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Neural structural abnormalities behind altered brain activation in obesity: Evidence from meta-analyses of brain activation and morphometric data

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ABSTRACT

Obesity represents a risk factor for disability with a major bearing on life expectancy. Neuroimaging techniques are contributing to clarify its neurobiological underpinnings. Here, we explored whether structural brain abnormalities might accompany altered brain activations in obesity. We combined and compared data from brain activation studies for food stimuli and the data reported in structural voxel-based morphometry studies. We found that obese individuals have reduced grey matter density and functional activations in the thalamus and midbrain. A functional connectivity analysis based on these two clusters and its quantitative decoding showed that these regions are part of the reward system functional brain network. Moreover, we found specific grey matter hypo-densities in prefrontal cortex for the obese subjects, regions involved in controlled behaviour. These results support theories of obesity that point to reduced bottom-up reward processes (i.e., the *Reward Deficit Theory*), but also top-down theories postulating a deficit in cognitive control (i.e., the *Inhibitory Control Deficit Theory*). The same results also warrant a more systematic exploration of obesity whereby the reward of food and the intentional control over consummatory behaviour is manipulated.

1. Introduction

Overweight and obesity are defined as excessive fat accumulation that may impair health. The two conditions are usually defined using a Body Mass Index (BMI), a simple ratio of weight-for-height squared (kg/m^2). A BMI greater or equal to 25 indicates overweight; a BMI greater or equal to 30 indicates obesity . Worryingly, obesity rates have nearly tripled since 1975, making it one of the biggest health problems in modern times. Despite the causes of overweight and obesity may appear straightforward (i.e., an individual's intake of food exceeds the homeostatic energy needs), the fine mechanisms underlying the overeating behaviour remain to be established. For sure, food-oriented behaviour is determined by both biological (genetic) and environmental (cultural or energetic expenditure) factors (Kopelman, 2000).

Structural and functional neuroimaging techniques have been fundamental to investigate the neurobiological underpinnings of food overconsumption and obesity. These discoveries have raised the general interest on obesity in the field of cognitive neuroscience: the concept of "*food addiction*" has become popular and its exploration under the same conceptual framework used to explore substance abuse (Fletcher and Kenny, 2018). These imaging studies are now sufficiently numerous and diverse to justify a quantitative review of the cumulative evidence. In a recent meta-analysis, we described the patterns of altered brain activity specific for the obesity condition and their interaction with the satiety state and modality of presentation of food related stimuli (Devoto et al., 2018). Here, we aimed to further expand these findings, investigating whether brain structural abnormalities might accompany altered activations in obesity. To do so, we re-analysed our previous functional brain imaging (fMRI) meta-analytical data, making them comparable with those extracted with the same approach from structural voxel-based morphometry (VBM) studies.

In what follows, we briefly introduce the main theories on neural vulnerability factors associated with obesity that drove our predictions and previous imaging findings. As individual imaging and structural studies represent the "raw data" for the present meta-analysis, we avoid discussing each of the single previous empirical studies, even though

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these are all cited. Rather, in this introduction we summarize the evidence derived by previous meta-analyses. Crucially, our analytical approach allowed us to discuss to what extent various neurocognitive theories on overeating could be supported by the evidence of a conjunction of functional and structural imaging findings.

1.1. Neurocognitive theories of obesity

Several models try to address the development of obesity from a neurocognitive perspective. These theories typically associate the dysregulation of food intake with alterations of the reward system or the cognitive control system, as highlighted by a recent systematic review on the main neurocognitive factors beyond obesity (Stice and Yokum, 2016). For example, the "**reward surfeit theory"** (Davis, Strachan and Berkson, 2004) of obesity suggests that pathologic food consumption is related to greater reward responsivity to food cues. In line with this hypothesis, previous studies demonstrated that normal-weight population at higher risk of obesity is characterized by augmented brain activity in reward regions when exposed to food stimuli (Shearrer et al., 2018; Stice et al., 2011).

The "**reward deficit theory"** (Wang, Volkow, and Fowler, 2002) postulates the opposite hypothesis, suggesting that obese individuals overeat to compensate for a lowered responsivity of reward brain regions in response to food consumption. A dopamine deficiency may be responsible for this mechanism, as it has been suggested that D2 receptors expression in subcortical regions is reduced in obese compared to normal-weight individuals (Volkow et al., 2008). Evidence showing a diminished activation of reward regions in response to food consumption corroborates this hypothesis (Stice et al., 2008).

The **"incentive sensitization theory"** suggests that prolonged overfeeding and exposure to high hedonic foods would cause an enhanced reactivity to palatable substances via an incentive salience mechanism (Berridge et al., 2010). Specifically, associative mechanisms lead the "tempted brain" to respond also to anticipatory food stimuli (e.g., visual cues), rather than only to food consumption (Rothemund et al., 2007; Stoeckel et al., 2008). Support for this theory comes from studies showing an increased attentional bias to visual food stimuli (Carters et al., 2015).

The "**inhibitory control deficit theory"** (Nederkoorn et al., 2006) calls into play higher-level cognitive control functions and it focuses on the inhibitory role of frontal regions in food overconsumption. In line with this hypothesis, previous studies found that obese patients, compared with normal-weight controls, show a preference for immediate rewards (Amlung et al., 2016) and a more frequent presence of trait impulsivity (VanderBroek-Stice et al., 2017).

Finally, a recent model of pathological food consumption tries to synthesize the previous theories into a "**dynamic vulnerability model of obesity"** (DVM, Burger and Stice, 2011), but see also its refined form**, the R-DVM** (Stice and Yokum, 2016). Based on this model, an augmented responsivity of reward regions to food cues and genetic variables or bias would represent risk factors for the future development of obesity. This increased brain activation also constitutes the basis of cue-reward learning to food cues, resulting in incentive sensitized regions that also respond to palatable cues rather than only food consumption, which, consequently, support long-term food overconsumption. The R-DVM predicts that the repeated overeating, leading to weight gain, contributes to the blunted responses of the reward system to palatable high-calories food intake. It is worthy to note that the R-DVM is based on a series of prospective neuroimaging studies reporting (the lack of) significant associations between brain activity in response to food cues (visual, gustatory) and future weight gain (see Stice and Yokum, 2016 for a complete review of the prospective neuroimaging evidence). Nevertheless, it is not clear whether and how the neurofunctional predictors of weight gain map into the brain abnormalities associated with chronic obesity.

1.2. Brain structural and functional abnormalities in obesity: previous meta-analyses.

Several studies investigated the structural and functional abnormalities in obesity, and an increasing number of quantitative meta-analyses summarizing these findings have been published.

Three meta-analyses of structural imaging studies have been conducted so far, and they all highlighted the important role of grey matter density reduction in obesity. For example, García-García et al. (2019) reported a negative association between the BMI and the volume of several brain regions, including the medial prefrontal cortex, the cerebellum, and the left temporal pole (García-García et al., 2019). Another meta-analysis (Herrmann et al., 2019) associated the obese status with reduced grey matter volumes in the left inferior frontal gyrus, the left-middle frontal gyrus, and the right inferior frontal gyrus (including the insula). The same study showed that obesity was also linked with reduced grey matter volume in regions outside of prefrontal cortex - the left middle temporal cortex, left precentral gyrus, and left cerebellum and superior temporal gyrus, including the amygdala and the lenticular nucleus (Herrmann et al., 2019). Finally, Chen and colleagues (2020) highlighted the importance of orbitofrontal cortex volume in obesity (Chen et al., 2020). These results are graphically summarized in Supplementary Fig. S1, upper panel.

For what concerns the fMRI literature of obesity-related abnormalities, the vast majority reported obesity specific hyper-activation of limbic and frontal structures, whereas the most convergent hypo-activations were reported in the left dorsolateral prefrontal cortex and left insula (Brooks et al., 2013). The latter finding was replicated by a meta-analysis that explored the effect of satiety on the neural visual food-cue reactivity, showing that obese individuals exhibit persistent activity to food images in striatal and frontal regions, despite their satiety state (Kennedy and Dimitropoulos, 2014).

