Alterations of the Salience Network in Obesity: A Resting-State fMRI Study

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Abstract: Obesity is a major health problem in modern societies. It has been related to abnormal functional organization of brain networks believed to process homeostatic (internal) and/or salience (external) information. This study used resting-state functional magnetic resonance imaging analysis to delineate possible functional changes in brain networks related to obesity. A group of 18 healthy adult participants with obesity were compared with a group of 16 lean participants while performing a resting-state task, with the data being evaluated by independent component analysis. Participants also completed a neuropsychological assessment. Results showed that the functional connectivity strength of the putamen nucleus in the salience network was increased in the obese group. We speculate that this abnormal activation may contribute to overeating through an imbalance between autonomic processing and reward processing of food stimuli. A correlation was also observed in obesity between activation of the putamen nucleus in the salience network and mental slowness, which is consistent with the notion that basal ganglia circuits modulate rapid processing of information. *Hum Brain Mapp* 34:2786–2797, 2013. © 2012 Wiley Periodicals, Inc.

Key words: obesity; resting state; salience; putamen; fMRI; reward

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INTRODUCTION

Obesity is a major health problem in modern societies [World Health Organization, 2011]. Its heterogeneity and complexity are unlikely to be explained by the functional breakdown of a single cerebral region [Hammond, 2009]. Rather, obesity is considered to be associated with abnormal functional organization of brain networks that are believed to process homeostatic (internal) and/or salience (external) information (for reviews, see Grill et al., 2007; Kenny, 2011; Volkow et al., 2011).

Previous neuroimaging studies using single-photon emission tomography have shown differences in regional

cerebral blood flow during the resting condition in obese persons when compared with lean individuals. Specifically, an elevated body mass index (BMI) was found to be associated with decreased regional blood flow in the prefrontal cortex in healthy participants [Willeumier et al., 2011].

Studies using functional magnetic resonance imaging (fMRI) have highlighted differences in the processing of food stimuli between obese and lean participants. Obese individuals show increased activation in response to visual food stimuli in the orbitofrontal cortex, insula, anterior cingulate cortex, striatum, amygdala, and thalamus [Holsen et al., in press; Martin et al., 2009; Rothenmund et al., 2007; Stice et al., 2010a; Stoeckel et al., 2008, 2009]; these cerebral structures belong to the reward system [Haber and Knutson, 2010] and also to a network formed by the insula and the anterior cingulate cortex, that is, the salience network [Seeley et al., 2007]. Accordingly, participants with obesity show greater insular activation in response to the anticipated intake of a chocolate milkshake [Stice et al., 2008a]. However, obese participants show lower activation in the caudate nucleus in response to the consumption of food than their lean counterparts [Stice et al., 2008a]. Furthermore, striatal (caudate and putamen) activity in response to food intake is negatively correlated with BMI [Stice et al., 2008b].

There is also evidence of altered functional network dynamics in response to food cues in individuals with obesity. One recent study [Tregellas et al., 2011] found that while viewing food cues, obese participants following a weight-loss program had abnormal connectivity of the default mode network (DMN) in comparison with lean participants. Specifically, greater default network activity was observed in the lateral inferior parietal and posterior cingulate cortices.

The investigation of spontaneous fluctuations in the brain system using resting-state networks (RSNs) offers a way of exploring functional connectivity between brain areas [Biswal et al., 2010; Fox and Raichle, 2007]. In this context, it has been suggested that functional connectivity describes the relationship between the neuronal activation patterns of anatomically separated (although functionally related) brain regions. In other words, connectivity in RSN reflects the level of functional communication between regions [van den Heuvel and Hulshoff Pol, 2010].

To our knowledge, only one study has examined differences in the intrinsic connectivity of RSN between obese and lean participants [Kullmann et al., 2012]. The authors reported altered connectivity strength in participants with excess weight (obese and overweight) when compared with lean participants after an overnight (more than 10 h) fasting condition. Specifically, they found differences in two RSNs: the DMN and the temporal lobe network. In the DMN, obese subjects showed increased functional connectivity strength in the posterior cingulate cortex/precuneus bilaterally and decreased strength in

the right anterior cingulate region. Furthermore, in the temporal lobe network, obese subjects showed decreased functional connectivity strength in the left insular cortex.

