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Volumetric Analysis of Subcortical Structures in Obese at 3T

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Obesity usually occurs due to homeostasis and hedonic food intake behavior caused by plasticity variation in both cortical and subcortical brain structures. However, little volumetric analysis has been done to study the relationships between obesity and subcortical structures. For this study, we aimed to investigate the volumetric differences of subcortical structures between 21 obese patients and 10 healthy controls using high resolution 3T MRI T1-weighted scans. Obese patients showed reduced subcortical gray matter volume in right caudate and right nucleus accumbens and enlarged volume in right amygdala. Vertex-wise shape analysis of subcortical structures showed bilateral caudate alterations in obese patients. Moreover, the bilateral amygdala negatively correlated with increasing age in obese patients. In conclusion, we present data showing association between obesity and subcortical brain structures. Various studies have shown that morphological changes can cause functional modifications in the brain. Therefore, we believe our analysis of volumetric differences in subcortical structures could be helpful for identifying neurophysiological changes that occur in obese patients.

Keywords : magnetic resonance imaging, obesity, volumetric MR imaging analysis, vertex analysis

1. Introduction

Obesity is one of the most crucial and rapidly growing public health problems, with rates nearly tripling in the last three decades. World Health Organization showed that in 2016, more than 1.9 billion adults with 18 years and older were overweight, 650 million of which were obese [1]. The increasing emergence of obesity is associated with multiple health risks, including type 2 diabetes [2], hypertension [3], cardiovascular disease [4], and cancer [5]. In addition, it has been found that obesity itself changes the structure of the brain due to physiological control disorders [6].

When the energy intake is higher than the energy consumption, the excessive energy is involved in weight increases [7]. Obesity is usually caused by homeostasis and hedonic food intake behavior due to the plasticity variation of cortical and subcortical brains [8]. Thus, unnatural eating behavior is an important factor in defining obesity as a disease [9]. Food intake is regulated by a variety of cognitive influences such as memorial representation, environmental circumstances, and emotional and compensatory characteristics of their hedonic effects [10]. These factors are regulated by signaling molecules through the corticolimbic neuronal brain systems, in which the basal ganglia play an important role in [11].

Previous imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) observed that obesity is associated with elevated glucose metabolism of the brain, as well as modified regional responses and altered connectivity [12]. One particular study showed increased amygdala and hippocampal volumes in elderly obese using 1.5T magnetic resonance imaging (MRI) [13]. Structural MRI study revealed that compared to the lean subjects, the obese individuals showed significantly reduced gray matter density in the post-central gyrus, frontal operculum, putamen, and middle frontal gyrus [14]. Subjects who were obese also had reduced gray matter volume particularly in the left dorsolateral prefrontal cortex (DLPFC) [15], and ventral diencephalon, and brainstem volumes compared to controls [8].

Another study found that increased body mass index (BMI) is associated with particular regional alterations in

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left lateral occipital cortex and right ventromedial prefrontal cortex area [6]. Zhang *et al*. [9] showed that obese men showed a significantly enlarged gray matter volume (GMV) in the left putamen and positive correlation with BMI. Additionally, a study showed that obesity was associated with higher waist-hip ratio and waist circumference, but lower total brain volume (TBV) and GMV [16].

A number of studies have conducted research on the relationship between obesity and brain structure, mainly focusing on GMV. However, very little studies utilize volumetric analysis of obesity on subcortical gray matter structures and its visualization to study the relationship between obesity and brain structures. The purpose of this study was to explore whether subcortical structures including thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, and nucleus accumbens are volumetrically different between obese and healthy control groups using 3T MRI. To do this, we used FMRIB's Software Library (FSL), which involved using a tool to measure the attenuation of subcortical subregions and shape changes in seven pairs of subcortical gray matter structures [17]. One of the tools of the FSL, vertex analysis is used to measure partial differences in morphology inter-groups [18]. Particularly, vertex-based shape analysis offers helpful data information regarding the position and range of the local alterations in the subcortical gray matter [19]. We hypothesized that there would be significant subcortical structural brain alteration in male obese patients. In addition, we performed linear regression analysis to investigate the correlation between the volumes of subcortical structures and clinical characteristics.