Similarly, Chen and Zeffiro (2020) investigated factors that modulate neural responses towards sweet palatable substance consumption: to this end, they performed a meta-analysis using both a categorical and a meta-regression analysis, a method whereby-one can perform regression analyses between brain activity and continuous variables at the meta-analytic level. It was found that obese participants, during consumption of sweet substances, have a reduced activation of the supplementary motor area, the caudate and the globus pallidum. On the other hand, the BMI positively correlated with activity in post-central gyrus, angular gyrus, superior occipital gyrus, temporal gyrus, insula, and cerebellar lobule (Chen and Zeffiro, 2020). In a recent study from our lab, we applied a meta-analytical factorial design to show that obese individuals are characterized by a ventral striatum hyper-responsivity in response to pure tastes, particularly when fasting. Furthermore, we found that obese subjects displayed more frequent ventral striatal activation for visual food cues when satiated. We also reported a less frequent activation of thalamic and midbrain structures, suggesting that the reward system of obese individuals could be both up- and down-regulated (Devoto et al., 2018). These results are graphically summarized in Supplementary Fig. S1, lower panel.

1.3. Aims of the study and specific predictions.

This study aimed at evaluating to what extent structural and functional imaging studies in obesity have shown consistent results and whether any such consistency may support one of the major neurocognitive theories of overeating and obesity.

To do so, we analysed the previous fMRI/VBM literature on obesity, and we classified the structural/functional peaks associated with either obese or normal-weight individuals in different but homogeneous datasets. We then ran two separate meta-analyses with the same Activation Likelihood Estimate analytical approach (ALE, Eickhoff et al., 2012). The results of the meta-analysis of functional neuroimaging studies and the meta-analysis of structural neuroimaging studies were

statistically overlapped via a conjunction analysis. The results of this conjunction analysis were used as regions of interest for an independent seed-based functional connectivity analysis conducted on resting-state data collected in normal-weight subjects. This last step aimed at exploring which functional brain network the clusters showing both structural and functional abnormalities normally belong. Importantly, we interpreted the results based on what is predicted by the neurocognitive theories of overeating and obesity. The "reward surfeit theory" would predict a hyper-activity and possibly, but not necessarily, an augmented grey matter density of the reward circuitry (midbrain, striatum, orbitofrontal cortex, OFC) in obese participants. The opposite pattern may support the "reward deficit theory", as the compulsion to eat in obesity may be associated with dopaminergic deficiency in the reward system, expressed as grey matter hypo-densities and reduced brain response. On the other hand, the "inhibitory control deficit theory", emphasizing the role of the neural circuits underlying inhibition processes, would forecast a reduced activity and grey matter volume at the level of prefrontal regions involved in high-level cognitive processes such as inhibitory control (i.e., ventromedial prefrontal cortex, dorsolateral prefrontal cortex). Finally, the "incentive sensitization theory" would anticipate a hyper-activity and augmented grey density of brain regions involved in both salience attribution (insula, amygdala, parahippocampal gyrus, hippocampus) and reward (midbrain, striatum, OFC).

Of course, the predictions spelled out above are based on the hypothesis of a perfect fit and same directions of the brain activations and density behind each of the scenarios. Yet, it is possible that some dissociations might be observed, like for example reduced activations in the reward circuitry in the absence of changes of grey matter density, or, indeed, the observation of grey matter abnormalities not mirrored by the functional imaging patterns, inevitably constrained by the nature of the tasks considered: what matters, however, is that convergent and divergent results can be interpretable due to the similarly well sized samples and homogeneous meta-analytical techniques employed. As we will discuss below, the present quest for joint morphometric and functional deficits in obesity limits the spectrum of effects that one could test, as the morphometric data derived by the simple comparison of obese and lean people are deprived of the necessary functional nature needed to support inherently functional theories like, for example, the enhanced brain responsivity to the consummatory or anticipatory aspect of food experience (key aspects of the Reward Surfeit and Incentive Sensitization theories, respectively). This implies that the combination of meta-analyses of structural and functional techniques limits the theories that one can test.

2. Materials and methods

Our PRISMA-compliant meta-analysis (Page et al., 2021; see also Supplementary Fig. S2 and Supplementary Fig. S3) involved a series of analytical steps, starting from selecting the raw data (data collection and data preparation) to the classification of the peaks associated with changes in grey matter density or functional activation in obese subjects with respect to normal-weight individuals (see Fig. 1). We created two different datasets for structural and functional data, respectively. Then, using the software *GingerALE* (Turkeltaub et al., 2012; https://www.brainmap.org/ale/) and following the best practices for fMRI meta-analyses (Müller et al., 2018), we conducted two separate meta-analyses: one for structural data and one for functional data.[2] Finally, the results of these analyses were formally compared. The meaning of any overlap was further explored with a seed-based functional connectivity analysis on resting-state fMRI data.

2.1. Structural imaging dataset

We identified neuroimaging studies exploring the structural changes in obese individuals, using the following procedure, illustrated in Supplementary Fig. S2. First, in December 2020, we entered the following queries in the PubMed database (https://pubmed.ncbi.nlm.nih.gov): "Obesity and Voxel Based Morphometry", "Obesity and VBM", "Obesity and Grey Matter", Obesity and Structural MRI", "Obesity and Morphological MRI". After removal of duplicates, the initial dataset comprised a total of 381 studies. Then, we ran a preliminary selection based on the titles and abstracts of the papers, through which we included only the studies that matched the following criteria:

- Studies including obese and normal-weight subjects.
- Studies reporting results using stereotaxic coordinates (either MNI or Talairach atlases).
- Studies reporting whole-brain peaks (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.
- Absence of other clinically relevant conditions present in only one experimental group. In case of clinically relevant conditions, we selected only results coming from obese participants, not suffering from any other condition or we included peaks resulting from the comparison between the two samples.
- Local maxima peaks resulting from a direct comparison between obese and normal-weight participants.

This selection, initially based on titles and then on abstracts, yielded to the identification of 36 candidate papers for the first meta-analysis of structural data. We made a further selection by inspecting the entire manuscripts and applying the inclusion criteria in detail. Further, we conducted an up-to-date manual scan of the references of the selected articles, to ensure that all relevant papers had been included. All manuscripts were screened independently by three reviewers (GG, SZ, and FG); any discrepancy was resolved through a collaborative discussion with another reviewer not involved in the screening process (LZ). All the relevant data were then entered on the predefined spreadsheet by three investigators independently (GG, SZ, and FG).

By applying such criteria, we included 27 papers yielding a total of 29 experiments and 36 contrasts and 570 foci; a flowchart of the selection process is available in Supplementary Fig. S2.

The final dataset comprised a total of 7650 participants, of which 497 could be classified as normal-weight volunteers, and 315 were classified obese patients. The remaining 6838 subjects are taken from correlational analyses between grey matter density and BMI and specifications were not given on whether they fell into the obesity class or normal weight class (as an example, see: Hayakawa et al., 2018 Janowitz et al., 2015; Kharabian Masouleh et al., 2016; Taki et al., 2008). The mean age of the participants classified as obese was 36.65 years (age range: 14.9–77.2), while the mean age of the normal-weight participants was 36.49 years (age range: 16.4–77.5). The mean BMI of the obese group was 36.27 (32.81–43.17), the mean BMI of the normal-weight group was 22.22 (20.83–24.02).

532 local maxima, resulting from 29 contrasts were associated with grey matter density reduction in obese individuals, while 38 peaks derived from 7 contrasts were associated with increased grey matter density in obese participants. Talairach coordinates were converted using the Talairach to MNI (SPM) transformation tool implemented in the GingerALE software.

In order to study the effects of decreased and increased grey matter density in obesity, different meta-analyses should be conducted for foci

[2] It is worthy to note that any information about the absolute changes in grey matter volume (mm^3, for VBM studies) and in brain activity (% signal change, for fMRI studies) between the groups in the original studies is lost during the meta-analytical process. In other words, the ALE method is not aimed at quantifying the differences in grey matter volume (or BOLD activity), rather it aims at quantifying the *degree of convergence across a set of studies*.

