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Research report

Correlation between brain circuit segregation and obesity

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ABSTRACT

Obesity is a major public health problem. Herein, we aim to identify the correlation between brain circuit segregation and obesity using multimodal functional magnetic resonance imaging (fMRI) techniques and analysis. Twenty obese patients (BMI = 37.66 ± 5.07) and 30 healthy controls (BMI = 22.64 ± 3.45) were compared using neuroimaging and assessed for symptoms of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS). All participants underwent resting-state fMRI (rs-fMRI) and T1-weighted imaging using a 1.5T MRI. Multimodal MRI techniques and analyses were used to assess obese patients, including the functional connectivity (FC), amplitude of low-frequency fluctuations (ALFF), regional homogeneity (ReHo), graph theoretical analysis (GTA), and voxel-based morphometry (VBM). Correlations between brain circuit segregation and obesity were also calculated. In the VBM, obese patients showed altered gray matter volumes in the amygdala, thalamus and putamen. In the FC, the obesity group showed increased functional connectivity in the bilateral anterior cingulate cortex and decreased functional connectivity in the frontal gyrus of default mode network. The obesity group also exhibited altered ALFF and ReHo in the prefrontal cortex and precuneus. In the GTA, the obese patients showed a significant decrease in local segregation and a significant increase in global integration, suggesting a shift toward randomization in their functional networks. Our results may provide additional evidence for potential structural and functional imaging markers for clinical diagnosis and future research, and they may improve our understanding of the underlying pathophysiology of obesity.

1. Introduction

Obesity is a pervasive public health problem and is highly associated with significant increases in morbidity and mortality [1–4]. Approximately 300,000 deaths annually in the United States are attributed to overweight- and obesity-related diseases, making obesity the second leading cause of preventable death behind tobacco use [5]. Furthermore, the World Health Organization (WHO) predicts that obesity may soon replace more traditional public health concerns such as malnutrition and infectious diseases as the most significant cause of poor health.

Structural MRI provides information to qualitatively and quantitatively describe the shape, size, and integrity of gray and white matter structures in the brain [6]. Epidemiological studies have revealed an association between obesity and cognitive impairment in otherwise healthy subjects [7–9]. In addition, adults with obesity exhibit clinically significant deficits in cognitive functions [10]. Furthermore, obesity is associated with significant reductions in both gray and white matter volumes, particularly within the frontal lobes [11]. For example, a replicated finding among individuals with obesity is volumetric deficits in the prefrontal cortex (PFC), which has been implicated in executive functioning (e.g. planning, initiation, sequencing, monitoring, and inhibition of behaviours; working memory).

Functional magnetic resonance imaging (fMRI) measures brain

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activity by detecting changes associated with blood oxygenation level-dependent (BOLD) signals. Previous studies have demonstrated alterations of cerebral networks that regulate ingestive behavior in obese subjects. For example, Kullmann et al. discovered an altered functional connectivity strength in the default mode network (DMN) and temporal lobe network of obese subjects, which was associated with food regulation [12]. Kilpatrick et al. found that obese women had greater connectivity between the hypothalamus and nucleus tractus solitarius after ingestion of high-sucrose than lean women [13]. García-García et al. observed abnormal activation of the putamen nucleus in obese subjects, which may contribute to overeating via an imbalance between autonomic processing and reward processing of food stimuli [14].

Recently, the connectome has been proposed as a conceptual framework for brain research [15–19]. Tacit to this model is the structural and functional organization of the human brain into complex networks, allowing for the segregation and integration of information processing. Based on topology, graph theoretical analysis quantitatively provides a novel insight to the connectome by using nodes (i.e. neurons or brain regions), edges (i.e. synapses or axonal projections) and several additional topological parameters, such as clustering coefficient, characteristic path length and small-worldness [20,21].

Recently, there has been increased interest in the differential activation of certain brain regions or networks between obese and lean subjects using neuroimaging techniques. Obesity will not only harm the structure of the human brain but also affect its function as well as alter mental and cognitive ability. There is a scarcity of research reporting on the associations between change of activation pattern in brain areas in functional MRI, obesity, and psychiatric illness. To gain insight we used multimodal functional and structural MRI techniques and analyses, including functional connectivity (FC), amplitude of low frequency fluctuations (ALFF) and regional homogeneity (ReHo) with voxel-based statistical analysis (VBA), and voxel-based morphometry (VBM), to investigate the effect of obesity on brain structure and function and possible associations with measures of depressive symptoms. We also used graph theoretical analysis (GTA), and network-based statistical (NBS) analyses to identify the functional network differences between the obesity and control groups.

