Garcia-Garcia I, Jurado MA, Garolera M, Marques-Iturria I, Horstmann A, Segura B, Pueyo R, Sender-Palacios MJ, Vernet-Vernet M,Villringer A, Junque C, Margulies DS, Neumann J. **Functional network centrality in obesity: A resting-state and task fMRI study**.Psychiatry Res. 2015;233:331-8.

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Highlights

• We examined functional network centrality in obesity.

• We acquired resting-state and task-related data from the same subjects.

• We found obesity-related lower degree centrality in the middle frontal gyrus.

• Differences in the middle frontal gyrus seemed to be trait-dependent.

Abstract

Obesity is associated with structural and functional alterations in brain areas that are often functionally distinct and anatomically distant. This suggests that obesity is associated with differences in functional connectivity of regions distributed across the brain. However, studies addressing whole brain functional connectivity in obesity remain scarce. Here, we compared voxel-wise degree centrality and eigenvector centrality between participants with obesity (n=20) and normal-weight controls (n=21). We analyzed resting state and task-related fMRI data acquired from the same individuals. Relative to normal-weight controls, participants with obesity exhibited reduced degree centrality in the right middle frontal gyrus in the resting-state condition. During the task fMRI condition, obese participants exhibited less degree centrality in the left middle frontal gyrus and the lateral occipital cortex along with reduced eigenvector centrality in the lateral occipital cortex and occipital pole. Our results highlight the central role of the middle frontal gyrus in the pathophysiology of obesity, a structure involved in several brain circuits signaling attention, executive functions and motor functions. Additionally, our analysis suggests the existence of task-dependent reduced centrality in occipital areas; regions with a role in perceptual processes and that are profoundly modulated by attention.

Abbreviations

AFNI, Analysis of Functional Neuroimages; BMI, body-mass index; FSL, FMRIB Software Library; fMRI, functional magnetic resonance imaging; ICA, independent component analysis; SCID-I, Structured Clinical Interview for DSM-IV; SPM, statistical parametric mapping

Keywords

Body-mass index; fMRI; Functional connectivity; Graph analysis; Brain

1. Introduction

Obesity is a chronic multifactorial health problem defined by excessive adiposity or body fat. Although obesity is not usually strictly considered a brain disorder, multiple lines of neurobiological research have revealed the existence of structural and functional brain alterations associated with obesity (Dagher, 2012). Relative to normal-weight participants, obese populations exhibit lower gray matter volume, cortical thickness and glucose metabolism in the prefrontal cortex (Pannacciulli et al., 2006, Willeumier et al., 2011 and Marqués-Iturria et al., 2014). In striatal structures, individuals with obesity seem to exhibit lower dopamine D2/D3 receptor availability (Wang et al., 2001 and De Weijer et al., 2011; but see Eisenstein et al., 2013) and increased gray matter volume (Horstmann et al., 2011). Additionally, functional neuroimaging studies have observed differences between participants with obesity and normal-weight controls during reward processing. In response to food stimuli, participants with obesity exhibited higher activation of the parahippocampal gyrus/amygdala, putamen and superior frontal gyrus, along with lower activation of the insula and occipital areas (Nummenmaa et al., 2012, Brooks et al., 2013 and García-García et al., 2014). To summarize, relative to normal-weight controls, participants with obesity seem to present a widely distributed pattern of structural and functional brain differences. This raises the question whether obesity is also associated with alterations in the functional connectivity between brain regions. In this article, we apply graph-theoretic measures of functional connectivity to both resting-state and task functional magnetic resonance imaging (fMRI) data to address this issue.

Functional brain connectivity describes the relations between distinct brain areas based on the correlation between fMRI time series (e.g., Lohmann et al., 2013). In obesity research, several groups have examined functional connectivity by applying seed-based analysis or independent component analysis (ICA). Studies using seed-based analysis have reported obesity-related differences in connectivity between the hypothalamus and the medial prefrontal cortex and striatum (Lips et al., 2014 and Kullmann et al., 2014a). Studies on ICA have shown that, relative to lean counterparts, overweight and obese individuals displayed alterations in the default mode network (Tregellas et al., 2011 and Kullmann et al., 2012), increased connectivity within the salience network (Garcia-Garcia et al., 2013a and Kullmann et al., 2013) and decreased connectivity within networks that include visual brain areas (Kullmann et al., 2013 and Garcia-Garcia et al., 2013b).