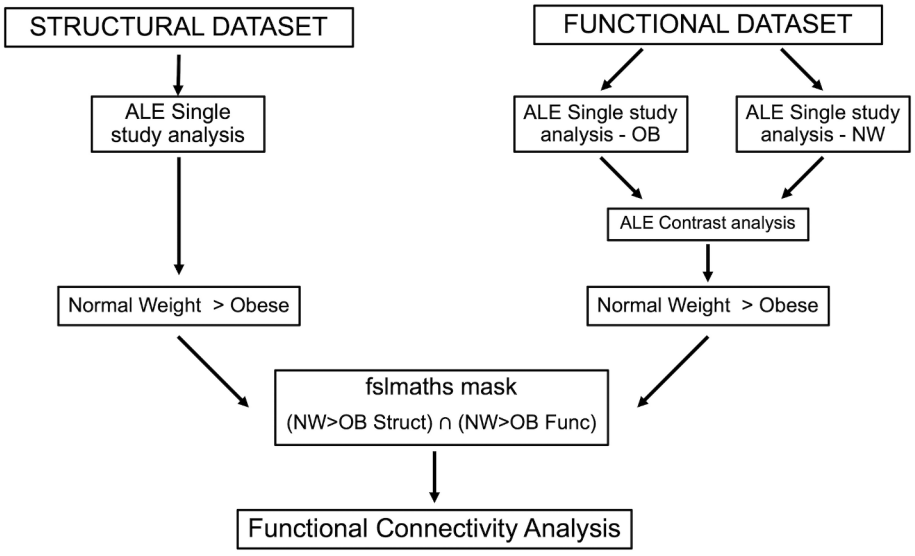

Fig. 1. Graphical summary of the analytical flow-chart. NW = normal-weight individuals; OB = obese individuals.

indicating increases or decreases of grey matter density in obese participants. However, the number of contrasts reporting a positive association between BMI and grey matter volumes was too small (#7) to perform a meta-analysis (Eickhoff et al., 2016). Therefore, we computed a quantitative meta-analysis only including grey matter volume reductions in obese participants. Peaks included in the dataset resulted from a contrast (e.g., Normal-weight > Obese individuals), or from a negative correlation between BMI and grey matter density (e.g., brain

Table 1
Studies selected for the structural meta-analysis. BMI = Body Mass Index; NW = normal-weight individuals; OB = obese individuals; GM = Grey Matter; [a] = body mass percentiles (BMI%) were converted according to US grow charts (Kuczmarski et al., 2002); [b] = BMI standard deviations were converted according to UK grow charts (Cole et al., 1995). Note: for studies reporting contrasts between obese and normal-weight individuals, we reported the descriptive statistics of each sample. For studies reporting results on a single sample (including normal-weight and obese individuals), we reported the descriptive statistics of the whole sample (for further details, see Supplementary Table S1).

#	First Author	Year	Contrast	Sample size (NW/OB)	BMI (NW/OB)	Gender (M/F)	Age (NW/OB)	N foci
1	Bond	2014	Negative correlation between GM and BMI	55	24	31/24	22.15	7
2	Brooks	2013	GM volume NW > GM volume OB	97/59	22.1/33.7	70/86	75	11
3	Figley	2016	Negative correlation between GM and BMI	32	24.85	16/16	29.8	9
4	Hayakawa	2018	Negative correlation between GM and BMI	269	22	0/269	55.2	10
5	Hayakawa	2018	Negative correlation between GM and BMI	523	24.7	523/0	55.3	31
6	Hidese	2018	GM volume NW > GM volume OB	107/7	22.2/33.2	56/58	41.1/38.	25
			Negative correlation between GM and BMI					25
7	Horstmann	2011	Positive correlation between GM and BMI	122	26.7	61/61	25.29	4
8	Janowitz	2015	Negative correlation between GM and BMI	2344	27.3	1087/1257	48.05	57
9	Jauch-Chara	2015	GM volume NW > GM volume OB	15/15	23.2/36.3	30/0	24.6/24.7	19
			Negative correlation between GM and BMI					15
10	Karlsson	2013	GM volume NW > GM volume OB	22/23	24.02/43.17	12/33	46.45/47.30	9
11	Kennedy	2016	Negative correlation between GM and BMI	137	20.5[a]	69/68	14.89	7
12	Kharabian Masouleh	2016	Negative correlation between GM and BMI	617	27.54	359/258	68.7	23
13	Kurth	2013	Negative correlation between GM and BMI	115	25.02	54/61	45.17	34
14	Mathar	2016	GM volume NW > GM volume OB	23/19	21.8/33.6	22/20	25.2/27	2
15	Nouwen	2017	GM volume NW > GM volume OB	19/20	20.83/32.81[b]	10/29	16.4/14.9	6
16	Opel	2015	Negative correlation between GM and BMI	139	25.74	61/78	37.59	6
17	Opel	2017	Negative correlation between GM and BMI	330	24.5	158/172	39.2	8
18	Opel	2017	Negative correlation between GM and BMI	347	26.3	192/155	51.6	16
19	Pannacciulli	2006	GM volume NW > GM volume OB	36/24	22.7/39.4	36/24	33/32	7
			GM volume OB > GM volume NW					6
20	Raji	2009	Negative correlation between GM and BMI	94	27.63	44/50	77.5/77.2	5
21	Shott	2015	GM volume NW > GM volume OB	24/18	21.64/34.78	0/42	27.42/28.67	8
22	Taki	2008	Negative correlation between GM and BMI	690	23.41	690/0	44.5	22
			Positive correlation between GM and BMI					17
23	Tuulari	2016	GM volume NW > GM volume OB	29/47	23.2/42.2	11/65	45.9/44.9	31
24	Walther	2010	Negative correlation between GM and BMI	95	28.26	0/95	69.3	18
25	Wang	2017	GM volume NW > GM volume OB	49/31	21.87/34.38	52/28	29.55/39.58	17
			GM volume OB > GM volume NW					3
26	Weise	2017	Negative correlation between GM and BMI	875	26.6	386/489	28.8	46
			Positive correlation between GM and BMI					3
27	Yao	2016	Negative correlation between GM and BMI	109	28.26	47/62	35.15	37
			Positive correlation between GM and BMI					4
28	Zhang	2016	GM volume NW > GM volume OB	18/15	21.60/38.10	11/22	27/25.8	21
29	Zhang	2017	GM volume OB > GM volume NW	20/20	21.48/33.56	40/0	24	1

regions showing a decrease in grey matter volume for greater BMI). For a summary of studies, description of the local maxima included and number of peaks, please refer to Table 1.

2.2. Functional imaging dataset

Given the main aim of the present work, the functional dataset (i.e., peaks of activation associated with reductions or enhancements of activity in obese participants) was adapted starting from a recent meta-analysis conducted in our lab (Devoto et al., 2018). This was done to obtain a dataset comparable with the structural one. The flowchart of the selection process is available in Supplementary Fig. S3.

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. 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:

- Studies including either obese and normal-weight subjects, or both (for the obese participants, we considered only populations with BMI above or equal to 30).
- Studies reporting results using stereotaxic coordinates (either MNI or Talairach atlases).
- Studies reporting whole-brain peaks (no region-of-interest analyses).
- 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 (Kishinevsky et al., 2012; Weygandt et al., 2013) or requiring explicit inhibitory processes (Hendrick et al., 2012; Hsu et al., 2017), not reflecting simple anticipatory processing, have been excluded.
- 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.

The final dataset included 707 peaks of activation derived from 22 papers yielding a total of 22 experimentsand 67 contrasts); it comprised a total of 507 participants, of which 194 were normal-weight voluneers, and 313 were obese patients.

The mean age of the normal-weight sample was 33.04 years (age range: 21.01–57.8), while the mean BMI was 22.40 (BMI range: 20.85–24.1). For what concerns the obese sample, the mean age was 37.06 years (age range: 23–58), while the mean BMI was 35.37 (BMI range: 31.6–43.87).

Foci were labelled according to the analysis they were drawn from. For a summary of all the studies initially selected, see Table 2. A detailed description of each paper included is listed in Supplementary Table S2.

