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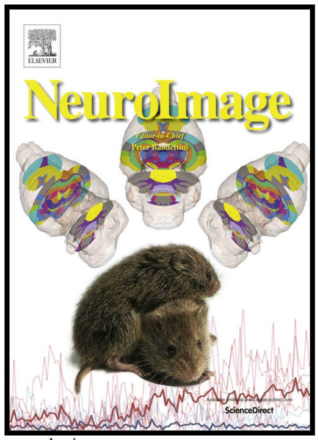

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Independent functional connectivity networks underpin food and monetary reward sensitivity in excess weight

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Abstract:

Overvaluation of palatable food is a primary driver of obesity, and is associated with brain regions of the reward system. However, it remains unclear if this network is specialized in food reward, or generally involved in reward processing. We used functional magnetic resonance imaging (fMRI) to characterize functional connectivity during processing of food and monetary rewards. Thirty-nine adults with excess weight and 37 adults with normal weight performed the Willingness to Pay for Food task and the Monetary Incentive Delay task in the fMRI scanner. A data-driven graph approach was applied to compare whole-brain, task-related functional connectivity between groups. Excess weight was associated with decreased functional connectivity during the processing of food rewards in a network involving primarily frontal and striatal areas, and increased functional connectivity during the processing of monetary rewards in a network involving principally frontal and parietal areas. These two networks were topologically and anatomically distinct, and were independently associated with BMI. The processing of food and monetary rewards involve segregated neural networks, and both are altered in individuals with excess weight.

Keywords: food reward, functional connectivity networks, fMRI, monetary reward, obesity

Introduction

Obesity is one of the most important health problems in developed countries, as it is linked to leading causes of mortality (e.g., cardiovascular disease, diabetes) (Flegal et al. 2013). In recent decades, the prevalence of obesity has reached worldwide epidemic proportions (Ng et al. 2014) and this growth has been linked to the availability of highly processed food rich in sugar and fat (Stice et al. 2013). Obesity is increasingly conceptualized as a disorder of reward-based decision-making, according to cognitive neuroscience evidence showing that obese people predominantly make food choices based on the rewarding aspects of food products, instead of their homeostatic or health properties (Burger and Stice 2011; Kenny 2011; Volkow et al. 2011).

Value-based choices rely on the function of a well-defined network of brain regions central to reward processing, including the anterior cingulate, orbitofrontal and dorsal prefrontal cortices, the ventral striatum, the midbrain and the amygdala (Haber and Knutson 2009). Individuals with excess weight show significantly increased activation in these areas in response to high caloric food cues (Dimitropoulos et al. 2012; Martin et al. 2010; Rothemund et al. 2007; Simon et al. 2014; Stoeckel et al. 2008). However, despite evidence that these reward-related regions behave as an integrated network, it is as yet unclear how network-level disturbances relate to altered brain reward processing in obesity. Functional connectivity studies have examined discrete elements of the brain's reward-processing system (e.g., prefrontal cortex, striatum), but these studies have reported contradictory findings. While some studies in excess weight adults have found enhanced functional connectivity of prefrontal and striatal areas during processing of highly palatable food (Carnell et al. 2014; Kullmann et al. 2013; Nummenmaa et al. 2012; Stoeckel et al. 2009) other studies found reduced functional connectivity in prefrontal areas (García-García et al. 2013).

In addition, it remains unclear whether disruptions of the neural systems supporting reward-based decision-making in this population are specific to the processing of food-related stimuli or represent a general sensitization of reward processes. The existence of a general deficit of reward-processing, (i.e., independent of the specific stimulus), predicts that obese people will have generic problems in evaluating natural reinforcers, which, in turn, may have a broad impact on day-to-day choices and hence physical and mental health (Rangel 2013). Nevertheless, few studies have examined the brain's reward system activity in excess weight individuals during the processing of generic stimuli, such as monetary reward. Balodis et al. (2013) found increased activity in the ventral striatum and ventromedial prefrontal cortex in anticipation of monetary reward. This is consistent with evidence of altered structural connectivity in fronto-striatal circuits in obese individuals, and implies a general reward-processing deficit (Marqués-Iturria et al. 2015). However, other studies have failed to find an association between brain monetary processing and body mass index (BMI) (Simon et al. 2015). These inconsistencies underscore the need for a comprehensive characterization of the functional connectivity of the reward network in excess weight adults across food-related and other types of stimuli.

We used functional magnetic resonance imaging (fMRI) to map brain functional connectivity alterations in the reward system of individuals with excess weight relative to normal weight controls. Both groups performed two tasks: one assessing the processing of food-related rewards and one assessing the processing of monetary rewards. Functional connectivity was assessed with a data-driven graph theoretic approach to characterize whole brain network-level between-group differences in both tasks. Based on prior work (Nummenmaa et al. 2012; Stoeckel et al. 2009), we hypothesized that excess weight individuals would show disrupted functional connectivity in frontal and striatal regions. If excess weight individuals show a general reward-processing deficit, then these disruptions should also be evident during the processing of monetary reward. Finally, we predicted that these network-level functional connectivity disruptions would be associated with behavioral measures of sensitivity to reward and physical measures of adiposity.

