (bottom right) and in the left caudate head/nucleus accumbens (bottom left). Values greater than one indicate a higher probability for the cluster to be specific for that particular combination of factors.