To compare the data derived from obese subjects and normal weight subjects, we first run two single-study ALE meta-analyses for the peaks assigned to normal-weight and obese participants (within-group contrasts); we then compared the results of these within group meta-analyses with "contrast study" ALE meta-analyses. We are aware that the best way to make the fMRI data comparable with the VBM data would have been the inclusion of only between-group contrasts in a single-study ALE meta-analysis. However, unfortunately, the number of between group contrasts available in the literature was too small (4) to perform a form too small (to perform a formal meta-analysis (Eickhoff et al., 2016).

Therefore, the first functional datasets for the two single-study meta-analyses included only main effects within the normal-weight or obese sample. 390 foci (36 contrasts) were associated with normal-weight subjects, while 117 peaks (14 contrasts) were associated with the obese sample.

2.3. Activation likelihood estimation meta-analyses

Coordinate-based ALE meta-analyses estimate the spatial convergence of coordinates between experiments relative to the null hypothesis that these experiment foci are uniformly and randomly distributed across the brain. Specifically, the analyses that we conducted evaluated the most probable location where differences in grey matter volume or functional activations occur given the BMI status relative to the null hypothesis that these experiment foci are randomly distributed across the brain.

In a "single dataset" analysis (e.g., using activation foci from obese subjects only), the algorithm computes a map which contains, in every voxel, the probability that a given peak of activation included in the database lies within that specific voxel. This statistical index is named Activation Likelihood Estimation (ALE), and it represents the probability that at least one local maxima of activation lies within a specific voxel. A statistical computation is then made on all voxels to identify foci that consistently represented a convergence of the results derived from the studies that were entered into the meta-analysis.

In the subsequent "contrast datasets" analysis (Eickhoff et al., 2011), it is possible to quantitatively compare the results obtained from two different single dataset analyses (e.g., comparison of activation foci of normal weight and obese subjects). Through this computation, the user can identify the foci that are specifically associated with either a single dataset, more than the other, or the "conjunction" between two datasets.

We applied the ALE algorithm to two different datasets: (i) a 'structural' dataset, comprising peaks associated to grey matter volume reductions in obese individuals (since the number of contrasts indicating the opposite direction was too low to be submitted to a meta-analysis) and (ii) a 'functional dataset', comprising peaks associated to reductions of functional activations in obese individuals. While the former meta-analysis on the structural data was achieved by computing the ALE maps on coordinates derived from natively between-group comparisons, for the functional data an intermediate contrast analysis between obese and normal weight subjects was needed first (see Fig. 1).

In all single-study analyses we applied, as recommended, a cluster-level threshold of $p < 0.05$ family-wise error (I) corrected, and a cluster-forming threshold of $p < 0.001$ uncorrected (Müller et al., 2018).

In the contrast-analysis of the functional dataset, we employed a threshold of $p < 0.001$ uncorrected and 10,000 permutations.

Results were the visualized on a ch2better template using the MRIcroGL software (Rorden and Brett, 2000).

Meta-analytic results were quantitatively compared, to identify a common cluster associated to both volumetric and functional abnormalities in obese individuals: the thresholded images resulting from the different meta-analyses were masked with each other using the *fslmaths* function of the FSL package (Jenkinson et al., 2012; Smith et al., 2004). This conjunction cluster was then used as a ROI in the subsequent seed-based functional connectivity analysis.

2.4. Resting-state functional connectivity study.

With the aim of further exploring our meta-analytical results, we ran a functional connectivity analysis based on resting-state data. Despite not being specific to cognitive-motivational processing, analysis of resting-state data was done to investigate the functional brain network associated with the clusters displaying both structural and functional abnormalities. We selected as ROIs the clusters associated with both morphometric and functional abnormalities in obese individuals. Seed-based resting-state functional connectivity was calculated from the extracted ROIs, in a normal-weight sample. This approach, backed up by the meta-analytical results, can provide complementary information about possible system-level dysfunctions.

Table 2
Studies selected for the functional meta-analysis. BMI = Body Mass Index; NW = normal-weight individuals; OB = obese individuals (for further details, see Supplementary Table S2).

#	First Author	Year	Contrast	Subjects (NW/OB)	BMI (NW/OB)	Gender (M/F)	Age (NW/OB)	N foci
1	Blechert	2016	NW	32/0	22.4/0	16/16	22.4	25
			NW					23
			NW					37
			NW					10
2	Cornier	2009	NW	22/0	21.6/0	12/10	34.4	23
3	Cornier	2012	OB	0/12	0/33.3	7/5	38.2	8
4	Cornier	2013	NW	25/0	20.85/0	14/11	31.4	6
			NW					9
5	Dimitropoulos	2012	OB > NW	16/22	22.7/31.6	17/21	24.6/24.8	7
			OB > NW					22
			NW > OB					14
6	Gautier et al.	1999	NW	11/0	< 25 (not better specified)/0	11/0	< 25 (n.a.)	13
			NW					6
7	Geliebter	2013	OB	0/31	0/36.55	17/14	35	8
			OB					7
			OB					9
			OB					6
8	Haase	2011	NW	9/0	23.15/0	9/12	22.96	14
			NW	12/0	22.76/0			7
			NW	12/0	22.76/0			2
			NW	12/0	22.76/0			9
			NW	12/0	22.76/0			18
			NW	9/0	23.15/0			8
			NW	9/0	23.15/0			6
			NW	9/0	23.15/0			6
			NW	12/0	22.76/0			1
			NW	12/0	22.76/0			6
			NW	12/0	22.76/0			2
			NW	12/0	22.76/0			3
			NW	21/0	22.96/0			21
			NW	21/0	22.96/0			13
			NW	21/0	22.96/0			10
			NW	21/0	22.96/0			24
9	Jastreboff	2013	OB	25/25	22.9/32.6	31/19	26.2/26.2	6
			NW					1
10	Karra	2013	NW	24/0	21.95/0	24/0	22.55	5
11	Killgore	2003	NW	13/0	22.1/0	0/13	23.5	11
			NW					7
			NW					7
			NW					3
12	Lundgren	2013	OB	0/14	37.9	2/12	33.6	5
			OB					1
			OB					2
13	Luo	2013	OB	0/13	0/34	0/13	23	18
14	Martin	2010	OB > NW	10/10	22.1/34.0	n.a.	10/10	25
			NW > OB					2
			OB > NW					7
15	Murdaugh	2012	OB	0/25	0/32.86	6/19	48.04	15
			NW	13/0	22.64/0	5/8	45.15	11
16	Murray	2014	NW	20/0	23.09/0	10/10	22.8	9
17	Nummenmaa	2012	OB > NW	16/19	24.10/43.87	n.a.	47.75/45.74	1
			NW > OB					19
18	Puzziferri	2016	NW	15/15	22.3/42.7	0/30	45.1/40.6	13
			OB					22
			NW > OB					31
19	Rothemund	2007	OB > NW	13/13	20.9/36.3	0/26	29/31	5
			OB > NW					7
			OB > NW					2
			OB					7
			OB					3
			NW					1
20	St-Onge	2014	NW	25/0	23.6/0	13/12	34.7	20
21	Szalay	2012	OB > NW	12/12	21.42/34.05	6/18	38.3/37.1	9
			OB > NW					26
			OB > NW					16
22	Van Bloemendaal	2014	OB > NW	16/16	23.2/32.6	16/16	57.8/58	4
			OB > NW					3

2.5. Participants.

Twenty-two normal-weight subjects (mean age: 46.64 ± 11.35 years; mean education level 14.95 ± 3.08 years; 6 males and 16 females; mean BMI: 23.21 ± 1.48) without any cognitive, neurological, or psychiatric illness participated in the resting-state fMRI study. They were all right-handed as assessed by the Edinburgh handedness inventory (Oldfield, 1971). Each subject was asked to stay with their eyes closed, awake and, as far as possible, not to think about anything. The study protocol was approved by the local Ethics Committee (IRCCS San Raffaele, prot. CONSUME), and informed written consent was obtained from all subjects.

2.6. fMRI data acquisition and analysis.