Materials and Methods

Participants

Seventy-six right-handed adults, aged between 25 and 45 years old were classified in two groups according to the criteria of the World Health Organization to define excess weight (=overweight or obesity). The groups were comprised of 39 participants with excess weight (BMI>25) and 37 participants with normal weight (controls). The groups did not differ significantly in terms of age ($t_{(1,74)}$=-0.40, p=0.69), sex ($t_{(1,74)}$=-0.02, p=0.99), years of education ($t_{(1,74)}$=0.72, p=0.47), or monthly income ($t_{(1,74)}$=-0.63, p=0.39) (Table 1).

Table 1: Sociodemographic characteristic and body composition by group.

	Normal weight (n=37) Mean (SD)	Excess weight (n=39) Mean (SD)
Age	33.00 (6.53)	33.59 (6.23)
Sex (male/female)	17 / 20	18 / 21
Years of education	18.35 (3.71)	17.74 (3.65)
Monthly income		
<600€	21.6%	10.3%
601-1000€	10.8%	10.3%
1001-1500€	18.9%	28.2%
1501-2000€	16.2%	12.8%
2001-2499€	10.8%	17.9%
>2500€	21.6%	17.9%
BMI (kg/m^2)	22.28 (1.77)	30.41 (3.69)
Fat (%)	19.71 (6.07)	30.99 (8.65)

SD, Standard Deviation; BMI, Body mass index.

Participants were recruited through general hospitals and media advertisements. The exclusion criteria were: (i) history or current evidence of neurological or psychiatric disorders, including substance use disorders, indicated by semi-structured interviews conducted by Masters-level professional psychologists; (ii) medical comorbidities associated with obesity (e.g., diabetes, hypertension); (iii) significant abnormalities on structural MRI or any contraindications to MRI scanning. All participants had normal or corrected-to-normal vision. The study was approved by the Human Research Ethics Committee of the University of Granada. All participants signed an informed consent form and received a 50€ compensation for their time commitment in the study.

Experimental paradigm

Each participant performed two tasks during the fMRI session, a monetary reward task (Monetary Incentive Delay task) and a food-related reward task (Willingness to Pay task). To ensure that participants were familiar with the food stimuli used in the Willingness to Pay task, participants attended a tasting session two weeks before scanning. During this session participants tasted the 18 foods that we would later present, as visual stimuli, in the task. These foods belonged to two groups, defined a priori by the research team, based on their degree of palatability: highly palatable food, including sweet and fatty food (e.g., chocolate, cheese cake, burger) versus plain food (e.g., yoghurt, omelet). The tasting session had two aims. The first was to ensure that all participants had tried the food stimuli that we would subsequently present in the scanner. The second aim was to collect subjective ratings of “liking” after tasting the actual foods, and thus to validate the categories that we had established “a priori” i.e. to check that highly palatable foods were more “liked” than plain foods. All tasting sessions were conducted at 6:00 pm, and participants were instructed to taste each of the foods offered and to rate how much they liked them using a 1-10 scale. Both groups showed higher "liking" rating for highly palatable compared to plain food (all $p<0.05$), validating our prior classification.

BMI and fat percentage were obtained before the fMRI scan using a body composition analyzer TANITA BC-420 (GP Supplies Ltd., London, UK). During the fMRI session, to control the potential effects of hunger/satiety levels, participants rated their appetite using a 10-cm visual analogue scale (VAS) three times along the fMRI session: prior to scan, immediately before the food-stimuli task and immediately after leaving the MRI room.

fMRI tasks

Willingness to Pay task (WtP)

We used a modified version of the Willingness to pay task (Plassmann et al. 2007). Participants were presented with a picture of each of the 18 foods previously tasted. All pictures were shot ad hoc for the study, using standardized presentation and lightning conditions. Therefore, all images were matched for visual properties and serving size. Highly palatable and plain food naturally differed in caloric content based on nutrition facts, although we did not code or analyzed this variable quantitatively. Each stimulus was presented once for two seconds followed by a four-second response period, during which time participants answered the question: "How much would you pay for it?" They could choose between four monetary options, ranging from 20 cents to 10 euros. Each selection was followed by a variable fixation period lasting between 3 and 5 seconds. Our goal in this task was to examine brain activity and functional connectivity in high palatable food trials compared to plain food trials.

Monetary Incentive Delay task (MID) (Knutson et al. 2000; Nestor et al. 2010)

In each trial, participants were shown one of two cues (green or blue squares) indicating potential winnings or no financial outcome. The incentive value of each trial was indicated by the number of lines crossing the green or blue squares (one line for 0.2€, two for 1€ and three for 5€). The order of the four cues (the three cues signaling different reward magnitudes and the one cue signaling no reward) was randomized across participants. Each cue was presented for a fixed duration, 750msec, followed by a cross-fixation (3 to 5 sec), and a reaction-time task: respond to a white target star appearing for a variable period (150–450 ms) with a button press. Then participants received feedback (hit/miss) for 750ms, together with the information about the money won in that trial (when adequate, e.g., correct responses in reward cued trials). Finally, another fixation period (750 ms) was included before the next trial. Therefore, total trial duration ranged between 5700 and 7000 ms, enabling precise desynchronisation from the repetition time (TR) of 2000 ms.

