Altered baseline brain activities before food intake in obese men: A resting state fMRI study

Bin Zhang\textsuperscript{a,b}, Derun Tian\textsuperscript{a,c}, Chunshui Yu\textsuperscript{c}, Jing Zhang\textsuperscript{c}, Xiao Tian\textsuperscript{a}, Karen M. von Deneen\textsuperscript{d,e,f}, Yufeng Zang\textsuperscript{f}, Martin Walter\textsuperscript{b}, Yijun Liu\textsuperscript{c,g}

\textsuperscript{a} Department of Anatomy, Tianjin Medical University, Tianjin, China
\textsuperscript{b} Clinical Affective Neuroimaging Laboratory, Department of Psychiatry, Otto von Guericke University, Magdeburg, Germany
\textsuperscript{c} Department of Radiology, Tianjin Medical University General Hospital, Tianjin, China
\textsuperscript{d} School of Life Sciences and Technology, Xidian University, Xi'an, China
\textsuperscript{e} Department of Psychiatry, McKnight Brain Institute, University of Florida, Gainesville, FL, USA
\textsuperscript{f} Center for Cognition and Brain Disorders, The Affiliated Hospital at Hangzhou Normal University, Hangzhou, China
\textsuperscript{g} College of Engineering, Department of Biomedical Engineering, Peking University, Beijing, China

HIGHLIGHTS

• Regional homogeneity (ReHo) is a useful tool in investigating the mechanisms of obesity.
• Frontal cortex signaling disordered during fasting in obesity.
• There is hypo-functioning reward circuitry during the hunger state in obese individuals.

ABSTRACT

Obesity as a chronic disease has become a global epidemic. However, why obese individuals eat more still remains unclear. Recent functional neuroimaging studies have found abnormal brain activations in obese people. In the present study, we used resting state functional MRI to observe spontaneous blood-oxygen-level dependent (BOLD) signal fluctuations during both hunger and satiety states in 20 lean and 20 obese men. Using a regional homogeneity (ReHo) analysis method, we measured temporal homogeneity of the regional BOLD signals. We found that, before food intake, obese men had significantly increased synchronicity of activity in the left putamen relative to lean men. Decreased synchronicity of activity was found in the orbitofrontal cortex (OFC) and medial prefrontal cortex (MPFC) in the obese subjects. And, the ratings of hunger of the obese subjects were higher than those of the lean subjects before food intake. After food intake, we did not find the significant differences between the obese men and the lean men. In all participations, synchronicity of activity increased from the fasted to the satiated state in the OFC. The results indicated that OFC plays an important role in feeding behavior, and OFC signaling may be disordered in obesity. Obese men show less inhibitory control during fasting state. This study has provided strong evidence supporting the hypothesis that there is a hypo-functioning reward circuitry in obese individuals, in which the frontal cortex may fail to inhibit the striatum, and consequently lead to overeating and obesity.

© 2014 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Obesity has reached epidemic proportions globally to become a major public health problem. Obesity-related health problems are numerous including strokes, cardiovascular disease, diabetes mellitus, and increased risk for developing cancer [15]. Obesity, caused by excessive energy intake, is largely due to abnormal eating behavior which is modulated by the central nervous system [3]. Functional imaging techniques have been applied to examine differential activations in certain brain regions between obese and lean subjects. A previous positron emission tomography (PET) study found increased activity in response to taste stimulation in hungry obese individuals [21]. Decreased brain activity was present...
in the insula, orbitofrontal cortex (OFC) and anterior medial temporo lobe in obese individuals compared with lean individuals who reached a similar satiated state [7].

Functional MRI (fMRI) has also been widely applied to the study of feeding behavior based on a psychological signal using a top-down approach. In a study of non-obese women by Schur et al. [19], they showed that viewing fattening food pictures compared with non-food objects resulted in significantly greater activation in the brainstem, hypothalamus, left amygdala, left prefrontal cortex (PFC), left OFC, right insular cortex, bilateral striatum and occipital lobe. Also, in Passamonti and his colleagues’ study [15], they found that viewing pictures of appetizing food resulted in alterations in functional connectivity among the striatum, amygdala, anterior cingulate and premotor cortex compared to bland food photos in non-obese subjects. According to the previous studies, we could arrive at the conclusion that altered brain function response to food cues.