MRI scanning was performed with a Siemens *Avanto* 1.5 T scanner equipped with gradient-echo echo-planar imaging. Before the acquisition of functional data, high-resolution T1-weighted structural images were acquired (flip angle 35∘, TE 5 ms, TR 21 ms, FOV 256 × 192 mm, matrix 256 × 256, TI 768, 160 slices with 1 mm × 1 mm × 1 mm voxels). Echo-planar imaging gradient-echo fMRI scans [flip angle 90∘, echo time (TE) = 60 ms, TR = 2000 ms, field of view = 250 × 250 mm, and matrix = 64 × 64, slice thickness = 4 mm] were then acquired (450 volumes).

Resting state BOLD raw data were pre-processed and analysed with CONN (https://web.conn-toolbox.org; Whitfield-Gabrieli and Nieto-Castanon, 2012).

Pre-processing was performed according to the default pipeline implemented in the CONN toolbox. Functional images were first realigned to the first scan of the session and slice-time corrected. After outlier detection, functional data were directly co-registered to the structural data and smoothed using a 10-mm isotropic Gaussian kernel.

After preprocessing, data of each subject were explored and quality checked; then, denoising was conducted to remove any source of signal noise in the data. We applied a band-pass filtering between 0.008 and 0.09 Hz; a component-based noise correction method was used to identify and remove the principal noise components from different tissue classes; moreover, movement parameters were estimated for each subject and their confounding effect was subtracted from our analyses.

In the first level analysis, the toolbox computes the Pearson's correlation coefficients between the time course of the fMRI signal of the seed regions selected and the time course of each voxel in the brain separately to generate the parametric seed- to-voxel correlation map. A seed-to-voxel correlation map was computed for each subject from the previously extracted seed region. Correlation coefficients were then converted to z-scores using the Fisher's transform to allow for subsequent analysis.

In the second level analysis, we performed a one sample *t*-test to extract the group connectivity map of the ROIs that were used as seeds. The regions described survived a canonical cluster-level FWE p-value $<$ 0.05 correction (voxel-wise uncorrected threshold: $p < 0.001$), in line with recent suggestions by Flandin and Friston (2019).

2.7. Further methods for the interpretation of the data.

Besides typical forward inferences based on the experimental design and interaction of factors, we also considered the strength of associations between the actual statistical maps of a given analysis (our meta-analyses) and neuroscientific semantics as indexed by specific keywords. Specifically, the clusters representing the functional/structural abnormalities and the map of the functional network of these clusters were loaded into the Neurosynth.org database and analysed by means of the "decoder" function (https://neurosynth.org/decode/; Yarkoni et al., 2011). The decoder function of Neurosynth allows one to retrieve the Pearson correlation of the keywords that are most associated with the input image, containing the clusters identified by the meta-analysis, based on the NeuroVault repository. The r-value associated with each keyword reflects the correlation across all voxels between the input map and the map associated with a particular keyword in NeuroVault.

In other words, while not replacing the typical forward inferences in the current study, the quantitative associations returned by Neurosynth may provide some valuable information for our line of discussion.

3. Results

3.1. Structural data meta-analysis

The first meta-analysis conducted on structural data highlighted three different clusters consistently associated with reduced grey matter volumes in obese individuals compared to healthy controls. These regions were located in the orbitofrontal cortex, in the medial prefrontal cortex, in the anterior cingulum and subcortically in the thalamus and the midbrain (see Table 3 and Fig. 2a).

3.1.1. Neurosynth decoding of the brain structural abnormalities.

Besides auto-referential anatomical correlations (e.g., dorsomedial, medial prefrontal, thalamus…), the first functional domain terms that correlated with this anatomical pattern were "social" (Correlation coefficient: 0.15), "traits" (Correlation coefficient: 0.136), "mental states" (Correlation coefficient: 0.133), "personality traits" (Correlation coefficient: 0.125), and "craving" (Correlation coefficient: 0.104).

3.2. Neurofunctional data meta-analysis.

Information about the single dataset analyses conducted on within group effects are available in Supplementary Table S3.

The contrast-study meta-analysis conducted on neurofunctional data produced eleven clusters, which weighted centres were located subcortically in the thalamus and in the midbrain bilaterally. These regions were significantly less activated in the obese sample compared to healthy controls (see Table 4 and Fig. 2b).

Finally, the results of the two meta-analyses were overlapped by masking the thresholded images with each other using the *fslmaths* function of the FSL package (Jenkinson et al., 2012; Smith et al., 2004). This procedure resulted in two clusters located in the thalamus and in the midbrain bilaterally (see Fig. 2c). This conjunction cluster was then used as ROI in the subsequent seed-based functional connectivity analysis. The peaks that contributed to these clusters were derived by studies passive perception of high-caloric food images, of chocolate, or the consumption of sucrose.

3.2.1. Neurosynth decoding of the brain functional abnormalities.

Besides auto-referential anatomical correlations (e.g., thalamus, subcortical, midbrain… and themselves), the first functional domain terms that correlated with this functional anatomical pattern were "pain" (Correlation coefficient: 0.138) and "sexual" (Correlation coefficient: 0.131) followed by the keyword "reward" (Correlation coefficient: 0.104) and "anticipation" (Correlation coefficient: 0.103).

3.3. Functional connectivity analysis.

The seed located in the bilateral thalamus and the midbrain, which, according to our results, was associated with obesity-related structural and functional impairments, resulted to be functionally connected with the anterior cingulum bilaterally, the right middle cingulum, the right medial superior frontal gyrus, the left insula, and the right striatal regions such as the putamen, the pallidum and the thalamus itself. See Table 5 and Fig. 2d.

3.3.1. Neurosynth decoding of the functional connectivity pattern.

Besides auto-referential anatomical correlations with the seeds used for the functional connectivity analysis of the fMRI data (e.g., the

Table 3
Results of the ALE meta-analysis conducted on structural data, representing brain regions consistently associated with reduced grey matter volumes in obese individuals. For each cluster we reported the anatomical label, the spatial extent in mm^3 (k), the ALE-scores, the Z-scores and the MNI coordinates.

Cluster ID	Brain region	ALE-score	k	Z-score	MNI coordinates of the Weighted Center					
					Left Hemisphere			Right Hemisphere		
					x	y	z	x	y	z
1	Thalamus	0.0071	10080	5.5	−4	−14	−2	–	–	–
2	Medial orbitofrontal cortex	0.0080	8624	6.2	–	–	–	10	56	−22
3	Superior medial frontal gyrus	0.0068	5240	5.3	−8	54	26	–	–	–
3	Anterior cingulate cortex	0.0046		3.5	−4	42	14	–	–	–