The eucaloric condition captures the hunger state that most individuals experience as they approach their next meal, which is a time when individual differences in food reward would impact caloric intake [Yokum et al., 2011]. Given that obesity has been related to differences in the processing of reward, it would be of interest to determine whether differences in brain activity between obese and lean participants arise in this condition.

Differences in brain activity in obesity may also be related to differences in cognitive performance, and several lines of evidence suggest that obesity is associated with lower cognitive function. For example, neuropsychological studies have found that obese individuals perform worse on executive function tasks [Gunstad et al., 2010; Mobbs et al., 2011; Verdejo-García et al., 2010]. Some studies have also reported a relationship between a high BMI and poorer results in memory and learning performance [Elias et al., 2003; Nilsson and Nilsson, 2009] and in the speed of cognitive/mental processing [Cournot et al., 2006; Waldstein and Katzel, 2006]. Although it has been established that deficits in executive function may be detectable at earlier ages [Verdejo-García et al., 2010], little is known about the effects of obesity on memory and learning and speed of processing in young adults.

Deficits in cognitive function are accompanied by abnormalities in gray matter volume in participants with obesity. Walther et al. [2009] found that when compared with lean participants, obese women at advanced ages (around 67 years) performed worse on executive function and had smaller gray matter volume in several brain areas such as the orbitofrontal cortex and the inferior frontal gyrus. Additionally, gray matter volume predicted performance in executive function, memory, and visuomotor speed. Thus, although a relationship has been established between cognitive performance and structural differences in the obese brain, the relationship between resting-state connectivity in obesity and cognitive function has yet to be examined.

The current study had two main goals. (1) To investigate the possible alterations of cerebral connectivity in the RSN of participants with obesity in comparison with lean participants using independent component analysis (ICA). Based on neuroimaging studies described above, we will focus on the salience network and the DMN. The salience network includes limbic and paralimbic areas and is associated with the processing of homeostatic and salience information. The DMN includes areas associated with self-monitoring behavior. (2) To examine whether abnormal RSN activity may be related to cognitive performance in young adults with obesity.

MATERIALS AND METHODS

Participants

Thirty-four participants (participants with obesity = 18; normal-weight participants = 16) aged 16–40 years (64.71% women) were included in the study. They were recruited from public medical centers belonging to the *Consorci Sanitari de Terrassa*. The study was approved by the institutional ethics committee and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each participant or their legal tutors prior to taking part in the study.

The current analysis was conducted as part of a cross-sectional study whose objective was to determine neuropsychological and neuroimaging patterns associated with obesity. Potential participants were first contacted by telephone and invited to take part in the study. If they agreed to participate they then underwent a screening interview and blood analysis. Individuals were excluded from the study if they had a history of any neurological or psychiatric disorder, a history of any disorder that could be related to obesity, if they presented with diabetes, hypertension, hyperglycemia, high levels of triglycerides or cholesterol, and if they showed global cognitive impairment [estimated IQ below 85, assessed with the Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III)]. The presence of anxiety, depression, or binge-eating disorder was also an exclusion criterion, and these were evaluated with the Hospital Anxiety and Depression Scale (HADS) and the Bulimia Inventory Test of Edinburgh (BITE), respectively. A cutoff score of 11 was applied to each scale of the HADS [Herrero et al., 2003], whereas a cut-off of 20 was used in the BITE [Henderson and Freeman, 1987].

Finally, participants were included in the obesity group if their BMI was equal to or higher than 30, and in the lean group, if their BMI was less than 25. They then underwent a comprehensive neuropsychological assessment by two trained neuropsychologists (I.M.I. and I.G.G.).

Participants were invited to take part in the MRI session. None of them had contraindications for MRI (claustrophobia or metallic objects in the body). Similar to other studies in the field of obesity [Yokum et al., 2011] and for standardization purposes, participants were asked to consume a typical breakfast or lunch, but to refrain from eating or drinking (except water) for 3–5 hours immediately before their scan. Prior to the scan, participants rated their subjective degree of hunger on a 10-cm visual analog scale. They also described their last meal before the scan session. We determined the mean calorie intake prior to scanning using an Internet-based database (<http://www.bedca.net>). For female participants, we also calculated the phase of the menstrual cycle. For the resting-state scan, which lasted about 8 min, participants were told to keep still with their eyes closed, not to think of anything in particu-

lar, and not to fall asleep. Directly after the scan, they were asked whether they had fallen asleep, and none of them reported that they had. Scans were performed between 9:00 a.m. and 8:30 p.m.