2. Subjects and Methods

2.1. Subjects

Thirty-one male subjects, including 21 obese patients (age = 23.6 ± 3.4, BMI = 29.81 ± 3.9) and 10 healthy controls with normal weight (age = 23.3 ± 1.5, BMI = 22.6 ± 1.17) were recruited from Chungbuk National University. BMI was calculated as body weight in kilograms divided by the square of height in meters. Obesity was designated as a BMI ≥ 25.0 kg/m^2 using the adjusted Korean guideline [20]. Subjects with neurological abnormality, history of psychiatric illnesses, illicit drug dependence or alcohol abuse were excluded from this study. This study was approved by the Institutional Review Board by College of Medicine Chungbuk National University in Cheongju, Korea. All of the subjects provided written informed consent after detailed instructions of the study.

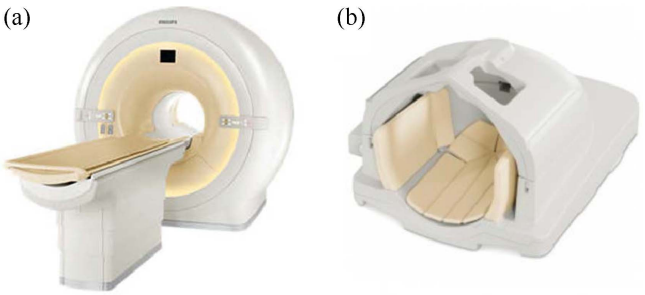

Fig. 1. (Color online) 3T MRI system (a) and 32-Channel head coil (b).

2.2. MRI Acquisition

Brain imaging data were acquired on a 3T MRI system and the 32-Channel head coil (Philips Healthcare, U.S.A) (Fig. 1). Structural images were acquired using a high-resolution T1-weighted three-dimensional magnetization-prepared rapid gradient echo with the following parameters: TR = 7 ms, TE = 3 ms, flip angle = 9º, slice thickness = 1.2 mm, FOV = 256 mm × 256 mm, and matrix = 243.

2.3. Image Processing

MRI image data were converted from DICOM to NIFTI files using MRIcron software (http://www.cabiatl.com/micro/mricron/index.html) [21]. Tools from the FSL (v.5.0, Oxford Center for Functional MRI of the Brain, UK) were used for data processing [22]. Brain extraction tool, which uses a deformable model that develops to arrange the surface of the brain by the application of a set of locally adjustive model forces was carried out on the T1-weighted images [23]. Images of each subject were then registered to the standard T1 Montreal Neurological Institute template. The volumes of the gray matter, white matter, and total brain were extracted and normalized using the normalization factor from SIENAX to reduce the effects of individual variability in head size [22]. Integrated Registration and Segmentation Tool (FIRST) was utilized to perform the segmentation as well as to measure the volumes and vertexes of subcortical structures including the thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala and nucleus accumbens bilaterally [24].

FSLstats from FSL's command line was used to measure each structure's volume. To correct the differences in head size among individual participants, volumes of each subcortical structures were calculated by Normalized Brain Volume (NBV) using the following equation:

$$V_{standard} = (V_{roi}/V_{NBV}) \times 10^6$$

where $V_{standard}$ represents the standardized volume correct-

ed with NBV, V_{roi} represents the absolute volume of each segmented structure, and V_{NBV} represents NBV [17].

2.4. Vertex-based Analysis

By using a deformable mesh model, FIRST makes a surface mesh for each individual subcortical structure. The mesh consists of a series of triangles, and the top point of triangles is called a vertex. Because the vertices of each structure are fixed, it is possible to compare the groups of vertices corresponding to each [25]. Vertex analysis was executed using first utils and using generalized linear model to design the statistical matrix [22]. Randomise was used to perform permutation inference on the segmented structures [26]. Statistical maps were rendered on each structure's surface, showing the regions where the subcortical structure altered significantly at $p \leq 0.05$ level.

2.5. Statistical Analysis

Statistical analysis was performed using IBM® SPSS® Statistics (version 23). Analysis of variance (one-way ANOVA) model was used to compare group-wise mean differences in clinical characteristics including age, body weight, skeletal muscle mass, fat mass, BMI, percent body fat, and waist hip ratio. Multivariate analysis of covariance (MANCOVA) model was applied to investigate group-wise differences in subcortical volumes while controlling for age. Correlation analysis was used to compare subcortical alterations and clinical characteristics.

3. Results

3.1. Clinical Characteristics

The group comparisons of demographic and clinical characteristics are presented in Table 1. The body weight, skeletal muscle mass, fat mass, BMI, percent body fat and waist hip ratio of obese patients were significantly higher ($p \leq 0.05$) than those of healthy controls. The two groups had similar characteristics in age, gray matter, white matter and TBV with no significant differences ($p > 0.05$).