Seed-based functional connectivity and ICA methods have proved extremely useful in examining connectivity patterns for individual brain regions or specific components of interest. However, studies are beginning to adopt the view of the brain as a complex large-scale network characterized by interregional interactions. Along this line, graph theory offers a powerful

approach for studying complex whole brain functional connectivity patterns (Bullmore and Sporns, 2009). As previously mentioned, studies have provided evidence that obesity is associated with functional differences in a widespread number of regions and components (e.g., Brooks et al., 2013; Kullmann et al., 2013). Therefore, the use of methodological frameworks accounting for the complexity of brain organization might certainly enrich our understanding of the brain's role in obesity.

Functional centrality is a graph-theoretic measure that assesses the connectivity of nodes (anatomical parcellations ranging from single voxels to extended brain regions) with the entire network (Rubinov and Sporns, 2010). As such, centrality measures facilitate the localization of functionally important brain regions based on the connection patterns associated with them (Buckner et al., 2009 and Zuo et al., 2012). Two commonly used measures of centrality are degree centrality and eigenvector centrality. Degree centrality indexes the total number of connections for a given node (Buckner et al., 2009). Eigenvector centrality, on the other hand, favors nodes that are strongly correlated with other nodes that are themselves central within the network (Lohmann et al., 2010). Differences in degree centrality can be considered 'local', given that this metric captures the amount of direct connections with a given node (Zuo et al., 2012). Differences in eigenvector centrality, on the other hand, can be generally regarded as 'global' in the sense that this metric captures 'indirect' functional connectivity (Zuo et al., 2012). In the field of obesity, differences in whole-brain functional connectivity have been scarcely addressed, with only one study examining obesity-related differences in eigenvector centrality. The authors found an age-dependent association between eigenvector centrality in the cerebellum and visceral fat distribution. The association was negative in the case of participants younger than 46 years and positive in participants older than 64 years (Raschpichler et al., 2013). This study was insightful in identifying brain regions that exhibit centrality differences in obese participants. However, more research is needed to characterize obesity-specific alterations in network centrality, especially among young adults.

Functional connectivity can be analyzed using task-free (or resting-state) and task-based fMRI protocols. Previous research on functional connectivity has shown that task-related co-activation patterns correspond well with brain systems that are measured at rest (Smith et al., 2009 and Mennes et al., 2010). However, there is also evidence that task-based acquisitions may capture specific dynamic neural responses in regions with a key role in task processing (Buckner et al., 2009 and Mennes et al., 2013). Here, we compared participants with obesity and normal-weight controls in degree centrality and eigenvector centrality. To capture a broader repertoire of functional activity, we analyzed resting-state and task fMRI data acquired form the same subjects. Previous studies have reported regional structural or functional brain changes emphasizing the role of the prefrontal cortex in obesity. As such, we expected to find lower

functional centrality in obesity in the prefrontal cortex. Additionally, previous studies in food processing suggest regional obesity-related differences extended to other brain areas, such as the amygdala, insula or occipital cortex. Therefore, for the task fMRI condition, we expected to observe further differences in these areas in participants with obesity.

2. Methods

2.1. Participants

Forty-one participants [20 participants with obesity (14 women); 21 normal-weight participants (12 women)] aged 20–40 years were included in the study. Participants were included in the obesity group if their body mass index (BMI) was ≥30 kg/m2 and in the normal-weight group if their BMI was between 18.5 and 25 kg/m2 (exclusion criteria are detailed in the Supplementary material). Before the scan, participants rated their subjective degree of hunger on a 10 cm visual analog scale. The study was approved by the institutional ethics committee of the University of Barcelona and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each participant before the study began.

This study forms part of a broader line of research that aims to characterize obesity-related differences in brain structure and function. Some of the participants in this report have been included in other publications addressing different research questions. Previously, we examined dopaminergic polymorphisms and executive functions (Ariza et al., 2012; 90% of the current sample and 47 additional participants), cortical thickness (Marques-Iturria et al., 2013: 90% of the sample; Marqués-Iturria et al., 2014: 100% of the current sample and 20 additional adolescent participants) and functional brain components extracted from ICA analyses (Garcia-Garcia et al., 2013a and Garcia-Garcia et al., 2013b: 71% and 88% of the current sample, respectively). Here, we combine for the first time resting-state data and task-related fMRI data from the same subjects to examine the patterns of functional connectivity associated with obesity with a voxel-based network centrality approach.