Data Acquisition

Data were acquired on a 3-T TIM TRIO 3-T scanner (Siemens, Germany), using a multislice gradient-echo echo planar imaging (EPI) sequence [repetition time (TR) = 2,000 ms; echo time (TE) = 19 ms; flip angle = 90°; 40 axial slices; FOV = 220 mm × 220 mm axial slices providing whole brain coverage].

A T_1 -weighted structural image was also acquired for each subject with the MPRAGE 3D protocol (TR: 2,300 ms; TE: 2.98 ms; inversion time: 900 ms; FOV: 256 mm × 256 mm, 1-mm isotropic voxel).

Data Preprocessing: ICA

A probabilistic ICA [Beckmann and Smith, 2004] was implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) Version 3.10, part of FSL (FMRIB Software Library; www.fmrib.ox.ac.uk/fsl).

The following preprocessing was applied to the input data: removal of the first six volumes; motion correction using FLIRT [Jenkinson et al., 2002]; removal of nonbrain structures from the EPI volumes using BET [Smith, 2002]; spatial smoothing using a Gaussian kernel of FWHM 5.0 mm; high-pass temporal filtering (160 s) and low-pass temporal filtering (5.6 s); masking of nonbrain voxels; voxelwise demeaning of the data; and normalization of the voxelwise variance.

Preprocessed data were whitened and projected into a 11-dimensional subspace using probabilistic principal component analysis, where the number of dimensions was estimated using the Laplace approximation to the Bayesian evidence of the model order [Beckmann and Smith, 2004; Minka, 2000].

Two criteria were used to eliminate biologically irrelevant components: (i) those representing known artifacts, such as motion, high-frequency noise, or venous pulsation [Beckmann et al., 2005; De Luca et al., 2006]; and (ii) those with connectivity patterns not located mainly in gray matter or which included no coherent clusters of voxels [De Martino et al., 2007]. Finally, components of interest were compared against a freely available set of common RSN [Biswal et al., 2010] by using the spatial cross correlation. Six of the 11 components were identified as anatomically and functionally relevant resting-state networks.

Anatomical labeling of activations was checked with reference to the Harvard-Oxford cortical and subcortical structural atlases (<http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html>) implemented in the FSL. We

TABLE I. Demographic and clinical characteristics of the sample

	Participants with obesity (<i>n</i> = 18)	Lean participants (<i>n</i> = 16)
Age (years)	33.89 ± 6.69 (16–39)	31.44 ± 5.97 (19–40)
Gender (women/men)	13/5	9/7
Vocabulary (scalar score)	11.20 ± 2.33 (8–16)	12.12 ± 1.50 (9–15)
Body mass index*	36.45 ± 6.26 (30.25–49.69)	21.92 ± 2.34 (17.16–24.97)
Hours fasting	3.90 ± 0.78 (3–5)	3.70 ± 0.74 (3–5)
Caloric content (kcal) of the last meal	369.33 ± 238.40 (63–948)	400.81 ± 248.31 (35–780)
Hunger perceived (0–10)*	2.48 ± 2.34 (0–7.30)	4.86 ± 2.47 (0.4–8.40)

Note: Except for sex, all values are mean ± SD (range).

**P* ≤ 0.01.

overlaid activations onto the mean standardized structural *T*₁ 4-mm MNI template.

Statistical Analyses (Dual Regression)

Subject-specific statistical maps were created to test for differences between lean and obese participants in the identified RSN using a dual regression procedure (previously described in Filippini et al., 2009). This involves (i) using the full set of group-ICA spatial maps in a linear model fit (spatial regression) against the separate fMRI dataset to estimate subject-specific spatial maps, and (ii) using these time-course matrices in a linear model fit (temporal regression) against the associated fMRI dataset to estimate subject-specific spatial maps. Finally, the different component maps are collected across subjects into single 4D files and tested voxelwise for statistically significant differences between groups using nonparametric permutation testing (5,000 permutations) [Nichols and Holmes, 2002]. This results in spatial maps that characterize the between-subject/group differences. For each RSN, the resulting statistical maps were thresholded at $P \leq 0.05$ (threshold-free cluster enhancement-corrected for family-wise errors) for the main group effects. Finally, the effect size was calculated using Cohen's *d* as an effect size measure. Cohen [1988, 1992] interpreted this statistic as follows: $r = 0.10$, small effect; $r = 0.30$, medium effect; and $r = 0.50$, large effect.