Recently, there has been increased interest in differential activations in certain brain regions or networks between obese and lean subjects using resting state fMRI (rs-fMRI) [6,9–11,28]. Previous studies found that there are alterations of cerebral networks regulating ingestive behavior in the obese. Kullmann and her colleagues, they found obese women had greater connectivity between the hypothalamus and nucleus tractus solitaries after ingestion of high-sucrose than lean women [9]. In a study by García-García and his colleagues [6], they found abnormal activation of putamen nucleus in obese which may contribute to overeating through an imbalance between autonomic processing and reward processing of food stimuli.

In the study describe here, we used regional homogeneity (ReHo) as a local measure to assess differences in baseline brain activity between obese and lean men during both hunger and satiety states. ReHo was developed as a new analysis method for resting state fMRI [27]. ReHo measures the similarity or coherence of low frequency fluctuations of the blood-oxygen-level dependent (BOLD) signal, which might reflect the coherence of spontaneous neuronal activity [14]. The ReHo method has been used to investigate schizophrenia [13], Alzheimer’s disease [8], autism spectrum disorders [15] and attention deficit hyperactivity disorder (ADHD) [29]. Abnormal ReHo has been suggested to be potentially related to temporal changes in the baseline or spontaneous brain activities in specific functional brain regions. In the present study, we employed this method to explore differences in the obese compared to lean individuals, before and after a liquid meal.

2. Methods and procedures

2.1. Subjects

In the present study, 20 lean men and 20 obese men were included. All of the subjects were right-handed and nonsmokers. They had no history of illicit drug dependence or alcohol abuse and were not currently dieting to lose weight. All subjects were recruited from a nearby college via poster advertisement. This study was approved by the local ethics committee, and all participants gave written informed consent to participate.

All of the subjects completed the paradigm between 5:30 PM and 8:00 PM. On the day of the scan, subjects were fasted 6–8 h prior to scanning. After lunch, subjects were asked not to ingest anything except drinking water until the beginning of the experiment. In order to reach to satiation, a liquid formula meal (55% carbohydrate, 30% fat, 15% protein; Ensure-Plus 1.5 kcal/ml) was administered orally. The flavor of the liquid meal was vanilla. Every subject received a liquid meal in an amount proportional to their body size, which provided 40% of the personal resting energy expenditure [7,12,24]. Resting energy expenditure was assessed by indirect calorimetric analysis (Vmax Encore, Sensormedics, United States).

During the fasted state, we assessed the degree of hunger before the MRI scan using Visual Analog Scales (VAS), in which subjects were asked to rate their sensations of hunger on a 100 mm scale, that ranged from 0 (‘not at all hungry’) to 100 (‘very hungry’). After food intake, VAS assessments were also administrated before the scanning.

2.2. Data acquisition

The fMRI involved two sessions, before and after the liquid meal. Brain imaging data were acquired with a 3-T MR imaging system (Signa-HDX, General Electric, United States) with an echo-planar imaging sequence: repetition time/echo time (TR/TE) = 2000/30 ms; flip angle 90°; slice thickness 4 mm (no slice gap); matrix 64 × 64; FOV 240 mm × 240 mm, and voxel size 3.75 mm × 3.75 mm × 5 mm. Each brain volume was comprised of 40 axial slices, and each functional run contained 180 image volumes, resulting in a total scan time of 360 s. All participants were instructed not to focus their thoughts on anything in particular, to keep their eyes closed and not to fall asleep during the resting state MR acquisition. All participants reported that they had complied with these instructions.

Blood samples were drawn before every scan session, and taken from cubital vein. Plasma glucose concentrations were determined by an automated clinical chemistry analyzer (Medical Cooperation, USA) and plasma insulin concentrations by a chemiluminescence immunoassay (CLIA) (Siemens Diagnostics, USA).

2.3. Data processing

Functional image preprocessing was performed by using statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes of each functional time series were discarded for the magnetization equilibrium. The remaining 170 images were corrected for time delay between different slices and realigned to the first volume. Head motion parameters were computed by estimating translation in each direction and the angular rotation on each axis for each volume. Each subject had a maximum displacement of less than 2 mm in any cardinal direction (x, y, z), and a maximum spin (x, y, z) less than 2°. Following this step, all data were spatially normalized to the standard Montreal Neurological Institute template and each voxel was resampled to a voxel size of 3 mm × 3 mm × 3 mm cubic voxels. Further processing was performed using the Resting State fMRI Data Analysis Toolkit (REST, http://www.restfmri.net), including temporal band-pass filtering (0.01–0.08 Hz) to reduce low-frequency drift.