2.2. MRI acquisition

Two hundred forty resting-state volumes were collected using a multi-slice gradient-echo EPI sequence [echo time (TE): 19 ms; repetition time (TR): 2000 ms; 3-mm slice thickness; 40 slices per volume; 25% interslice gap; 90° flip angle; 220 mm field of view (FOV); matrix size 128×128; voxel size: 1.7×1.7×3.0 mm^3] covering the whole brain. Resting-state scanning was followed by fMRI task data acquisition. Two hundred ten T2-weighted volumes were acquired using a multi-slice gradient-echo EPI sequence (TE: 19 ms; TR: 2000 ms; 3-mm slice thickness;

40 slices per volume; 25% interslice gap; 90° flip angle; 220 mm FOV; matrix size: 128×128; voxel size: 1.7×1.7×3.0 mm^3) covering the whole brain.

A T1-weighted structural image was also acquired for each subject with the MPRAGE 3D protocol (TE: 2.98 ms; TR: 2300 ms; 1-mm slice thickness; 50% interslice gap; 9° flip angle; inversion time: 900 ms; 256 mm FOV; matrix size: 256×256; voxel size: 1.0×1.0×1.0 mm^3).

The task protocol was a 7-min block design experiment in which participants were presented visual stimuli subdivided into four categories: high-calorie food, low-calorie food, neutral non-food and rewarding non-food images. Detailed information on the task fMRI protocol is presented in Garcia-Garcia et al. (2013b) and in the Supplementary material. Since the duration of the task was not long enough to permit the examination of centrality in each of the conditions separately, the whole time-series of the fMRI task was used for the centrality analyses.

2.3. Preprocessing

All functional data were preprocessed using AFNI (Analysis of Functional Neuroimages; http://afni.nimh.nih.gov/afni/; Bethesda, MD) and the FMRIB Software Library (FSL) (www.fmrib.ox.ac.uk; Oxford, UK). Preprocessing was based on the fcon1000 scripts (available at: http://fcon_1000.projects.nitrc.org). Specifically, preprocessing steps included: (i) discarding the first six volumes from each subject; (ii) skull-striping of initial anatomical T1 scan; (iii) slice time correction; (iv) motion correction; (v) 6-mm full width at half-maximum (FWHM) spatial smoothing; (vi) mean-based intensity normalization of all volumes by the same factor; (vii) linear and quadratic detrending; (viii) segmentation of skull-stripped T1 images into white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF) masks; (ix) linear registration of WM and CSF signals to native functional space; (x) linear registration of the WM/CSF masks to Montreal Neurological Institute (MNI) space; (xi) masking WM/CSF masks with MNI binarized tissue prior maps; (xii) thresholding WM mask at a probability of 0.66 and CSF mask at a probability of 0.4; (xiii) band pass temporal filtering (0.005–0.1 Hz); (xiv) regression of the eight nuisance signals (WM, CSF and six motion parameters).

The output of these preprocessing steps was a 4D residual functional volume in native functional space, for each participant. The 4D native data were registered to the MNI152 template with 3-mm resolution using affine transformation.

2.4. Centrality measures

After preprocessing, we analyzed degree centrality and eigenvector centrality using the LIPSIA software package (Lohmann et al., 2001). Degree centrality attributes a greater value to a voxel if it has strong connections with many other voxels in the brain. Let A denote an n×n similarity matrix with non-negative values only, where entries aij contain a pairwise similarity measure between the time series in voxels i and j. The degree xi of a node i is defined as

$$x_i = \sum_j \quad a_{ij}$$

Eigenvector centrality, in contrast, identifies nodes that are connected to other nodes that are themselves central within the network (Lohmann et al., 2010). Nodes with this property are usually referred to as hubs (Rubinov and Sporns, 2010). As above, let A denote an n×n similarity matrix with non-negative values only. The eigenvector centrality xi of node i is defined as the i-th entry in the normalized eigenvector x belonging to the largest eigenvalue λ of similarity matrix A:

$$A\mathrm{x} = \lambda x or \mathrm{equivalen}, x = \frac{1}{\lambda} Ax, \mathrm{and} x_i = \mu \sum_{j=1}^{n} a_{ij}\, x_j$$

with proportionality factor μ = 1/λ.

Following the approach by Zuo et al., (2012), we restricted our functional connectivity analysis to GM only, using a mask that contained all n voxels with GM tissue probability of 20% or higher. This GM template was released as part of tissue priors in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/sortware/spm8).

Degree centrality requires a thresholded similarity matrix. We used a Pearson's correlation coefficient thresholded at r≥0.5. In general, Pearson's correlation might include spurious relations in the similarity matrix, an effect that might be enhanced in the current analysis given the relatively large number of GM voxels in the brain. To alleviate this problem, we chose this relatively high correlation threshold. In the case of eigenvector centrality, we did not threshold the n×n similarity matrix as this is not required by the method (Fig. 1). Before the statistical analysis, we transformed the individual centrality maps to ensure Gaussianity.