Analysis of Neuropsychological Variables

Three indexes of cognitive domains were created using the following tasks:

- Verbal memory and learning: total learning, delayed memory loss (free immediate recall minus free delayed recall), and false positive errors from the California Verbal Learning Test, 2nd edition [Delis et al., 2000].
- Speed of processing: scores for the dominant and non-dominant hand on the Grooved Pegboard [Klve, 1963]; oral and written scores on the Symbol-Digit Modalities Test [Smith, 2005].

- Executive functions: perseverative errors from the Wisconsin Card Sorting Test [Kongs et al., 2000]; Trail Making Test B-A score [Reitan, 1958]; and interference score from the Stroop test [Golden, 1995].

All raw data were transformed into *z* scores and then grouped to form the three cognitive domains. We performed group comparisons controlling for Vocabulary scores of the WAIS-III, as this measure has widely being considered as an indicator of general cognitive function in healthy and instructed people [Lezak et al., 2004]. Correlations between RSN values and cognitive domains were examined separately in the obese and control groups using PASW® Statistics v.18.

RESULTS

Demographic and Clinical Characteristics of the Sample

There were no differences between the groups in age, gender, or estimated intelligence quotient (Table I). Time of food deprivation and caloric content of the last meal were also equivalent in the two groups. The frequency of women in the luteal and follicular phases ($P = 0.827$) and the frequency of participants that ate breakfast, mid-morning snack, or lunch before the scan ($P = 0.636$) were equivalent between groups. As expected, the two groups differed in BMI. We found differences in subjective degree of hunger: lean participants experienced more hunger than lean participants.

Additionally, we calculated the frequency of participants scanned before (09:00–13:00 h), during (13:01–16:00 h), and after (16:01–20:30) regular lunch time in Spain. Chi-squared test revealed that participants with obesity and lean participants did not differ in this variable ($P = 0.717$).

Independent Component Analysis

ICA revealed six robustly reproducible functional networks extracted from the resting state in both groups. Anatomical distribution was in line with previous studies

TABLE II. Results obtained from the independent component analysis

Networks	Explained variance (%)	Total variance (%)	MNI coordinates				Region
			Voxels	X	Y	Z	
Frontoparietal network	12.95	1.79	6,594	30	30	36	Middle frontal gyrus, frontal pole, inferior frontal gyrus, superior frontal gyrus, supramarginal gyrus, lateral occipital, angular gyrus, thalamus, and caudate and anterior cingulate cortex
			13	-22	22	-16	Orbitofrontal cortex
			13	-26	-46	-48	Cerebellum
Basal ganglia network	12.48	1.72	6,259	-2	-58	-36	Cerebellum, brainstem, parahippocampal gyrus, hippocampus, amygdala, temporal pole, pallidum, putamen, subcallosal cortex, caudate, insular cortex, frontal operculum, anterior cingulate cortex, posterior cingulate cortex, thalamus, precuneus, and occipital lobe
			19	-42	-54	44	Angular gyrus and superior parietal lobe
			10	42	30	4	Inferior frontal gyrus
Salience network	10.66	1.47	6,848	46	6	-4	Insular cortex, anterior cingulate cortex, temporal pole, central opercular cortex, precentral gyrus, postcentral gyrus, supramarginal gyrus, thalamus, globus pallidum, amygdala, orbitofrontal cortex, putamen, caudate, accumbens, paracingulate gyrus, and supplementary motor area
			22	2	-42	-44	Brainstem
			7,641	-46	-62	40	Lateral occipital cortex, posterior cingulate cortex, angular gyrus, supramarginal gyrus, precuneus, thalamus, amygdala, hippocampus, pallidum, putamen, caudate, accumbens, temporal pole, frontal pole, frontal operculum, orbitofrontal cortex, middle frontal gyrus, superior frontal gyrus, paracingulate gyrus, and anterior cingulate cortex
DMN	8.99	1.24	41	10	-50	-24	Brainstem
			38	18	-98	16	Occipital pole
			9,480	-26	-30	68	Postcentral gyrus, precentral gyrus, supplementary motor cortex, thalamus, caudate, putamen, middle frontal gyrus, superior frontal cortex, lateral occipital cortex, superior parietal lobule, precuneus, opercular cortex, globus pallidum, insula, and planum polare
Sensorimotor network	8.48	1.17	12	-22	-58	-36	Cerebellum
			11	-2	-26	-8	Brainstem
			6,054	-10	-94	28	Occipital pole, cuneus, lingual gyrus, precuneus, intracalcarine cortex, occipital fusiform gyrus, lateral occipital cortex, angular gyrus, planum temporale, frontal operculum, orbitofrontal cortex, middle temporal gyrus, supplementary motor cortex, precentral gyrus, and postcentral gyrus
Visual network	5.23	0.72	125	-6	10	-8	Accumbens
			25	46	2	-28	Middle temporal gyrus
			11	2	-10	-20	Brainstem