Participants performed the task in two sessions of 48 trials each, yielding a total of 96 trials. Imaging analyses examined brain activity changes during two events: (i) reward-anticipation, which occurred between the presentation of the cue and the response; and (ii) reward-feedback period, which occurred at the time of the feedback.

Both tasks were administrated using Presentation software (version 1.8; http://www.neurobs.com). Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology Inc), and responses were recorded through Evoke Response Pad System (Resonance Technology Inc).

Imaging data acquisition and preprocessing

Participants were scanned using a 3T Philips Intera Achieva System. T2*-weighted echo-planar imaging (EPI) sequences were acquired with the following parameters: repetition time, 2000 ms; echo time, 35ms; flip angle, 90º; field of view, 240 mm; number of slices, 21, voxel dimension, 3 x 3 x 4 mm; gap, 1mm. Specifically, we performed a 149-volume scan session for the WtP task, and two 216-volume scan sessions for the MID task. Structural images were obtained as an isotropic T1-weighted turbo-gradient-echo sequence in the sagittal plane (TR, 8.3ms; TE, 3.8 ms; flip angle, 8º; FOV 240mm; number of slices, 160; voxel dimension, 1 x 1 x 1 mm).

Image preprocessing and analysis were performed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK), running under Matlab R2009 (MathWorks). Preprocessing steps included realignment to the mean image of the time series, slice timing correction, normalization, using affine and smoothly non-linear transformations, to an EPI template in the Montreal Neurological Institute (MNI) space, and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum (FWHM) = 8 mm). Data were high-pass filtered to remove low-frequency noise (1/128 Hz) and corrected for temporal autocorrelation using an autoregressive AR model.

Behavioral analyses

Behavioral data were analyzed with SPSS19 (Chicago, IL, USA). We conducted a 2 (Group) x 2 (Type of Food) ANOVA on WtP scores, and a 2 (Group) x 4 (Type of Cue) ANOVA on MID scores of money paid and response time.

Task-related functional connectivity analysis

Graph analysis (Bullmore and Sporns 2009; Rubinov and Sporns 2010) was used to characterize brain functional connectivity during both tasks. Each brain network was modeled as a graph composed of N nodes connected by M edges. Regions showing significant activation or deactivation on the one-sample analyses, across the whole group of participants, of the three main contrasts [i.e., (i) high palatable food > plain food; (ii) anticipation during high reward trials > medium reward trial anticipation > low reward trial anticipation > no outcome trials anticipation; and (iii) win > miss trials], were selected as nodes for the functional connectivity analysis (for details of task activation mapping procedures, see Supplementary Material). All nodes, regardless of the activation contrast used to identify them, were used in the analyses of both tasks. In this way, we were able to examine context-specific changes within a single, reward-related network. ROIs were then generated as 4 mm spheres centered on the voxel with the highest t score in each significant cluster. To prevent overlap between nodes, regions whose central points were closer than 8mm in Euclidean space were identified (n = 60) and a new node was created with a centroid that was equidistant from the two original foci. A total of 126 nodes were defined with this method. Each region-of-interest was masked by the SPM a priori probability image of grey matter in order to weight each voxel value according to its grey matter probability.

Averaged signal time courses for each of the 126 nodes were extracted from the non-smoothed images for both tasks. To measure task-related functional connectivity, we used the correlational psychophysiological interaction (cPPI) methodology ((Fornito et al. 2012); http://www.nitrc.org/projects/cppi_toolbox). Separate analyses were conducted to investigate task-related functional connectivity in relation to (i) food-related reward processing; (ii) anticipation of monetary reward; and (iii) receipt of monetary reward. (See additional information for this method in Supplementary Material)

The cPPI analyses resulted in three $N \times N$ functional connectivity matrices (one for each contrast of interest) per subject, where N = 126. Each matrix represents task-related functional connectivity between every pair of nodes. In the food reward task, a higher correlation indicated that two regions showed coherent BOLD signal fluctuations such that activity was, on average, higher in the High palatable condition compared to the Plain food condition. In the monetary reward anticipation analysis, a higher correlation indicated stronger connectivity associated with the linear contrast High>Medium>Low>No Reward. In the monetary reward feedback analysis, a higher correlation indicated coherent fluctuations such that activity was stronger in win compared to miss trials. Functional connectivity was measured for a total of $(N^2-N)/2$=7875 edges in each network, separately for each of the three task contrasts.