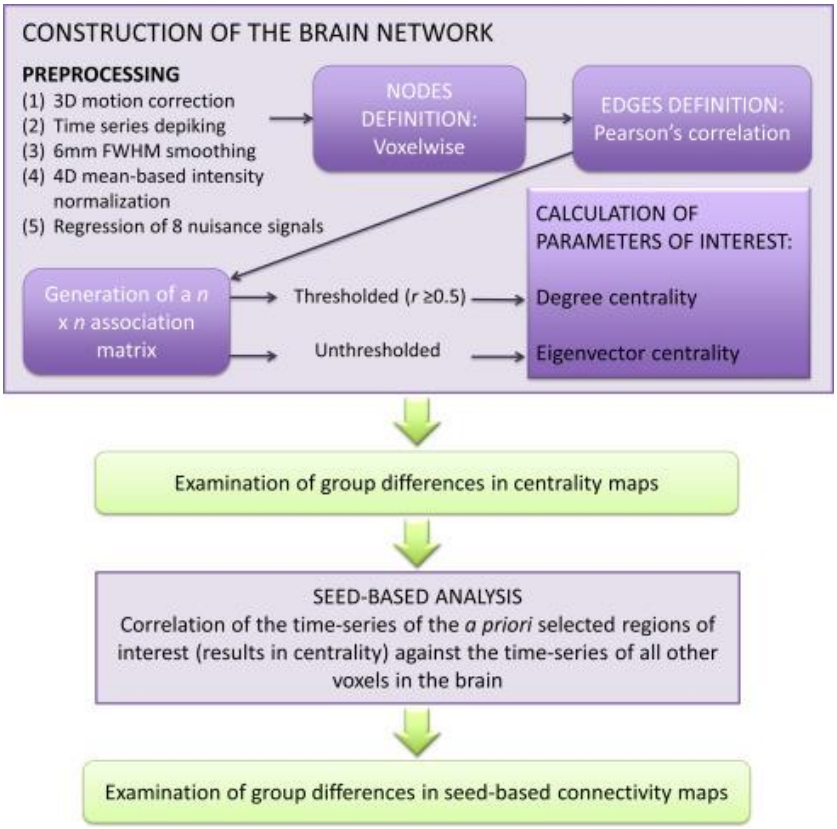

Figure. 1. Schematic illustration of the analyses. We examined differences between participants with obesity and normal-weight individuals in functional centrality. In those areas showing group differences in centrality, we additionally conducted group comparisons using seed-based analyses.

2.5. Seed-based connectivity analyses

To examine in more detail the connectivity patterns of the identified centrality changes, centrality analyses were complemented by seed-based analyses, choosing as regions of interest areas showing group differences in centrality measures. Seeds were constructed by drawing a 6-mm radius sphere around the center voxels of these regions, and the time series for each seed was extracted from the preprocessed data. Time series were averaged across all voxels in each seed's sphere. For each individual dataset, the correlation between the time series of the seed and every other voxel in the brain was determined. This analysis was implemented using 3dfim+ (AFNI) to produce for each subject individual correlational maps of all voxels that were positively or negatively correlated with the seed's time series. Finally, individual correlation maps were converted to Z-value maps using Fisher's r-to-z transformation.

Since we thresholded the n×n association matrix in degree centrality at r≥0.5, seed-analyses derived from results in degree centrality were only reported if the average functional correlation between regions was r≥0.5 as well.

2.6. Statistical comparisons

We conducted all the following analyses using SPM8.

First, we assessed general differences in functional centrality between resting-state and task conditions. To do so, we conducted a voxel-wise paired t-test comparing the two fMRI acquisitions across all participants.

Second, we compared obese and normal-weight subjects with the individual eigenvector and degree centrality maps for the fMRI resting-state and task conditions separately.

Third, for the seed-based analysis, we compared the individual correlational maps between groups (Fig. 1).

In all analyses, we entered as covariates sex and the subjective degree of hunger. Groups differed on subjective degree of hunger, so we controlled for the possible effect of this variable. Additionally, we decided to covay by sex given that previous studies have shown a sex effect in centrality measures (e.g., Zuo et al., 2012).

We considered as significant results at $p<0.001$ uncorrected that additionally met a FDR correction at a cluster level $p<0.05$ (thresholds obtained with SPM8).

3. Results

3.1. Demographic data

Participants with obesity and normal-weight controls were comparable in age, sex distribution, years of education, vocabulary scalar score from the Wechsler Adult Intelligence Scale-III, anxiety, depression and toxic habits. They differed significantly in BMI and on the symptom scale of the BITE test, a measure of compulsive eating behavior. Despite reporting being in a similar fasting condition, participants with obesity reported diminished subjective degree of hunger relative to normal-weight individuals (Table 1). Supplementary material presents a further characterization of the participants including menstrual cycle phase and time of day at which the scan was conducted.