Note: Explained variance: variations captured by the ICA model. Total variance: intensity variations from various sources in the image time series.

Figure 1.

Results of resting fMRI analysis in the salience network ($P \leq 0.05$, corrected). MNI coordinates are provided with a 1 mm resolution.

[Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Laird et al., 2011] and significantly correlated with a set of previously defined maps [Biswal et al., 2010]. We labeled these networks as (1) frontoparietal network ($r = 0.23$); (2) basal ganglia network ($r = 0.27$); (3) salience network ($r = 0.43$); (4) DMN ($r = 0.26$); (5) sensorimotor network ($r = 0.47$); and (6) visual network ($r = 0.40$). Detailed information about the different brain areas involved in each network is given in Table II (see also Supporting Information Figs. S1 and S2).

Group Comparisons in RSN

When compared with lean participants, participants with obesity showed significantly ($P \leq 0.05$, corrected)

greater connectivity strength in the salience network, specifically in a cluster of voxels, whose local maxima and most of its voxels (54%) were located in the left putamen nucleus (Fig. 1). The effect size was large ($d = 1.538$). There were no differences in the other networks examined. As the small sample size may compromise the statistical power of the results, we applied a less restrictive statistical threshold ($P \leq 0.001$, uncorrected) to evaluate the presence of other subtle differences in the salience network. Differences were found in the amygdala, putamen, lateral occipital cortex, middle temporal gyrus, and superior parietal lobule (Table III).

We analyzed whether the differences obtained might be due to potential confounders. First, we extracted individual values of activation of the putamen nucleus within the

TABLE III. Cluster localizations for group differences (obese > lean) in the salience network

Region	MNI coordinates			Voxels	<i>T</i>	<i>P</i>	<i>d</i>
	X	Y	Z				
<i>P</i> ≤ 0.05, corrected							
L putamen	−26	−2	−8	35	4.476	0.0112	1.538
<i>P</i> ≤ 0.001, uncorrected							
L amygdala (extending to insula, pallidum and putamen)	−34	−2	−20	222	2.944	0.0002	—
R putamen	26	−10	16	164	2.021	0.0002	—
	30	−6	4	28	1.558	0.0002	—
R lateral occipital cortex	38	−86	4	75	2.446	0.0002	—
L middle temporal gyrus	−54	−54	−8	24	1.798	0.0002	—
L superior parietal lobule	−14	−50	60	21	2.790	0.0002	—
	−38	−46	44	21	3.090	0.0002	—

Figure 2.

Relationship between speed of processing and activation of the salience network at the putamen.

salience network. Using an analysis of variance, we tested whether or not activity in the putamen nucleus within the salience network was influenced by the following factors: gender, time of fasting, perceived hunger, and caloric content of the last meal. We also examined whether these factors modulated differences between the two groups of participants. None of them were associated with the results nor did they interact with the group of participants variable (not even marginally in either case, $P > 0.1$; Supporting Information Table SII).