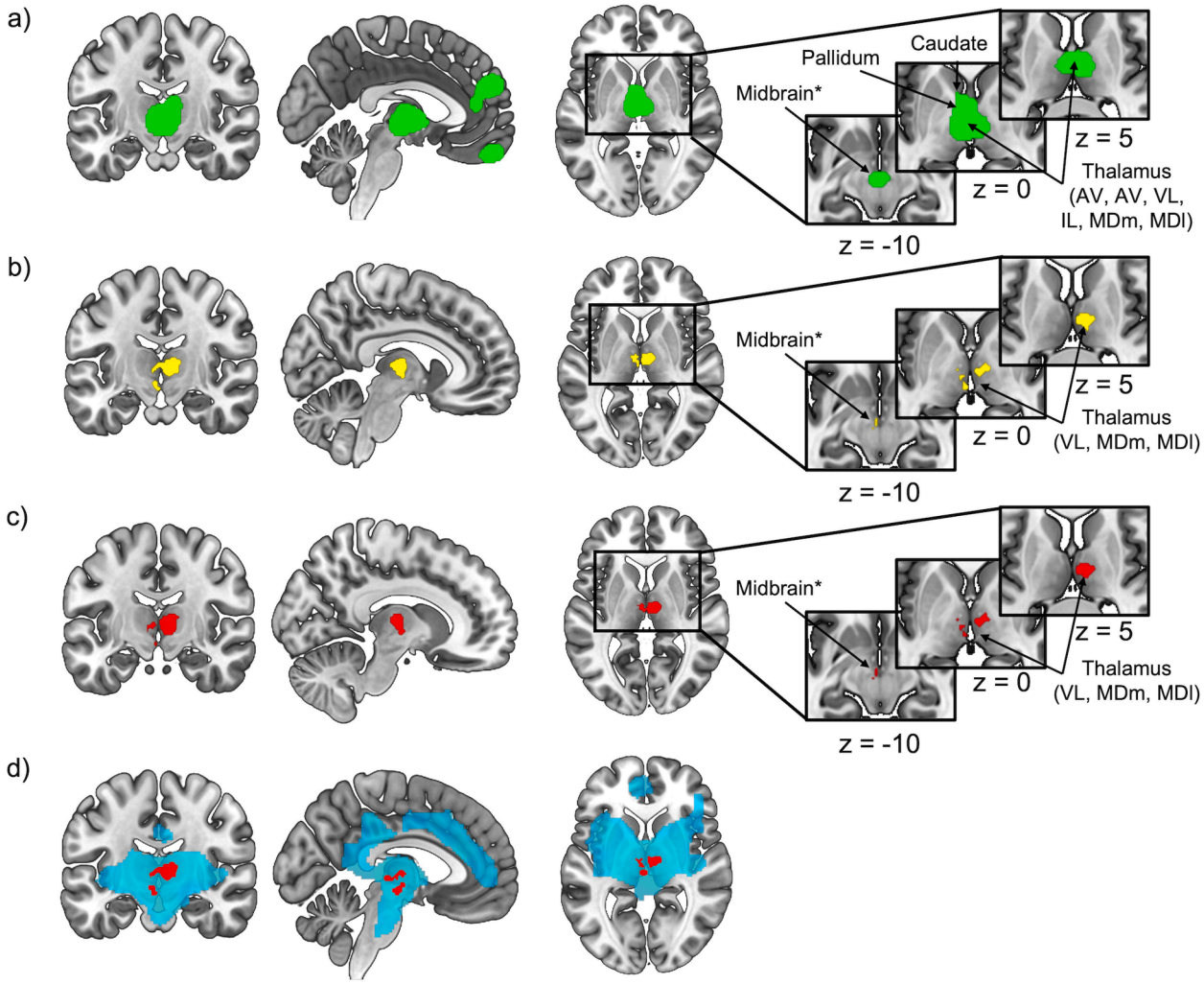

Fig. 2. Results of the meta-analyses and resting-state functional connectivity. a) Results of the meta-analysis on structural alterations in obesity. b) Results of the meta-analysis on neurofunctional alterations in obesity. c) Results of the conjunction analysis showing overlapping regions between structural and functional alterations in obesity. d) Results of the seed-based resting-state functional connectivity. Coordinates of the axial slices in MNI space. AV, anteroventral; IL, intralaminar; MDl, mediodorsal lateral; MDm, mediodorsal medial; VA, ventral anterior; VL; ventral lateral. * = foci compatible with the anatomical coordinates of the Ventral Tegmental Area (VTA, Gu et al., 2010; Trutti et al., 2021).

thalamus correlating with itself), the decoding procedure identified further anatomical structures corresponding to what reported in Table 5. The first functional domain terms that correlated with this functional anatomical pattern were the two antinomically correlated keywords "**pain**" (Correlation coefficient: 0.323) and "**reward**" (Correlation coefficient: 0.236), followed by the keyword "**gain**" (Correlation coefficient: 0.187).

4. Discussion

In this paper we performed a quantitative meta-analysis and measured to what extent obesity-related functional and structural brain abnormalities overlap. Our aim was to expand the results of our previous meta-analysis on fMRI studies in which we described the patterns of altered brain activity specific for the obesity condition, and their interaction with the satiety state and modality of presentation of food related stimuli (Devoto et al., 2018). Here we tested the hypothesis that - at least some of - these altered brain functional activations for food-related

Table 4
Results of the ALE meta-analysis conducted on neurofunctional data, representing brain regions consistently associated with reduced activity in obese individuals. For each cluster we reported the anatomical label, the spatial extent in mm^3 (k), the Z-scores and the MNI coordinates. * = foci compatible with the anatomical coordinates of the Ventral Tegmental Area (VTA, Gu et al., 2010; Trutti et al., 2021). VL = vetrolateral nucleus. MDm: medio-dorsal medial nucleus; MD-lat; medio-dorsal lateral nucleus. PV: paraventricular-nucleus. Identification of the thalamic nuclei was based on the AAL3 template for MRIcron (Rolls et al., 2020) and on Morel's stereotactic atlas of the thalamus (Morel, 2007).

Cluster ID	Brain region	k	Z-score	MNI coordinates of the Weighted Center					
				Left Hemisphere			Right Hemisphere		
				x	y	z	x	y	z
1	Thalamus VL	1576	3.9	–	–	–	10	−14	9
1	Thalamus MD-lat		3.5	–	–	–	8	−13	4
1	Thalamus MDm/PV		3.7	–	–	–	5	−18	8
1	Thalamus MDm/PV		3.2	–	–	–	2	−14.3	4.7
1	Thalamus MDm/PV		3.1	–	–	–	2	−11	1
1	Thalamus MDm/PV		3.4	−4	−14	6	–	–	–
2	Thalamus MDm/PV	88	3.2	−1.3	−24	1.3	–	–	–
6	Thalamus MDm/PV	16	3.2	−2	−20	−3	–	–	–
10	Thalamus MDm/PV	8	3.2	−4	−12	−4	–	–	–
11	Thalamus MDm/PV	8	3.1	−2	−20	6	–	–	–
3	Midbrain*	32	3.2	−2	−12	−9	–	–	–
4	Midbrain*	16	3.2	−4	−14	−8	–	–	–
5	Midbrain	16	3.2	–	–	–	0	−22	−3
7	Midbrain*	8	3.2	−4	−16	−10	–	–	–
8	Midbrain – Red Nucleus	8	3.2	−4	−18	−8	–	–	–
9	Midbrain	8	3.1	−6	−16	−6	–	–	–

Table 5
Results of the seed-based resting-state functional connectivity analysis. We reported the number of voxels that are included in each volume of interest of the Automatic Anatomical Labelling (AAL) template. We reported results surviving a cluster-level FWER ($p_{corrected} < 0.05$). We reported regions including at least 1000 voxels.

Brain regions (AAL)	Number of voxels	
	Left Hemisphere	Right Hemisphere
Medial superior frontal gyrus	4057	1481
Inferior frontal gyrus (orbitalis/ triangularis)	1324	2359
Anterior cingulum	9269	6772
Middle cingulum	9873	10,684
Posterior cingulum	2834	2322
Supplementary motor area	1881	1430
Precuneus	2783	5934
Heschl gyrus	–	1083
Superior temporal pole	1290	–
Superior temporal gyrus	1986	1569
Insula	10,991	7589
Caudate	1912	1815
Putamen	7838	8299
Pallidum	2285	2188
Amygdala	1098	1161
Thalamus	8588	8320
Hippocampus	1725	1732
Para-hippocampal gyrus	1453	1413

stimuli might be mirrored by specific structural abnormalities. We interpreted our results with reference to the different neurocognitive theories of obesity.

We found that two clusters located at the level of the thalami and the midbrain satisfied these criteria showing both reduced grey matter density and reduced functional activation in obese individuals when watching food-related stimuli or during consummatory gustatory behaviour. To further explore the functional meaning of these observations, we performed a seed-based functional connectivity analysis on an independent resting-state fMRI data set from normal-weight participants: this analysis revealed that the aforementioned brain stem and thalamic regions are part of a broader brain network including, among other areas, the cingulate cortex, the insula, and subcortical regions bilaterally of the striatum, a set of regions broadly overlapping with the so-called reward system of the brain.

Our results support the theory of obesity that points to reduced bottom-up reward processes (i.e., the *Reward Deficit Theory*) but also the top-down theory postulating a deficit in cognitive control (i.e., the *Inhibitory Control Deficit Theory*). In what follows we explain why this is so.