ReHo supposes that voxels within a functional brain area are more temporally homogeneous when this area is involved in a specific condition [27]. In our experiment, the individual ReHo map was calculated by REST. Each individual ReHo map was divided by the subject’s global mean Kendall’s coefficient of concordance (KCC) value within the brain mask. Standardized maps were smoothed with a Gaussian kernel (FWHM = 8 mm) for better anatomical comparability of ReHo values on a group level.

The differences between obese subjects and normal controls were examined with two-sample t-tests between the two groups to create a group difference map. Threshold correction was done by False Discovery Rate (FDR) using SPM with threshold at a p-value of p < 0.05 with a contiguity criterion of 10 voxels.

Since there were differences between two groups before liquid meal, we then projected the group difference map onto the mask. Within the mask, the differences between fasting and satiated state
were examined with paired-sample t-tests to create a state difference map. Threshold correction was done by False Discovery Rate (FDR) using SPM with threshold at a \( p \)-value of 0.05.

### 3. Results

Before liquid intake, the ratings of hunger of the obese subjects were higher than those of the lean subjects, however, there were no significant differences between lean and obese subjects. After administering the liquid meal, subjects reported significantly lower ratings of hunger, and there were no significant differences between the two groups (Table 1).

We used independent samples t-test to statistically compare the groups’ differences of plasma glucose and insulin. Plasma glucose levels were similar between lean and obese subjects before liquid intake; however, plasma glucose levels of obese subjects were significantly lower than in lean subjects after liquid intake. Plasma insulin concentrations of obese subjects were significantly higher than in lean subjects during the entire process (Table 1).

Before liquid intake, the obese men, compared to the lean men, had a significant increased synchronicity of activity in the left putamen, and had a significant decreased synchronicity of activity in the OFC, medial prefrontal cortex (MPFC) and right inferior temporal lobe (Table 2; Fig. 1, \( p \)-value < 0.05, FDR corrected). After liquid intake, we did not find the significant differences between the obese men and the lean men (\( p \)-value < 0.05, FDR corrected).

The lean men had a significant increased synchronicity of activity from the fasted to the satiated state in the OFC and right inferior temporal lobe. (Fig. 2, \( p \)-value < 0.05, FDR corrected). The obese men also had a significant increased synchronicity of activity from the fasted to the satiated state in the OFC and right inferior temporal lobe. (Fig. 3, \( p \)-value < 0.05, FDR corrected).

### 4. Discussion

We used the local metric of resting state activity to examine synchronicity of activity in lean and obese men, and the approach is minimally biased by choice of a seed region or task and focus on the local metabolic activity during resting state. ReHo analysis was able to depict several brain areas where local BOLD signal coherence

---

**Table 1**

Characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Lean (( n=20 ))</th>
<th>Obese (( n=20 ))</th>
<th>Group effect  ( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>24 ± 4</td>
<td>24 ± 4</td>
<td>0.015</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>63.52 ± 5.66</td>
<td>100.51 ± 13.32</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.48 ± 1.43</td>
<td>33.56 ± 3.53</td>
<td>0.003</td>
</tr>
<tr>
<td>REE (kcal)</td>
<td>1627.25 ± 175.77</td>
<td>2331.5 ± 360.80</td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>4.46 ± 0.44</td>
<td>4.12 ± 0.72</td>
<td>0.142</td>
</tr>
<tr>
<td>Postmeal</td>
<td>8.58 ± 1.86</td>
<td>6.84 ± 1.64</td>
<td>0.450</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>4.84 ± 5.30</td>
<td>14.81 ± 11.32</td>
<td>0.001</td>
</tr>
<tr>
<td>Postmeal</td>
<td>58.51 ± 27.13</td>
<td>143.12 ± 67.74</td>
<td>0.002</td>
</tr>
<tr>
<td>Hunger ratings (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>71.56 ± 9.61</td>
<td>72.92 ± 13.24</td>
<td>0.330</td>
</tr>
<tr>
<td>Postmeal</td>
<td>20.63 ± 12.89</td>
<td>17.06 ± 12.99</td>
<td>0.738</td>
</tr>
</tbody>
</table>