Relationship Between Connectivity of the Salience Network (Putamen Nuclei) and Performance on Cognitive Domains

The performance of both groups was compared on the three cognitive indexes (verbal memory and learning, speed of processing, and executive functions), controlling for Vocabulary score of the WAIS-III. The groups performed similarly on these measures (Supporting Information Table SI). We then correlated the performance of both groups with individual activation of the significant cluster identified in the left putamen in the salience network. This revealed a negative correlation between speed of mental processing and individual putamen activation in the obese group ($r = -0.629$; $P = 0.005$; Fig. 2).

We included an analysis to determine which variables within the additive component “speed of processing” were independently associated with connectivity of the putamen nucleus in the salience network. The analysis revealed correlations between scores for the nondominant hand on the Grooved Pegboard Test ($r = -0.623$; $P = 0.006$) and written scores on the Symbol-Digit Modalities Test ($r =$

-0.523 ; $P = 0.026$) in participants with obesity. To facilitate the comprehension of results, sign of z scores of the Grooved Pegboard Test was changed: higher scores indicate higher speed of processing.

DISCUSSION

This study examined functional changes in brain networks related to obesity. We found that participants with obesity showed altered functional connectivity strength in the salience network, specifically in the putamen nucleus. Greater RSN connectivity in the putamen nucleus was also related to a slower speed of mental processing in obese subjects alone.

ICA revealed six components or RSN that have been well described in previous studies [Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006]. Moreover, these RSNs were well matched with a set of previously defined set maps [Biswal et al., 2010]. This likely indicates a reliable intrinsic RSN.

Functional Significance of Alterations in the Salience Network in Obesity

A number of studies examining intrinsic functional networks in humans have consistently reported a coactivation of the insula and the anterior cingulate cortex during resting-state conditions. This has led researchers to consider that the two structures form a network [Biswal et al., 2010; Damoiseaux et al., 2008; De Luca et al., 2006; Laird et al., 2011]. Seeley et al. [2007] were the first to refer to this component as the “salience network,” proposing that it enables the integration of highly processed sensory data with visceral, autonomic, and hedonic markers so that the organism can decide what to do (or not to do) next.

Research to date has demonstrated that people with obesity show abnormal activation in the core structures of the salience network in response to visual food stimuli, and this may underlie differences in the reward processing of food stimuli [Kenny, 2011; Volkow et al., 2011]. This increased regional activation also involves other brain structures often included within the salience network, such as the amygdala and striatum [Holsen et al., in press; Rothmund et al., 2007; Stoeckel et al., 2008]. Visual food cues may elicit a physiological response similar to the anticipation of food intake. However, as the last-mentioned studies did not include a food delivery condition during scanning, it is not clear whether these studies really capture reward anticipation indeed [Stice et al., 2009]. In this line, there is a study that specifically investigated the response to anticipated receipt of food in obese and lean participants [Stice et al., 2008a]. The authors found that participants with obesity showed greater activation of opercular, insular, and anterior cingulated regions, which agrees with the above studies examining visual response to food. Our findings extend previous work showing that

the intrinsic connectivity strength of the salience network is abnormally enhanced at baseline activation in the obese brain after a short period of fasting (3–5 h). Of note, differences examined at a less statistically strict threshold were located in neural areas such as the insula and amygdala that, together with the putamen, have been widely implicated in the processing of the relevance attribute of food [LaBar et al., 2001; Schur et al., 2009]. We speculate that abnormal activation of the salience network may contribute to overeating in obesity, through an imbalance between autonomic processing and reward processing of food.

Recently, Kullmann et al., 2012 observed that after an overnight fasting condition, the insular cortex showed altered functional connectivity strength in the temporal lobe network. One of the explanations put forward by the authors was that obese participants could be interpreting the state of food deprivation as more threatening than lean participants. The temporal lobe network, described by the authors, was identified as the RSN involving the insular cortex and the primary and secondary auditory cortex. Although the temporal lobe network and the salience network both contain the insular cortex, there is an important difference between the two networks that must be noted: the salience network in our study also contains the anterior cingulate cortex, amygdala, and basal ganglia, and thus it would seem to include more limbic and paralimbic structures. In addition, the study by Kullmann et al., 2012 also reported differences in the DMN. Specially, an increased recruitment of the posterior cingulate gyrus/pre-cuneus and decreased recruitment of the anterior cingulate cortex were found in participants with excess weight. However, these differences were not observed in the current study. The discrepancy in results between this study and ours could be ascribed to differences in participants' characteristics and study design. In contrast to the previous study, participants with excess weight in our study were all obese, that is, their BMI was higher than 30. Second, in the current study, participants were in a eucaloric condition. It is conceivable that this condition yields different results when compared with a long fasting condition, especially in the DMN which is a network associated with self-monitoring behavior.