4.1. Structural data meta-analysis: do the patterns of grey matter alterations in obesity converge anatomically in a replicable manner, surviving to a formal meta-analysis?

The meta-analysis on brain morphometry data shows the existence of a negative relationship between the BMI and the volume of prefrontal, subcortical thalamic and brainstem regions (Fig. 2a). This is in line with what observed in previous meta-analyses exploring the same topic (Chen et al., 2020; García-García et al., 2019; Herrmann et al., 2019): in particular, as for what described by Chen and colleagues (2020), obesity (and overweight) was associated with grey matter density reduction at the level of the OFC (Chen et al., 2020).[3] However, our results expand this previous observation showing a grey matter density reduction also at the level of the medial prefrontal cortex – including the anterior cingulate cortex – and subcortically in the thalamus and the midbrain. These observations permit a more comprehensive discussion on how these morphometric findings may accompany some of the behavioural features that are staples of the obesity condition.

The OFC is a prefrontal region that integrates sensory modalities such as taste, smell, and vision, and, through its dense reciprocal projections into thalamic, midbrain, and striatal regions, it acts as a critical hub for decision-making when decisions are made on highly motivating stimuli such as food, drugs or sexual stimuli (Seabrook and Borgland, 2020).

Similarly to what is postulated for the disinhibited behaviour in drug addiction (see, for example, the model proposed by Baler and Volkow, 2006), a malfunction or dysregulation of the OFC may concur to the

[3] These additional results can be explained by slightly different inclusion criteria of the studies submitted to a meta-analysis: first, contrary to Chen et al. (2020), we did not consider studies in which there were no frankly obese participants but only overweight subjects. Therefore, two studies were excluded from our dataset (He et al., 2015; Smucny et al., 2012). Moreover, we did not include pre- and post-treatment data (Honea et al., 2016; Mueller et al., 2015). Finally, our literature search identified three further studies that were not included in previous meta-analyses (Jauch-Chara et al., 2015; Raji et al., 2010; Wang et al., 2017).

excessive salience given to food-related stimuli in obesity and to the excessive food-oriented behaviour.

However, as suggested by Baler and Volkov (2006, but see also Everitt and Robbins, 2016) the OFC is only one of the frontal cortical hubs involved in the control of goal oriented motivated behaviour: the picture would not be complete without considering also the anterior cingulate and the dorsomedial prefrontal cortex. Our meta-analysis of the morphometric data also showed obesity-related structural alterations of these cortices. These brain regions are significantly involved in intentional goal-directed behaviours. For example, the anterior cingulum can be considered as an "intentional" hub: it is significantly more active during intentional behaviour, compared to stimulus-driven actions, irrespectively on what aspect of intentional action is emphasized by the task, such as the content, the timing, or the actual possibility of acting intentionally (Zapparoli et al., 2018).

The mechanism whereby the volume of medial prefrontal cortices becomes reduced in obesity remains to be established: in any event, a malfunction here may explain why external motivationally salient stimuli, such as food visual cues, may trigger more easily stimulus-driven behaviour in obese individuals, with a reduction of higher-level and "more rational" intentional behaviour.

We believe that the present findings may provide a possible anatomical basis for the abnormal decision-making processes described in obesity (Yang et al., 2018). Coherently with this suggestion, we recently demonstrated that high-frequency bilateral deep TMS stimulation of the prefrontal cortex and the insula is effective in promoting weight loss in obese individuals. Crucially, these changes were specifically associated with an increase of the whole-brain functional connections of the OFC (Devoto et al., 2021). Thus, the brain mechanisms behind weight-loss may occur through an increased reliance on top-down decision-making processes mediated by the OFC and its connections (Devoto et al., 2021).

Finally, further obesity-related structural abnormalities were found in midbrain and thalamic regions: these, given their overlap with the functional alterations, will be discussed in the next paragraphs.

Crucially, it is important to note that the described structural differences between the obese and normal-weight individuals cannot be explained by age-related factors, since the two samples were comparable in terms of age.

4.2. *Neural structural abnormalities underlying altered brain activation in obesity: Do the findings of the two meta-analyses overlap in a meaningful manner?*

For what concerns the neurofunctional data, we re-classified the peaks of the studies included in the meta-analysis of Devoto and colleagues (2018) and we re-analysed these data with the ALE approach.[4] This was done to have a dataset coherent and comparable with the structural one. Even with a different analytical approach, we were able to replicate the less frequent activation in the obese sample of the thalamus and the midbrain[5] (Fig. 2b). In particular, the specific locations of the midbrain and thalamus corresponded, respectively, to the VTA, in a position corresponding to what described by Trutti et al. (2021), and in the most medial part of the dorso-medial thalamic nucleus, corresponding, according to Morel's (2007, page 9, Fig. 2D) stereotactic atlas of the thalamus , to the paraventricular nuclei (PVT). These regions are part of a broader brainstem-hypothalamic—thalamic—ventral striatal circuit involved in the regulation of energy intake and feeding behaviour (Kelley et al., 2005). Specific subregions of the thalamus, such as the PVT, receive information from dopaminergic, cholinergic, and serotoninergic nuclei in the midbrain (one of them being the VTA) as well as from the hypothalamus and diencephalic structures. PVT neurons then project to the ventral striatum, amygdala, and insular cortices (for a review, see Millan et al., 2017). Another important thalamic relay is the dorso-medial nucleus because of its connections with prefrontal cortex (Goldman-Rakic and Porrino, 1985). It is through these projections that thalamic subregions exert either a bottom-up or top-down control of food intake, playing a significant role in homeostatic and non-homeostatic feeding behaviour. Congruent with this suggestion, a previous meta-analytical study revealed that the medio-dorsal thalamus is consistently activated by different kinds of reward (i.e., monetary, erotic and food rewards) and is thought to bridge basic reward signals with higher-level cognitive processes, such as motivation and goal-directed behaviour (Sescousse et al., 2013).

We compared these results with the ones obtained with our structural meta-analysis, providing evidence that obesity-related neurofunctional alterations are partially associated with structural abnormalities in the same brain areas (Fig. 2c). Specifically, we showed that food over-consumption leading to obesity is associated with reduced grey matter volumes at the level of the thalamus and the midbrain, regions that already we found hypoactive in obese participants independently from the specific sensory modality (Devoto et al., 2018). A combined structural and functional impairment reveals that brain hypo-functionality here is complemented by structural alterations.

Previous studies suggest the existence of a direct relationship between structural and functional impairments. For example, animal studies showed that striatal regions in obese rats are characterized by a decreased concentration of D2 receptors (Fetissov et al., 2002; Hamdi et al., 1992; Huang et al., 2006), accompanied by a decreased dopamine release (Geiger et al., 2009). Similarly, other studies conducted on human subjects have demonstrated a decreased concentration of D2 and μ-opioid receptors in obese individuals respect to their lean counterparts: because of this diminished receptor availability, over-eaters are also characterized by a diminished dopamine metabolism (Van De Giessen et al., 2014) and reduced D2 receptor expression (Volkow et al., 2008).

How would these abnormalities translate into a reduction of grey matter tissue in a VBM analysis? This is of course a matter of speculation: one could argue that the underlying structural abnormality may be due to a reduction of the dendritic neuropil, the neuronal subdivision that is most sensitive to plastic changes due to "experience" in a broad sense (Kolb and Whishaw, 1998). A reduced dendritic tree may also translate into a reduced expression of dopaminergic receptors. There is some animal evidence for structural changes of the dendritic tree associated with obesity (Bocarsly et al., 2015): in a diet-induced model of obesity in rats, it was found that a combination of synaptic loss in prefrontal cortex, including reduced numbers of dendritic spines and expression of synaptic proteins, as well as structural alterations, the microglia, correlated with reduced cognitive performance.