Table 1. Demographic data.

	Participants with obesity (n=20)	**Normal-weight participants (n=21)**	**t/X²**	**p**
Body Mass Index	35.90±5.83 (30.10–49.69)	22.33±1.87 (19.53–24.97)	10.143	<0.001*
Age	33.55±5.61 (20–39)	31.33±5.96 (21–40)	1.225	0.228
Sex (female/male)	14f/6m	12f/9m	0.730	0.393
Education (years)	13.00±2.79 (10–20)	14.38±2.42 (10–18)	−1.696	0.098
Vocabulary (scalar scores from WAIS-III)	11.45±2.26 (8–16)	11.71±1.49 (9–15)	−0.444	0.659
Anxiety (HADS)	3.90±2.53 (1–10)	4.52±3.36 (0–10)	−0.669	0.507
Depression (HADS)	1.20±1.40 (0–5)	.91±1.38 (0–5)	0.681	0.500
BITE symptom scale	8.54±4.54 (1–18)	2.57±2.29 (0–8)	5.588	<0.001*
Subjective degree of hunger	2.71±2.21 (0–7.30)	4.93±2.46 (0.10-8.40)	−3.028	0.004*
Hours fasting	4.30±2.19 (3–13)	4.44±2.63 (3–12)	−0.189	0.851
Use of tobacco (smokers/non-smokers)	8/12	4/17	2.172	0.141
Intake of alcohol (drink alcohol/do not drink alcohol)	7/13	12/9	2.020	0.155

Note: Quantitative data are reported as mean±standard deviation (range).

*p<0.05

3.2. Differences between the fMRI resting-state and task conditions

We tested for possible differences in functional centrality between the fMRI resting-state and task conditions for all subjects. For degree centrality, the contrast resting-state fMRI>task fMRI showed higher degree centrality in the precuneus, posterior cingulate cortex and medial frontal

pole. The opposite contrast (task fMRI>resting-state fMRI) revealed an increased degree centrality in the occipital pole, lateral occipital cortex and fusiform cortex.

For eigenvector centrality, the contrast resting-state fMRI>task fMRI showed increased eigenvector centrality in the precuneus, angular gyrus, precentral and postcentral cortices, cuneus, posterior cingulate, middle temporal gyrus and right lateral occipital cortex. The contrast task fMRI>resting-state fMRI yielded increased eigenvector centrality in the right lateral occipital cortex, right lateral frontal pole and cerebellum (Supplementary Table S3 presents the coordinates of these analyses).

Additionally, we examined which brain areas exhibited the highest degree and eigenvector centrality for each acquisition. The results are presented in the Supplementary material (Table S4).

3.3. Centrality measures during the resting-state acquisition

Relative to controls, participants with obesity exhibited lower degree centrality in the right middle frontal gyrus during the resting-state condition (Fig. 2a; Table 2).

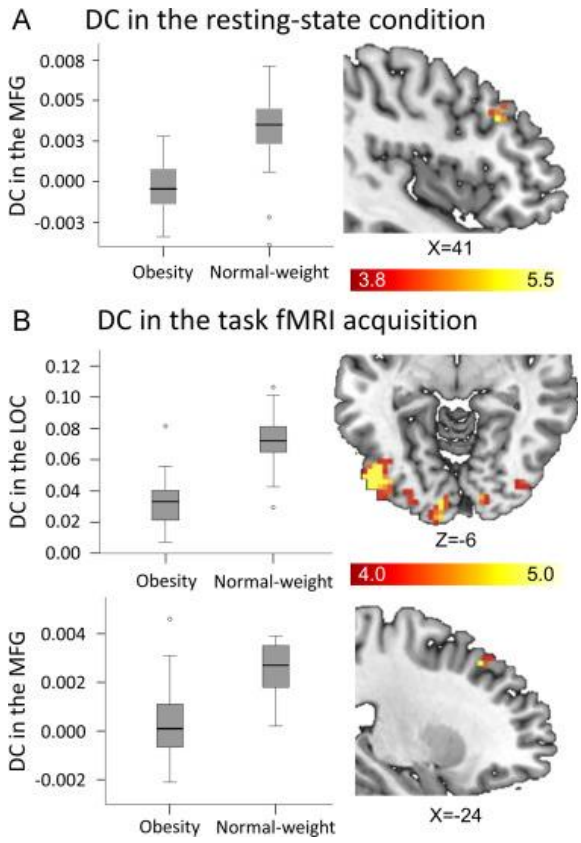

Figure 2. Group differences in degree centrality. During the resting-state condition, participants with obesity exhibited lower degree centrality (DC) in the right middle frontal gyrus (MFG). During the task condition, participants with obesity exhibited lower degree centrality in the lateral occipital cortex (LOC) and left middle frontal gyrus (MFG). We considered as significant results at $p<0.001$ uncorrected that additionally met a FDR correction at a cluster level $p<0.05$.