**Table 2**

Brain areas of significant ReHo differences between obese individuals and controls before liquid ingestion.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Peak t value coordinates</th>
<th>t-Score of peak voxel</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
<td>Z</td>
</tr>
<tr>
<td>Medial orbitofrontal cortex</td>
<td>6</td>
<td>63</td>
<td>−9</td>
</tr>
<tr>
<td>R superior orbitofrontal cortex</td>
<td>24</td>
<td>60</td>
<td>−3</td>
</tr>
<tr>
<td>R inferior temporal gyrus</td>
<td>66</td>
<td>−42</td>
<td>−9</td>
</tr>
<tr>
<td>L putamen</td>
<td>−33</td>
<td>−12</td>
<td>3</td>
</tr>
<tr>
<td>L medial prefrontal cortex</td>
<td>−3</td>
<td>57</td>
<td>18</td>
</tr>
</tbody>
</table>
Fig. 2. A T-statistical difference map between the fasted and the satiated state of normal controls ($p < 0.05$, FDR corrected). Warm colors indicate increased activity from the fasted to the satiated state.

differed between obese subjects and control subjects. Decreased or increased ReHo in obese subjects suggested that brain function in certain regions was more or less synchronized, compared to controls. And, we used the rating of hunger as the behavioral measurement to assess the degree of hunger. We found that it were higher in the obese subjects before food intake, however, there were no significant differences between lean and obese subjects.

The frontal lobe, which integrates the sensory and visceral afferents, feeds back the signals to the hypothalamus and limbic areas [18], thus motivating the individuals to behave in a manner intended to alleviate hunger. Our results showed that the synchronicity of activity increased from the fasted to the satiated state in the OFC. Previous studies showed that frontal lobe is implicated in response inhibition [2,21], and obese girls showed less activation of PFC when trying to inhibit responses to food images than lean ones [1]. Our results showed that the obese men had significantly decreased the synchronicity of activity in the OFC and MPFC before food intake, which indicated that obese men have a limited inhibitory ability when fasting. Our behavioral measurement also found that it were higher of hungry rating in the obese subjects before food intake.

There were lack of significant differences between obese and lean groups following the liquid meal. We infer that obese men ate more liquid food than healthy controls, and the differences between the fasted and satiated state were due to great impact of meal. From the VAS results, there were no differences of hunger ratings between two groups after food intake, either.

The dorsal striatum plays a role in consumed food reward [22]. In particular, the left putamen was activated when normal subjects were hungry compared to when they were satiated [24,25]. Low DRD2 receptor availability in obese individuals is related to the predisposition to compulsive eating or to DRD2 downregulation in response to chronic hyperstimulation from overeating [19]. In our study, obese men had significantly increased the synchronicity of activity in the left putamen before food intake, which may mean that dopamine was released more in the striatum of the obese men. At the same time, the frontal lobe could not inhibit control of their availability [2].

There are several limitations of our experimental approach. Firstly, we did not estimate the quantity of water ingested by the subjects. In order to improve the compliance of the subjects, they were allowed to drink water until the beginning of the experiment. However, we did not estimate the quantity of water ingested, which could effect gastric distension and may influence the subjects’ brain responses. In future work, we should measure the quantity of the water ingested and use this data as a variable in the analysis. Secondly, we did not estimate the palatability of the liquid meal in the subjects. Before the experiment, we estimated the palatability of the vanilla orally in all subjects. The result showed that they favored the taste. With that in mind, we decided to use this type of liquid meal in our experiment. However, we did not assess the degree of palatability using visual analog scale, in which subjects would have rated their taste palatability for the vanilla flavor. This is also one.
important factor in investigating brain activity. We should collect this data in future studies. Thirdly, We have only twenty subjects each group which is the small sample, so it may be the reason that there were the upward trend of the rating of hunger in the obese men, but there were no significant differences between the two groups.

In conclusion, observations from the present study suggest that obese individuals have a hypo-functioning reward circuitry in which the MPFC and OFC may fail to inhibit the left putamen leading to overeating during hungry state. Our results suggest that the MPFC and OFC may have a less inhibitory effect in obese men; therefore, food appears to be more attractive to obese subjects during hunger state, and it maybe lead to overeating. Our results also demonstrated that the ReHo method during the RS-fMRI analysis is a useful tool in investigating the underlying mechanisms of obesity in terms of the baseline brain activity.

Conflicts of interest

The authors declared no conflict of interest.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (81270927, 3087791) and Natural Science Foundation of Tianjin (07JCZDJC08100) to Derun Tian.

References