NBS analyses

We used the network-based statistic (NBS) to test for group differences in task-related functional connectivity in a data-driven, regionally-unbiased way (Zalesky et al. 2010). A separate analysis was conducted for each task contrast. Briefly, the NBS starts with a mass univariate analysis, in which statistical inference is performed independently at each of the 7875 connections in the network. In this case, the inferential test was a two-tailed t-test of the difference in group means between excess weight and normal weight individuals. The resulting matrix was thresholded at $p<0.05$, uncorrected (results obtained at lower p values ($p<0.01$, $p<0.005$) are provided in Supplementary Material). The sizes (in terms of number of edges) of the connected components of the remaining network of supra-thresholded edges were then computed, where connected components represent sets of nodes that can be linked by a set of supra-threshold edges. Group labels were then permuted and the analysis was repeated to generate an empirical null distribution of maximal component sizes. A total of 5000 permutations was used to generate this distribution. Since only the maximal component size is stored at each permutation, the resulting p-values for the observed sizes are familywise corrected at the component level (Nichols and Holmes 2002; Zalesky et al. 2012). We retained as significant all components surviving a threshold of $p<0.05$, component-wise corrected.

Results

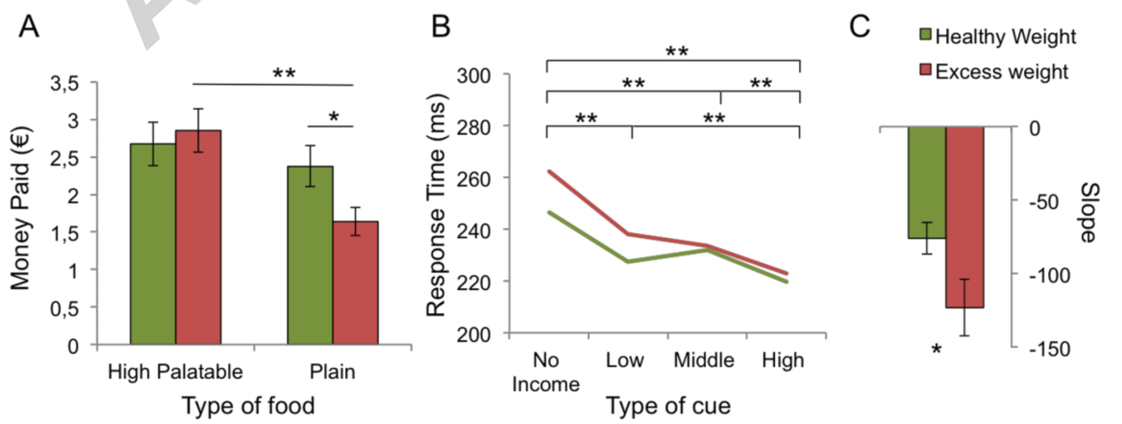
Behavioral Analyses

We found no significant between-group differences or interactions between Group and Time for subjective measures of appetite ($F(2,140)= 0.589$, $p=0.517$).

We found a significant "Group x Type of food" interaction ($F(1,74)=8.57$, $p=0.005$) in the WtP task. There were no significant differences in valuation of high palatable foods between the groups, but excess weight group showed a lower willingness to pay for plain food than controls ($t(74)=2.24$, $p=0.028$). Within the excess weight group, participants showed a higher willingness to pay money for palatable food versus plain food ($t(38)=5.75$ $p<0.001$). This difference between palatable and plain food was not significant in the control group (Figure 1A).

In the MID task, we found no significant differences on money won ($t(74)=0.379$, $p=0.704$) but there was a significant effect of cue type across groups on reaction time ($F(3,222)=48.18$, $p<0.001$), indicating that all participants made faster responses when they had the opportunity to win more money (Figure 1B). We found a trend-level interaction between Group and Type of cue in the reaction time ($F(3,222)=2.76$, $p=0.063$), suggesting that the excess weight group showed a greater change in reaction time across the different reward magnitude conditions, compared to the control group (Figure 1B). A second measure to assess reward sensitivity in the MID task is the slope of the linear regression of reaction time on cue type, ordered from no income, to low, middle and high magnitude. Comparing this measure, we found significant differences between groups ($t(1,74)=2.136$, $p=0.037$), suggesting greater responsivity to reward in the excess weight group (Figure 1C).