Table 2. Reduced centrality in participants with obesity compared with normal-weight controls, controlling for sex and subjective degree of hunger.

Brain region	**Cluster size (voxels)**	**MINI coordinates X**	**MINI coordinates Y**	**MINI coordinates Z**	**MINI coordinates Z**	**ClusterP (FDR-corr)**
Resting state acquisition						
Degree centrality:						
Right middle frontal gyrus	23	42	27	33	5.12	0.040
Eigenvector centrality:						
No significant results.						
fMRI task acquisition						
Degree centrality:						
Left lateral occipital cortex, cuneus	1649	−48	−81	−6	5.76	<0.001
Left middle frontal gyrus	25	−24	27	48	4.68	0.027
Left lateral occipital cortex, cuneus	1649	−48	−81	−6	5.76	<0.001
Eigenvector centrality:						
Lateral occipital cortex	15	−27	−87	39	4.38	0.010
Occipital pole	37	−3	−90	18	4.23	<0.001

Note: we considered as significant results at $p<0.001$ uncorrected that additionally met a FDR correction at a cluster level $p<0.05$.

No differences were observed in eigenvector centrality. Thus, subsequent seed-based analyses were run on the basis of the results in degree centrality only.

3.4. Centrality measures in the fMRI task acquisition

In the fMRI task acquisition, obese compared with lean participants exhibited lower degree centrality in the left lateral occipital gyrus and in the left middle frontal gyrus (Fig. 2b). In addition, participants with obesity showed smaller eigenvector centrality values in the lateral occipital cortex and in the left occipital pole (Table 2 and Fig. 3a).

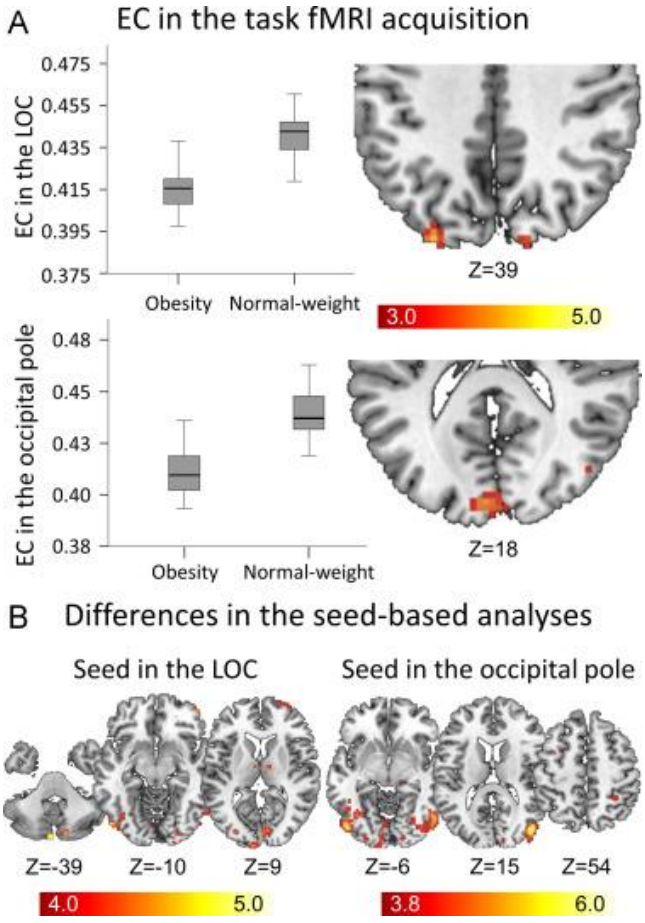

Fig. 3. Group differences in eigenvector centrality in the task acquisition. During the fMRI task condition, participants with obesity exhibited diminished eigenvector centrality in the occipital pole and lateral occipital cortex (LOC). We further examined connectivity differences on these areas using seed-based analysis. Participants with obesity exhibited lower connectivity between the occipital pole and the cerebellum, frontal lobe and thalamus. They also exhibited lower connectivity between the LOC and the superior parietal cortex as well as between clusters inside the LOC. We considered as significant results at $p<0.001$ uncorrected that additionally met an FDR correction at a cluster level $p<0.05$.