2. Methods

2.1. Participants and clinical characteristics

Twenty obese participants (mean BMI = 37.66 ± 5.07) between the ages of 22 and 58 years who were preparing to undergo bariatric surgery were recruited from a bariatric clinic in Jen-Ai Hospital, Taichung, Taiwan. Severe binge eating was operationalized as a total score > 27 on the Binge Eating Scale [22]. Individuals with obesity were compared to 30 non-obese control participants (mean BMI = 22.64 ± 3.45) without binge eating behaviour (i.e. total scores < 17 on the Binge Eating Scale). The normal weight control subjects were recruited from the same bariatric clinic in Jen-Ai Hospital, Taichung, Taiwan (Table 1).

All participants were evaluated by a physician and determined to not be suffering from psychiatric, neurological, and/or metabolic conditions. All participants were not taking psychotropic agents during the study period and were not in need of immediate psychiatric intervention, such as for suicidal ideation. The exclusion criteria for the controls included those who were pregnant or breastfeeding, or who had metallic implants or other MRI contraindications. All participants were assessed using structural and functional MRI, as well the Hospital Anxiety and Depression Scale (HADS). Within the 15 items of the HADS, seven items relate to anxiety and seven items relate to depression; higher scores indicate severe anxiety/depression (Table 1).

Table 1
Demographic and clinical characteristics.

	Obesity	Control	p-value
Age (years)	33.11 ± 8.86	45.03 ± 9.65	< 0.001*
Age range	23–54	22–58	< 0.001*
Gender (male/female)	8/12	3/27	< 0.001*
Education years	14.1 ± 2.34	14.3 ± 3.01	> 0.05
BMI	37.66 ± 5.07	22.64 ± 3.45	< 0.001*
Anxiety	6.74 ± 3.07	3.72 ± 2.86	< 0.001*
Depression	6.47 ± 3.73	2.93 ± 2.78	< 0.001*

Statistical data are shown as the means ± standard deviation.
Abbreviations: HADS, hospital anxiety and depression scale; BMI, body mass index.
* Significant difference.

2.2. MR image acquisition

Scanning was performed using a 1.5T Philips (Ingenia, Phillips, Netherlands) MRI with an 8-channel head coil. A high-resolution 3D gradient echo T1-weighted brain structural image, with magnetization-prepared 180° radio-frequency pulses, a rapid gradient-echo (MPRAGE) with repetition time (TR)/echo time (TE) = 7.6/3.5 ms, flip angle = 8°, 160 slices and resolution (voxel size) = 1.0 × 1.0 × 1.0 mm^3 was obtained. In addition, functional data were acquired using echo-planar imaging sequences. During resting-state MR image acquisition, all participants were instructed not to focus their thoughts on anything in particular and to keep their eyes closed. For all participants, the following sequence was used: TR = 2000 ms, TE = 30 ms, in-plane resolution (pixel size) = 3.9 × 3.9 mm^2, slice thickness = 5.0 mm, and the images were acquired in an interleaved order. Each brain volume comprised 20 axial slices, and each functional run contained 400 image volumes, resulting in a total scan time of approximately 13.3 min.

2.3. Voxel-based morphometry (VBM)

The VBM is an objective approach to estimate the local amount of a specific tissue voxel-by-voxel. VBM is commonly used to examine GM as well as WM, and comprises several preprocessing steps, including tissue classification, spatial normalization, and spatial smoothing, followed by the statistical analysis. The procedure was performed by Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK). Tissue classification was based on intensity values and basically served to segment the brain into GM, WM, and cerebrospinal fluid after removing any non-brain parts. This segmentation step involved an affine transformation of each scan to the template with subsequent back-projection into native space. Next, an automated brain extraction procedure with segmentation was used to remove non-brain tissue. The extracted GM images were then normalized to the group-specific GM template by the standard Montreal Neurological Institute (MNI) T1 MRI template. The normalization parameters were then applied to the original structural images in native space, thereby reducing any contribution from non-brain voxels and affording optimal spatial normalization of the GM. Finally, all normalized, segmented images were smoothed with a 6-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel.

We performed two-sample *t*-tests using SPM8 software to assess the difference in GM and WM between the two groups. Next, we calculated the correlation between GM/WM and BMI, HADS, using multiple regressions. We used age, gender and total brain volume as covariates to remove any effects caused by between-group differences. To view the results, we used the standard T1-weighted images as the underlying map (from SPM8).

2.4. Functional MRI preprocessing

Preprocessing was conducted using the data processing assistant for