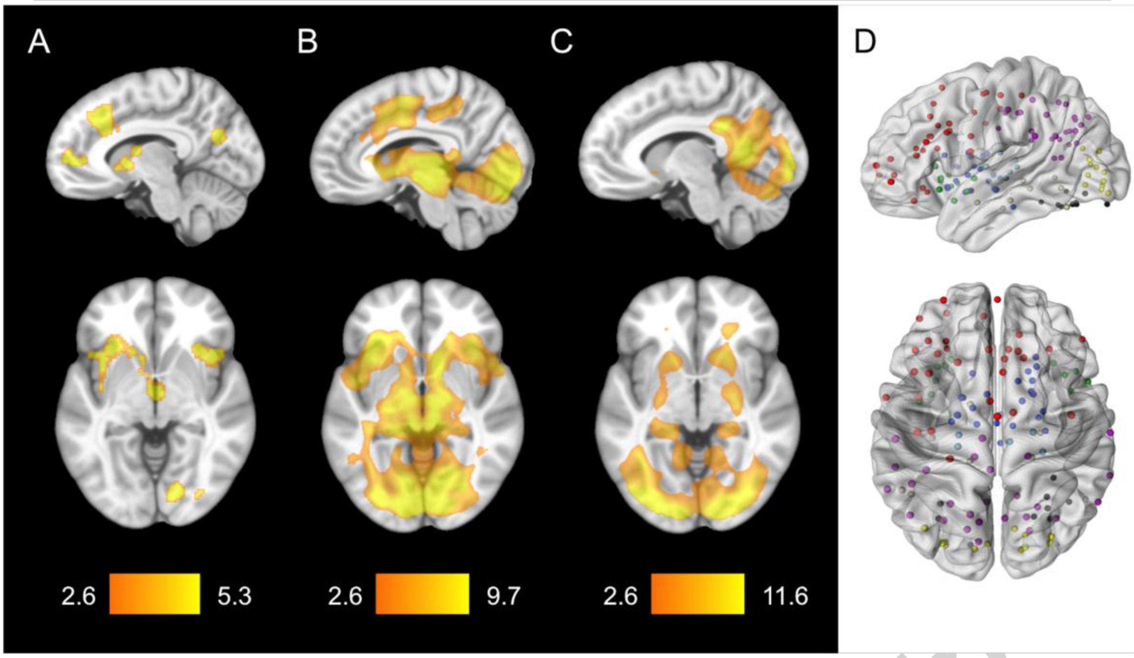
Figure 1. Behavioral differences between excess and normal weight individuals during the willingness to pay and monetary incentive delay tasks. ***A***. Average money paid during the WtP task. Errors bars represent sample standard error. ***B***. Average response time for each cue type. Both groups showed the same differences as a function of cue type. ***C***. Average slope of the linear regression equation across cue type in the MID task. Errors bars represent sample standard error. * $p<0.05$; ** $p<0.01$.



Task-related activation

Across both groups and the three contrasts (i.e., the WtP task contrast between high palatable versus plain food and the MID contrasts of anticipation and feedback), one-sample t-tests showed significant activation in reward-related areas, including the striatum and the prefrontal cortex (i.e., middle and lateral orbitofrontal gyri), as well as in the precuneus and the occipital cortex. (See further information in Figure 2 and Supplementary Tables S1, S2 and S3). There were no significant between-groups differences in regional activation for any contrast at the selected threshold.

Figure 2: Task-related activation during the willingness to pay (***A***) and anticipatory (***B***) and feedback (***C***) contrasts of the monetary incentive delay tasks. The color bar indicates t-value. Left hemisphere is displayed on the left. ***D.*** Spatial localization of the nodes. Color node reflects anatomical divisions [i.e., Frontal (red), Insula (green), Striatum (dark blue), Thalamus (light blue), Temporal (grey), Parietal (purple), Occipital (yellow) and Cerebellum (black)]. Left hemisphere is displayed on the left.



Functional connectivity

WtP task.

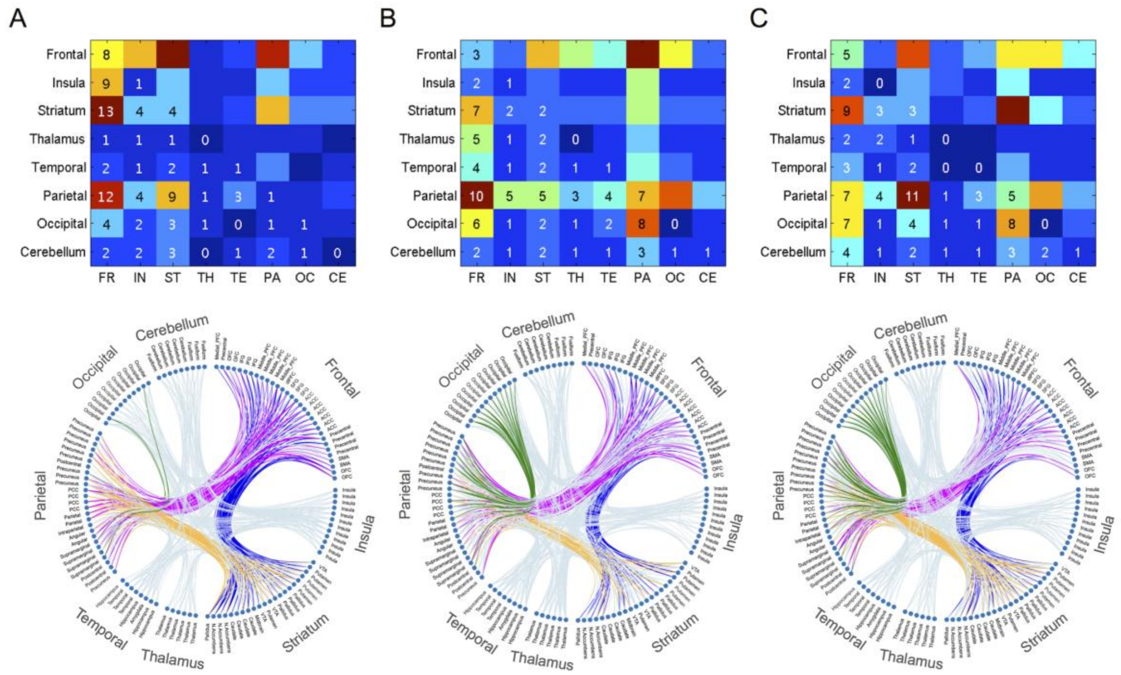
The excess weight group showed a significant reduction of functional connectivity in the WtP task compared to controls. The network showing reduced functional connectivity comprised 544 edges and 125 nodes (p=0.025, component-wise corrected). To better understand the anatomical distribution of this network, we categorized nodes into eight categories according to their anatomical designation: frontal, insula, striatum, thalamus, temporal & hippocampus, parietal, occipital and cerebellum. We found that more than half of the connections in this network involved frontal cortex (50.55%). Most of these edges linked the frontal cortex with the striatum (13%) or the frontal cortex with the parietal cortex (12%). Fronto-insular (8.6%) and fronto-frontal connections (8.3%) were also frequently implicated in this network (Figure 3A). We identified no subnetworks in which excess weight individuals showed significantly increased functional connectivity during the WtP task.