The Putamen Nucleus and Its Role in Salience Detection

It is well established that the basal ganglia mediate a full range of goal-directed behaviors, including emotions, motivation, and cognition [Haber and Knutson, 2010; Seger, 2006]. Specifically, there is convergent evidence that the putamen nucleus is activated when presenting salient stimuli, such as food stimuli [Fellsted et al., 2010; Frank et al., 2008; Porbuská et al., 2006; Siep et al., 2009; Spetter et al., 2010], nociceptive stimuli [Starr et al., 2011], or monetary stimuli [Zald et al., 2004], in comparison with the

activation observed in a neutral or control stimulation. This evidence strongly indicates that the putamen nucleus has an important role in the processing of highly salient information. Furthermore, consistent with its role in motor behavior and motivation, it has been proposed that the putamen may be important in promoting approach responses toward food stimuli [Szczypka et al., 2001].

Task-activation studies have suggested that participants with obesity overactivate the putamen nucleus and other limbic and paralimbic regions while perceiving visual fattening stimuli [Rothmund et al., 2007; Stoeckel et al., 2008]. This has led to the conclusion that individuals with obesity experience hyper-responsivity in regions that encode the reward value of cues. Although it is generally assumed that the increased reward circuitry response may constitute a marker of vulnerability to overeating [Davis et al., 2004], it has recently been hypothesized that sustained overeating behavior may also be able to reduce activity in neural areas such as the striatum in response to reward delivery (gustative food stimuli) [Stice et al., 2011]. The reduction in the striatal response is thought to be produced by dopaminergic neuroadaptation mechanisms, well described in the field of drug addiction [Koob and Le Moal, 2008]. Several findings in the field of fMRI support this hypothesis. In this regard, decreased striatal activity has been associated with higher BMI when a gustative and highly caloric stimulus is administered [Stice et al., 2008a, 2008b]. Similarly, weaker striatal activity predicted future weight gain in response to the delivery [Stice et al., 2010a] or the imagined intake of food [Stice et al., 2010b]. Furthermore, high reward reactivity seems to be a risk factor for developing obesity. Investigating neural activation in a sample of adolescents at high risk for developing obesity (youths with two obese or overweight parents) and adolescents at low risk for obesity (participants with two lean parents), Stice et al. [2011] designed a paradigm for assessing the responses to monetary reward and gustative food stimuli; they found that participants at high risk for obesity showed higher reward responsivity than participants at low risk.

Altogether, the above food-related fMRI activation studies in obesity suggest that the putamen nucleus has a biphasic response to food stimuli, which has been related to differences in reward mechanisms, that is, it is overactivated when the stimulus is expected or viewed and inhibited when the stimulus is delivered.

Cue-induced brain activation is closely related to activity during the resting condition [Anticevic et al., 2010; Zhang et al., 2011]. Although task-activation studies and resting-state functional connectivity analysis measure different types of brain activity, there seem to be some parallels between the above studies and our findings. The difference in recruitment of the putamen nucleus within the salience network found that our report here may be related to a higher propensity toward exacerbating the reward response to visual and anticipated food stimuli. It would be interesting to examine the salience network in a

food-delivery paradigm and to determine whether the putamen nucleus has a role in this condition.

In summary, although previous research has found that the putamen nucleus is abnormally recruited in the obese brain in the presence of visual food stimuli, we now explicitly delineate the presence of abnormal intrinsic connectivity networks between the putamen nucleus and corticolimbic areas involved in salience detection. Our findings seem to provide additional support to the hypothesis that obesity may be related to a failure to deactivate limbic food reward regions when required to do so.