There was a discrepancy between the fMRI data and the VBM meta-analyses: this might seem perplexing and yet it can be easily explained by the fact that the fMRI paradigms that we scrutinized did not contain studies that were stressing behavioural control, as these studies are still too few to be meta-analysed (see the recommendations on study numerosity needed for meta-analyses in Eickhoff et al. 2016). It is likely that having a larger number of these studies available the two meta-

[4] In the original paper, we performed the meta-analysis with the software CluB (Berlingeri et al., 2019), in order to assess the possible interactions between the factor BMI and the factors satiety and sensory modality. See also the next footnote.

[5] It is important to note that in Devoto et al. (2018) we also investigated the possible interactions between the factor body weight (obese vs normal-weight) and the factors sensory modality of food-related stimulation (visual vs gustatory) and satiety (fed vs fasted). This factorial design was suitable for reflecting both anticipatory (e.g., visual) and consummatory (i.e., gustatory) brain functional processing of food stimuli while controlling for the physiological status of satiety. This approach led to some further findings that are not described here since not crucial for the aim of the present work (i.e., addressing the relationship between structural and functional data). The data presented here are qualitatively equivalent to a description of a group – obese versus lean - main-effect in Devoto et al (2018).

analyses may converge better on the prefrontal anterior cingulate VBM observations.

To further investigate the functional meaning of our meta-analytical results, we explored the functional network of the brain clusters associated with both structural and functional alterations in obesity. This was done with a resting-state functional connectivity analysis of independent data collected in normal-weight participants. The motivation for such analysis on normal-weight participants data was simple, namely the desire of defining to what network the regions of reduced grey matter density and activation would normally project and belong. The results of this final analyses revealed that these regions are part of a large bilateral network including the anterior and middle cingulum, the operculum, the medial superior frontal cortex, the insula, the amygdala, subcortical regions such as the striatum, the hypothalamus, and, of course, the thalamus and midbrain themselves (Fig. 2d).

Once decoded through the Neurosynth.org decoding routine (https://neurosynth.org/decode/; Yarkoni et al., 2011) our functional connectivity results confirm that the regions identified by our study are part of what can be broadly seen as a reward circuit, including regions sensitive to "reward" and "gain" but also to what is normally antithetical, namely "pain". Indeed, prefrontal cortices, insula, and anterior cingulate cortices, as well as often subcortical limbic structures such as nucleus accumbens, ventral pallidum and amygdala are typically highlighted as a reward network of interacting brain regions activated by different kinds of pleasurable stimuli (e.g., food, sex, addictive drugs, friends and loved ones, music, art; for a review, see Berridge and Kringelbach, 2015).

Interestingly, this network largely overlaps with the regions involved in the so-called hierarchical model of taste proposed by Rolls (2019): indeed, the first tier of this hierarchy includes the insula and operculum, and it is involved in evaluating the intensity, temperature, and texture of tastes. The second tier includes the orbitofrontal cortex and the amygdala, implicated in monitoring and encoding the reward value of tastes. The third tier includes the medial prefrontal cortex areas and cingulate cortex, the striatum/basal ganglia, and lateral hypothalamus/insula regions, involved in decision-making and learning regarding food (Rolls, 2019).

This evidence supports the hypothesis that the highlighted brain circuit is implicated in the food tasting experience and in food-related reward processing.

4.3. *Present findings and neurocognitive theories of obesity: are these results in line, in part or completely, with the predictions of a particular neurocognitive theory on obesity?*

The last twenty years of imaging research on obesity have had, inevitably-one could say, the ambition of shedding new light on the phenomenon and to give a brain basis to pathological overeating: this study makes no exception.

Yet, the present quest for joint morphometric and functional deficits in obesity limits the spectrum of effects that one could test: the morphometric data lack the necessary functional nature required to support inherently functional theories like, for example, the enhanced brain responsivity to the consummatory aspect of food experience (a key aspect, for example, of the *Reward Surfeit Theory*).

While bearing in mind these limitations, there are some aspects of the available theories that are supported by our data and that may deserve further investigation.

For example, we believe that the shared morphometric and functional alterations of the VTA region and medial thalamus support the idea that overeating is associated with alterations in the reward circuitry, in line with what predicted by the *Reward Deficit Theory*. The nature of the regions of joint reduced grey matter density and activation, particularly the mesencephalic region compatible with the VTA, provides some indirect evidence for a specific alteration in the dopaminergic circuitry. This may contribute to altered activations in connected reward-related brain regions (e.g., ventral striatum), previously reported for the visual/gustatory processing of food-stimuli (for further discussion, see also Devoto et al. 2018, p. 280).

One other finding that may be useful, in a theory-driven perspective, is the reduced grey matter density in medial prefrontal cortex and anterior cingulate cortex: this finding could partially support an *Inhibitory Control Deficit Theory* of obesity, even though we still lack compelling – i.e., replicated several times - evidence of a reduced activation of these regions during voluntary control of action towards food stimuli. The reduced grey matter density here seems justified by experimental models of obesity in the rat (Bocarsly et al., 2015).

Moreover, all the decoding analyses made on the structural and functional results reported here point to cognitive dimensions implicated in the condition of obesity and altered reward processing: for example, "reward", "pain", "gain", "craving", "sexual". While not providing a mechanist explanation of the condition of obesity, these findings make good sense in the light of the brain abnormalities described.

We believe that our results warrant a more systematic exploration of obesity whereby the reward of food, the level of satiety and the intentional control over consummatory behaviour is manipulated. These studies may integrate theories of obesity that emphasize bottom-up processes (e.g., the *Reward Surfeit Theory* or the *Incentive Sensitization Theory*) with top-down theories postulating a deficit in cognitive control (e.g., *Inhibitory Control Deficit Theory)*. This may help defining the working of the normal and "obese" brain under the temptation of the reward of food.

4.4. *Limitations*

We believe that it is important to spend a few words of caution about what changes of grey matter density seen using VBM might mean in this context, and how these might pair with differences of brain activation. This also depends on the stage of life when this is observed. Let's assume that populations considered are young-middle aged adults whose brain maturation is complete and aging effects are not an issue yet.

Reductions of grey matter density in one such pathological condition is what is normally expected in degenerative disorders: this may come from an impoverished number of brain cells, their neuropil or both. The relative increase of grey matter in the sample of healthy controls is normally interpreted as the other side of the coin of a reduction of density in the pathological condition. It is more contentious what a relative increase of grey matter may mean in a pathological population compared with a sample of healthy age-matched controls: this may represent the effect of an abnormal maturation/plasticity leading to "local hypertrophy" due to less neuronal death or hypertrophic neuropil. What is not conceivable is an augmented grey matter density due to experience and neuronal cells proliferation, given the perennial nature of the vast majority of brain neurons. Yet, it remains conceivable a regional augmented grey matter density due to plastic changes of the neuropil (Kolb and Whishaw, 1998).[6] This may be observable in conjunction with augmented response at the functional level. However, the data behind coordinate based meta-analyses do not necessarily imply a between-group difference in the magnitude of the fMRI signal: these may simply represent a more frequent presence of a given "normal" activation in one group rather than an increased response due to greater grey matter density.

One further caveat should be considered: while the patterns of dysfunctional activations are mostly determined by the nature of the

[6] As a matter of facts, only a minority of VBM studies reported augmented grey matter density in obese subjects (# of statistical comparisons: 7) making a meta-analysis of these results using the ALE technique impossible and all considerations on the systematic occurrence of focal augmented density of grey matter a mere theoretical speculation.

task considered and the ensuing pattern of brain activity in the normal controls, changes of brain morphometry are task independent, unless a specific correlation with a behavioural pattern is attempted: yet they do have the potential of revealing latent correlations with altered behaviour not necessarily explicitly tested in the study considered and to be inferred by some form of – cautious - reversed inference.

CRediT authorship contribution statement

Laura Zapparoli: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Francantonio Devoto:** Conceptualization, Methodology, Writing – review & editing. **Gianluigi Giannini:** Methodology, Data curation, Formal analysis, Writing – original draft. **Sara Zonca:** Data curation. **Francesca Gallo:** Data curation. **Eraldo Paulesu:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Author contributions. LZ, FD, GG, SZ, FG, EP reviewed the data for the meta-analyses, performed the analyses, and drafted the manuscript.

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Study registration. The study was not pre-registered.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103179.

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Further reading

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