MID task.

During the MID task, the excess weight group showed a significant enhancement of functional connectivity, during both the anticipation and the feedback conditions, compared to controls. This pattern stood in stark contrast to the WtP task, where the excess weight group only showed evidence of reduced functional connectivity.

During reward-anticipation, one component, comprising 532 edges and 126 nodes (p=0.03, component-wise corrected), showed significantly increased functional connectivity in excess weight individuals. This network largely involved frontal and parietal areas, with 10% of connections being fronto-parietal, 7.5% parieto-occipital, 7.1% intraparietal and 7% fronto-striatal (Figure 3B). During reward-feedback, a component comprising 547 edges and 125 nodes (p=0.005, component-wise corrected) showed significantly increased functional connectivity in excess weight participants. This network predominantly involved frontal, striatal and parietal areas: 11% of the edges were parieto-striatal, 9% fronto-striatal, 8% parieto-occipital and 7.5% fronto-occipital (Figure 3C).

Figure 3. Functional connectivity disruption during the willingness to pay task **(*A*)** and the monetary incentive delay task's anticipation **(*B*)** and feedback **(*C*)** contrasts. Tables show the distribution of edges based to the anatomical division they connected. Connectograms (below) showed disrupted connections for each network. Edges of interest are grouped according to anatomical connections [i.e., Fronto-striatal (blue), fronto-parietal (purple), parieto-striatal (orange) and parieto-occipital (green)].



Consistency across task conditions

To examine whether there was a common dysfunctional network across task conditions, we computed the overlap in the binary topology of the three condition-specific dysfunctional networks identified in excess weight individuals. (See further details on overlap analyses in Supplementary Material).

We found that the dysfunctional networks identified during MID anticipation and feedback showed a statistically significant degree of overlap, sharing 112 edges in which task-related functional connectivity was increased in excess weight individuals ($p<0.001$). Most of these edges were parieto-occipital (14%), fronto-occipital (8.9%) and fronto-striatal (8.9%). This network thus comprises a core dysfunctional network for the processing of monetary reward in excess weight people.

In a second analysis, we examined the consistency between the dysfunctional network identified in the WtP task and the anticipation and feedback conditions of the MID task. The degree of overlap between the dysfunctional monetary feedback and food reward networks was significantly less than expected by chance (20 edges, $p<0.005$). A similar trend was observed for the overlap between the food and monetary anticipation networks (24 edges, $p = 0.055$). These findings suggest that abnormal processing of monetary and food-related rewards in excess weight individuals is related to dysfunction in spatially and topologically segregated neural systems.

Correlation analyses

We computed the first principal component of functional connectivity measures across the edges comprising the dysfunctional network identified in each task condition and correlated each individual's component score with behavioral and physical measures. For the WtP task, the first PC accounted for 7.16% of the variance; for anticipation it accounted for 7.60% and for feedback it accounted for 7.73%. Correlation analyses were conducted in the whole sample, collapsing the two groups (n=76). We established a significance criterion of $\alpha=0.05$ (two-tailed), and subsequently performed Bonferroni correction to protect against Type I error ($\alpha=0.05/12=0.004$).

Correlations with task performance

We found a negative correlation between functional connectivity of the dysfunctional network during the WtP task and the difference score of money paid for high palatable versus plain food ($r = -0.266$, $p = 0.020$) (Figure 4A). That is, lower functional connectivity was associated with a lower valuation of plain food.