3.5. Seed-based connectivity analyses

3.5.1. Seeds from degree centrality

We did not find significant group differences with a mean correlation value $r \geq 0.5$.

3.5.2. Seeds from eigenvector centrality

Participants with obesity exhibited diminished connectivity between the seed located in the lateral occipital cortex and the cerebellum, frontal pole and thalamus. They also exhibited lower connectivity between the occipital pole and the lateral occipital cortex, and right superior parietal lobe (Fig. 3b; Supplementary Table S5).

4. Discussion

In the present study, we compared obese participants with normal-weight individuals on measures of whole-brain degree centrality and eigenvector centrality. We conducted the analyses separately on fMRI resting-state data and fMRI task data acquired in the same subjects. Our results suggest that, relative to normal-weight subjects, obese participants show a diminished functional connectivity of the middle frontal gyrus and the lateral occipital cortex with the entire brain network.

In recent years, previous studies have used ICA-based analysis to examine functional connectivity in participants with obesity. Specifically, these studies have found differences between participants with obesity and normal-weight controls in the functional connectivity of several segregated functional networks, including the salience network (Garcia-Garcia et al., 2013a and Kullmann et al., 2013), default mode network (Kullmann et al., 2012; Tregellas et al., 2011) and visual networks (Garcia-Garcia et al., 2013b and Kullmann et al., 2013). Findings in ICA can be associated with the principle of segregation (or modularity) in functional connectivity, a principle that refers to the organization of the brain into a set of components (or independent functional networks) whose constituent regions exhibit dense interconnections (Sporns, 2013). In contrast, results in functional centrality, as applied in the current study, can be related to the principles of functional integration and influence. The principle of integration addresses how the network as a whole becomes interconnected and describes the ability to rapidly combine specialized information from distributed brain regions (Rubinov and Sporns, 2010 and Sporns, 2013). The principle of influence refers to the importance of a given network node in this process (Sporns, 2013). Therefore, the current study extends the previous work on parcellated functional components by suggesting that obese individuals might have a reduced

functional integration, i.e., diminished information exchange, of the middle frontal gyrus and the lateral occipital cortex with the entire brain network.

The middle frontal gyrus is a key structure in selective attention, working memory, inhibitory control and monitoring (Fuster, 2002). It is located in the lateral prefrontal cortex and is heavily interconnected with motor, auditory and visual areas (Fuster, 2008 and Barbey and Patterson, 2011). Studies of intrinsic functional connectivity have shown an involvement of the middle frontal gyrus in several circuits encompassing a broad array of functional domains, including the fronto-parietal network, the premotor network and the supplementary motor network (Laird et al., 2011). Consistent with the involvement of impulse control in eating, studies in eating behavior have found an increased activity of the middle frontal gyrus in conditions that require an enhancement of attention control processes, such as during increased mental effort in order to restrict food intake, as previously shown for healthy and lean participants (Hare et al., 2009 and Hollmann et al., 2011). Given the complexity of whole-brain networks, results of functional connectivity analyses often remain difficult to interpret. If one assumes behavioral relevance of altered functional architecture, the obesity-related decreases in degree centrality in the middle frontal gyrus might point at obesity-related deficiencies in inhibitory control. However, this hypothesis needs to be further addressed with specific fMR-suitable tasks that directly target inhibitory control processes, such as Stop Signal or Go/No-go tasks. We further analyzed the functional connectivity of the middle frontal gyrus with the rest of the brain by means of seed-based analyses. However, we did not observe group differences in this analysis. The lack of group differences might indicate that the lower degree centrality of the middle frontal gyrus is related to a lower total sum of connections rather than fewer strong connections to very localized areas. We observed obesity-related differences in the middle frontal gyrus both during the resting-state condition and during the task paradigm. This indicates the robustness of the finding and suggests the interesting possibility that alterations of the neural integration of the middle frontal gyrus may reflect a trait feature of obesity instead of constituting a state-dependent result.