One study found the activation of the putamen to be positively correlated with the subjective rating of appetite [Porbuská et al., 2006]. The region reported by these authors was very close to the region that we identified in the current analysis. It might seem logical that the results of altered connectivity within the salience network may be caused by an increase in the feeling of hunger in the obesity group. However, examination of the degree of hunger showed differences in the opposite direction, that is, participants with obesity showed a "lower" subjective feeling of hunger than lean participants. This result is in agreement with several studies indicating that the excess of energy intake in obesity is at least partly explained by the behavior of eating in the absence of hunger (e.g., Hill et al., 2008; Tanofsky-Kraff et al., 2008). The degree of hunger was neither associated with connectivity in the putamen nucleus within the salience network nor did it interact with the group of participants in the resting state (Supporting Information Table SII). We therefore suggest that our fMRI result is independent of the physiological state of hunger; in fact, we speculate that it may reflect a trait feature of obesity. However, we acknowledge that to draw a firm conclusion on this issue, it would be necessary to examine the connectivity in the salience network under different conditions of fasting and satiation.

Altered Functional Connectivity of the Salience Network in the Putamen Nucleus Is Related to Mental Slowness in Obesity

We found that increased RSN connectivity of the salience network in the putamen nucleus was inversely related to the speed of mental processing in obese participants.

As part of the dorsal striatum, the putamen is involved in the initiation, production, and sequencing of motor behaviors [David et al., 2005], which is consistent with the traditional view of the basal ganglia as structures closely associated with movement [Nauta and Mehler, 1966]. Basal ganglia circuits are thought to be in a unique position to modulate rapid processing of information [Leyden and Kleinig, 2008]. Furthermore, gray matter atrophy at the putamen has been found to be related to mental slowness in patients with multiple sclerosis [Batista et al., 2012].

Here, we suggest that the gain in functional connectivity in the putamen in participants with obesity underlies a cost-efficiency processing of information. In this line, some findings seem to relate increases in functional connectivity with losses in cognitive efficiency. A recent study by Hawellek et al., 2011 has found that decreased cognitive ability in multiple sclerosis was associated with a gain in functional connectivity among core parts of the DMN as well as a control network, despite the presence of strong and diffuse reductions of the central white matter integrity. Another study reported that elevated cross-network connectivity associated with the presence of a dopaminergic polymorphism (10/10 homozygosity of the dopamine transporter gene) may lead to a loss in cognitive efficiency and inattention (Gordon et al., in press). These studies suggest that integrity of cognition seems to depend on optimal network functional connectivity. Therefore, a significant relationship between high RSN connectivity in the putamen nucleus within the salience network and slow processing of information in obesity corroborates these previous results.

By decomposing the additive index of speed of processing, we found that differences in fMRI connectivity were related to performance on nondominant hand of the Grooved Pegboard Test and written scores on the Symbol-Digit Modalities Test. In addition to the speed of processing, these tests are thought to involve motor execution and selective attention [Strauss et al., 2006]. Although we did not find differences between both groups in cognitive measures, participants with obesity are characterized by programming and executing movements slowly [Waldstein and Katzel, 2006]. We suggest that the abnormal recruitment of the putamen within the salience network may also be reflecting this cognitive feature considering the role of the putamen in the control of movement and the correlation of its activation with processing mental speed.

Methodological Issues

The current study does have a number of limitations that need to be acknowledged. Like most studies that use convenience sampling, our sample represents a highly functioning subgroup of the population. Furthermore, the sample size is small, although it is larger than that used in some studies of RSN. Participants were scanned at different hours and were required not to eat during a short fasting period. This requirement may have changed their normal schedule. The study also has some strengths, notably that participants were similar on variables that are likely to influence RSN results, such as estimated general intelligence, anxiety and depression scores, or phase of the menstrual cycle in female participants. Nonetheless, the above-mentioned limitations may limit the generalization of our results.

CONCLUSION

Overall, the study adds two novel findings to the growing body of research on obesity. First, we have documented abnormally increased resting-state functional connectivity strength in the salience network in healthy young adults with obesity. Specifically, differences were found in the putamen nucleus. We speculate that this aberrant activation pattern may be related to overeating, through an imbalance between the processing of homeostasis and salience detection. In addition, there was a negative correlation between the activation of the putamen nucleus in the salience network and the speed of mental processing in obesity, which is consistent with the notion that basal ganglia circuits modulate rapid processing of information.

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