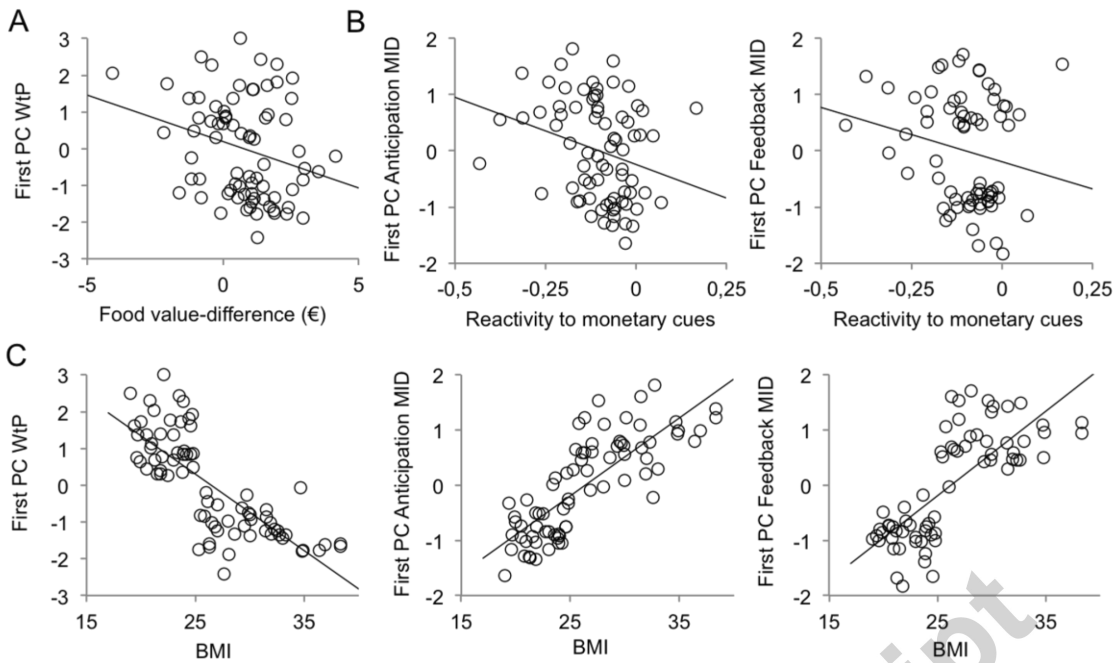
We also found a negative correlation between functional connectivity of the dysfunctional network during the MID contrast of anticipation to reward and the measure of reaction time change across reward magnitudes ($r = -0.269$, $p=0.020$) (Figure 4B). According to the negative sign of the slope of the linear regression of reaction time on cue type, this negative correlation indicates that higher functional connectivity during monetary reward anticipation was associated with greater behavioral sensitivity to reward magnitude. These correlations suggest conceptually plausible relationships between functional connectivity and behavioral performance. However, they did not survive Bonferroni correction ($\alpha=0.05/12=0.004$), and thus they require independent replication.

Correlations with adiposity

To examine whether dysfunction in the above-described networks showed a continuous association with BMI that did not depend on our cut-off for defining excess weight individuals, we also conducted correlations with BMI and body-fat percentage. There was a negative correlation between functional connectivity in the dysfunctional WtP network and BMI ($r = -0.77$, $p<0.001$). Therefore, lower functional connectivity during this task was associated with higher BMI. A similar correlation was found with body-fat percentage ($r = -0.53$, $p<0.001$). The two dysfunctional MID networks also showed significant correlations with BMI and fat percentage: $r = 0.80$ and $r = 0.49$, $p<0.001$ in the anticipatory monetary contrast and $r = 0.76$ and $r = 0.47$, $p<0.001$, in the feedback related contrast (Figure 4C). Each of these results survived Bonferroni correction (alpha = 0.004).

We also performed partial correlations in which functional connectivity in the dysfunctional WtP network was correlated with BMI while controlling for functional connectivity in the dysfunctional MID networks. This analysis still revealed a significant negative correlation ($r = -0.304$, $p<0.013$). Similarly, the positive correlation between functional connectivity of the dysfunctional MID anticipation and feedback networks and BMI remained significant when controlling for the WtP network ($r=0.481$, $p<0.001$ and $r=0.380$, $p=0.002$). These results indicate that brain networks that are dysfunctional in excess weight individuals during the processing of food and money reward are independently associated with BMI.

Figure 4. Altered networks in excess weight individuals correlate with task performance and BMI. ***A.*** Correlation between WtP network dysfunction and food value-difference measured as money paid for high palatable food minus money paid for plain food. Higher values reflect lower valuation of plain food compared to highly palatable food. ***B***. Correlation between MID network dysfunction and reactivity to monetary cues measured as the slope of the regression of response time across the reward cues. Lower values reflect higher sensitivity to reward magnitude. ***C.*** Correlations between altered networks and BMI.



Discussion

We used a data-driven, connectome-wide analysis to map neural systems showing altered functional connectivity in excess weight individuals during the processing of two distinct types of reward: food and money. We found consistent evidence for involvement of frontal, striatal and parietal areas across tasks; however, the specific neural systems identified as dysfunctional in the food and monetary contexts were different. Specifically, excess weight individuals showed reduced functional connectivity and reduced subjective valuation of rewards during food processing, and increased functional brain connectivity and higher behavioral sensitivity to monetary rewards. The specific set of brain functional interactions that were altered in these conditions showed statistical evidence of spatial and topological segregation. Network-level functional connectivity correlated with task performance and physical measures of weight.