The occipital cortex is organized hierarchically and is highly connected with many other cortical and subcortical areas, such as the middle temporal lobe, the parietal cortex, the thalamus and also lateral prefrontal areas, via long-range projections (Haxby et al., 1994). Visual areas respond robustly to visual food cues compared with neutral stimuli (e.g., Kroemer et al., 2013a; Huerta et al., 2014). Additionally, hunger seems to have a powerful impact in primary sensory areas. Studies presenting visual food stimuli have observed an increased activity in the occipital cortex associated with a state of food deprivation (LaBar et al., 2001 and Stockburger et al., 2009) and with high levels of the orexigenic peptide ghrelin (Malik et al., 2008 and Kroemer et al., 2013b). As such, it has been proposed that hunger signals may facilitate perceptual processes and selective attention towards food stimuli (LaBar et al., 2001 and Stockburger et al., 2009). In the

field of obesity, studies have reported obesity-related blunted activation in these areas in response to food stimuli (Nummenmaa et al., 2012). As such, it is possible that the diminished functional centrality in occipital areas may also underlie a reduced brain activity in these areas during the visualization of food stimuli in obesity.

In our study, group differences in centrality in occipital areas were only statistically significant during the fMRI task condition. It is well known that resting-state functional connectivity is closely associated with task-related neuronal responses (Cole et al., 2014 and Smith et al., 2009). Nevertheless, brain connectivity shows dynamic variations in regions with a key role in task processing (Buckner et al., 2009). Accordingly, Buckner et al. (2009) compared high centrality brain regions between a task-free condition and a semantic categorization task. While the overall topography of such regions was similar between task-free and task-based conditions, regions in the prefrontal and temporal cortex showed an increased degree centrality in the semantic categorization task. In a similar vein, we observed that, across all subjects, the fMRI task condition was associated with higher functional centrality in visual areas relative to the resting-state condition. This fact might have increased the sensitivity of the fMRI task for detecting significant group differences in occipital areas. Conversely, relative to the task condition, the resting-state condition was associated with higher functional centrality in areas ascribed to be part of the default mode network, including mid-line cortical areas, such as the precuneus, posterior cingulate or medial frontal pole (e.g., Greicius et al., 2003).

Functional connectivity differences in prefrontal and occipital areas have been previously observed in studies on eating disorders. Patients with a current or past diagnosis of anorexia nervosa exhibited lower degree centrality in the inferior frontal gyrus (Kullmann et al., 2014b), lower connectivity within visual networks (Favaro et al., 2012), and higher connectivity of the inferior frontal gyrus and precuneus within the default mode network (Cowdrey et al., 2012). Patients with bulimia nervosa presented lower functional connectivity between the paracentral lobule and the occipital cortex (Lavagnino et al., 2014). These alterations in the functional connectivity of prefrontal, parietal and occipital areas were interpreted as suggestive of possible alterations in inhibitory control behavior (e.g. Cowdrey et al., 2012; Kullmann et al., 2014b), ruminative behavior (Cowdrey et al., 2012), visuospatial difficulties (Favaro et al., 2012) and dysfunction in body-image processing (Lavagnino et al., 2014). The results in eating disorders and the current results in obesity may suggest that alterations in the functional connectivity of prefrontal and occipital areas could be associated with abnormal eating behavior. However, future studies addressing individual differences in the continuum between normal and abnormal eating behavior are needed to confirm this conclusion.

Our study presents several limitations that need to be acknowledged. (i) Eigenvector centrality and degree centrality are based on an n×n similarity matrix representing pairwise correlations. Such a matrix might contain spurious correlations. Specifically, despite a seemingly high correlation between them, two regions a and b might not be directly connected if the covariance between them can be explained by a third region c (Varoquaux and Craddock, 2013). (ii) Sample sizes were relatively small, albeit comparable to those in other studies on obesity. Nonetheless, this fact may have limited the statistical power of the analyses, and it hampered the analysis of potentially interesting interactions between gender and obesity. (iii) The fMRI task consisted of four different rewarding conditions. Given the short duration of the task, however, it was not feasible to examine functional centrality separately for each of the conditions. Future studies should address this issue. (iv) Participants with obesity scored lower in subjective degree of hunger, which could reflect the behavior of eating in the absence of hunger. To alleviate the influence of this group difference, the factor was included as a covariate in the analyses. (v) Finally, we ensured that both acquisitions (resting-state and task conditions) were long enough to permit functional centrality analyses. Nevertheless, the total duration of the resting-state and the task fMRI acquisition were different, which may have introduced subtle changes in the functional connectivity dynamical fluctuation.

In sum, here we compared whole-brain functional connectivity between obese and normal-weight subjects through the use of graph-theoretic network centrality measures. Our results suggest that participants with obesity might exhibit state-independent diminished functional integration of the middle frontal gyrus with the entire network, as well as task-dependent reduced centrality of the lateral occipital cortex.

Contributors

Study concept and design: IGG, MAJ, MG, AH, AV, CJ, DSM, JN.

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Drafting of the manuscript: IGG; JN.

Critical revision of the manuscript for important intellectual content: All the authors.

Conflict of interest

None reported.

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