Functional connections showing reduced coupling during the WtP food task in excess weight individuals predominantly linked frontal lobe nodes, which play an important role in self-regulation (Rangel 2013), with striatal regions involved in stimulus valuation (Montague and Berns 2002), parietal regions implicated in attentional control (Hopfinger et al. 2000), and insula regions relevant to interoception (Craig 2009). These results are consistent with a previous study that found reduced frontal cortex related functional connectivity in obese individuals during passive viewing of high palatable food images (García-García et al. 2013). Two recent studies have also reported altered white matter microstructure in fiber pathways linking frontal and subcortical areas in excess weight adults (Kullmann et al. 2015; Marqués-Iturria et al. 2015). Frontal areas play a crucial role in dietary choices. These areas code the relative value of food reward according to palatability, while also supporting behavior to achieve long-terms goal (Rangel 2013). Reduced functional connectivity between the frontal cortex and reward-related regions has been associated with failure of top-down regulation of behavioral control (Motzkin et al. 2014). This deficit has also shown to contribute to explain dietary choices in obesity (Rangel 2013). This interpretation is consistent with several studies that report difficulties in cognitive control and executive functions in obesity (Fitzpatrick et al. 2013). Modelling effective connectivity (Friston et al. 2003) within fronto-striatal systems may provide a useful test of the hypothesis that these circuit-level abnormalities are caused by deficient top-down signaling from the prefrontal cortex.

In the MID task, individuals with excess weight displayed enhanced functional connectivity in a similar network across reward-anticipation and reward-feedback. This network involves mainly parieto-occipital, fronto-occipital and fronto-striatal connections. Previous resting-state neuroimaging studies had demonstrated enhanced resting-state functional connectivity in individuals with obesity (Black et al. 2014; Dubbelink et al. 2008; Kullmann et al. 2012; Lips et al. 2014; Wijngaarden et al. 2015). Therefore, in obese people the pattern of functional brain connectivity during monetary reward resembles the tonic hyper-connectivity observed in resting-state studies. Fronto-occipital networks are involved in rapid feed-forward propagation of visual inputs and direct top-down modulation of early visual processing (Forkel et al. 2014). Parieto-occipital connections have also been implicated in the orientation and maintenance of visual attention (Foxe et al. 1998). The specific involvement of visual-attentional and goal-directed networks suggests that obese individuals have enhanced motivational sensitivity to monetary rewards.

The non-significant overlap between the dysfunctional reward-processing networks, as well as our partial correlation analyses, indicate that different neural systems independently correlate with excess weight. Reduced functional connectivity in frontal-striatal networks during processing of food-related stimuli may relate to weakening of self-regulation skills needed to control high-calorie food choices (Hollmann et al. 2012). Money-related hyper-connectivity in visual-attentional networks may relate to excessive weight via special attention to the financial value of cheap high-calorie foods (Bruce et al. 2014). Ultimately, different therapeutic approaches may be needed to tackle excess weight problems, one to strengthen frontal-striatal FC in response to food stimuli, and a different one to decrease fronto-parietal-occipital FC in relation to monetary reward processing.

In summary, excess weight individuals had increased functional connectivity in the monetary network, and reduced functional connectivity in the food network. These results provide evidence of a general disruption of reward processing in excess weight, and spatially segregated networks for monetary versus food reward. Our connectivity findings are correlational and hence future studies are required to establish mechanistic explanations, and to determine the role of separate network alterations on clinical and societal consequences of obesity. Moreover, we did not find significant group differences in brain activation in any of the three contrasts. These results suggest that reward processing in excess weight individuals is primarily driven by dysfunction of anatomically distributed neural systems, rather than isolated dysfunction of one or a few brain regions. Other studies have reported regional activation differences between obese individuals and normal weight controls during processing of highly palatable food (Rothemund et al. 2007; Stoeckel et al. 2008). However, most of the existing studies included participants with severe presentations of obesity (BMI>35) and other comorbid conditions, whereas our sample was carefully screened to exclude these important confounders. Our findings must be interpreted in the context of relevant limitations. First, as noted above, our exclusion criteria precluded selection of severe cases of obesity and thus results may not generalize to severe forms of obesity. Second, we did not examine individual differences in food preferences, relevant to the WtP task. Instead, we grouped the food stimuli a priori (highly palatable vs plain). Although subjective "liking" reports validated this classification, future studies can benefit from factoring. Third, we did not control the menstrual cycle phase of the female participants. Previous studies showed that menstrual cycle phase could modulate reward-related neural function in women (Dreher et al., 2007), and therefore this should be controlled in future studies. Fourth, our analyses were suited to define differential patterns of connectivity in participants with excess weight, but they do not establish a causal association between obesity and brain abnormalities. Related to this, and despite adequate control of relevant confounding variables, it is possible that differences in connectivity are partially explained by additional aspects linked to obesity, such as individual differences in trait characteristics or affective states. Finally, correlations between patterns of connectivity and behavior did not survive conservative Bonferroni correction, and hence they should be further investigated.

Conflict of Interest

The authors declare no conflict of interest

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Highlights

- Graph analyses unraveled connectivity alterations associated to excess weight.
- Excess weight is associated with reduced functional connectivity during food processing.
- Excess weight is associated with increased functional connectivity to monetary rewards.
- Altered networks linked to food and monetary reward processing were significantly different.