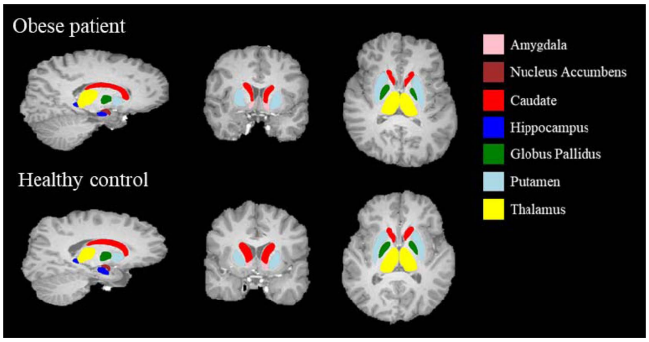

Fig. 2. (Color online) Representative FIRST segmentation of subcortical structures in obese patient (top) and healthy control (bottom).

Table 1. Demographic and clinical characteristics between obese and healthy controls.

Demographic and Clinical Variables	Obese patients Mean (SD) n = 21	Healthy controls Mean (SD) n = 10	*p*-value
Age (year)	24.05 (3.41) (range, 19-31)	23.60 (1.43) (range, 21-26)	0.695
Body weight (kg)	91.5 (11.79)	69.89 (5.23)	< 0.001*
Skeletal Muscle Mass (kg)	35.56 (3.57)	31.65 (2.23)	0.004*
Fat Mass (kg)	28.73 (9.95)	13.71 (4.16)	< 0.001*
Body Mass Index (kg/m^2)	29.81 (3.89)	22.60 (1.21)	< 0.001*
Percent Body Fat	30.81 (7.36)	19.45 (4.93)	< 0.001*
Waist-Hip Ratio	0.91 (0.03)	0.84 (0.02)	< 0.001*
Gray Matter (cm^3)	825.1 (38.1)	806.4 (35.9)	0.205
White Matter (cm^3)	702.4 (31.4)	699.6 (28.1)	0.811
Total Brain (cm^3)	1527.5 (55.6)	1506.0 (61.7)	0.339

Note: Demographic and clinical characteristics are presented as mean (SD) for continuous and proportions for categorical variables.
Group comparisons were made using one-way ANOVA.
*Significant differences at $p \leq 0.05$ level.
Abbreviations: Gray Matter; volume of normalized gray matter, White Matter; volume of normalized white matter, Total Brain; volume of normalized total brain volume.

3.2. Subcortical volumetric analysis

Examples of subcortical segmentation of an obese patient and healthy control are presented in Fig. 2. Group comparisons of mean volumes for all subcortical structures are shown in Table 2. The obese patients had significantly reduced volumes in the right caudate (R_Caud: $p = 0.034$) and right nucleus accumbens (R_Accu: $p = 0.043$) than the healthy controls. On the other hand, the obese patients showed significantly enlarged volumes in the right amygdala (R_Amyg: $p = 0.027$) than the healthy controls adjusted for age. None of the other subcortical structures volumes differed significantly between groups.

3.3. Vertex-based analysis

The results of vertex analysis are illustrated as statistical images of significant surface abnormalities within subcortical structures with $p \leq 0.05$ in Fig. 3. The vertex analysis between groups shows significant subregional alterations within subcortical structures including thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, and nucleus accumbens. After adjusting for age, the significant subregional alterations in subcortical structures were located in the bilateral caudate of obese patients,

Table 2. Subcortical volume differences between obese patients and healthy controls.

Subcortical structure	Obese patients Mean (SD) n = 21	Healthy controls Mean (SD) n = 10	*p*-value
L Thalamus (mm^3)	5819.00 (555.67)	5860.79 (452.90)	0.224
R Thalamus (mm^3)	5641.36 (519.58)	5622.14 (444.82)	0.221
L Caudate (mm^3)	2561.58 (316.54)	2792.93 (210.92)	0.062
R Caudate (mm^3)	2707.35 (329.94)	2889.83 (245.09)	**0.034***
L Putamen (mm^3)	3831.82 (317.51)	3809.62 (257.83)	0.980
R Putamen (mm^3)	3858.11 (383.21)	3884.77 (324.14)	0.937
L Globus Pallidus (mm^3)	1339.19 (118.38)	378.90 (82.06)	0.520
R Globus Pallidus (mm^3)	1364.89 (123.31)	1408.40 (99.46)	0.556
L Hippocampus (mm^3)	2754.26 (347.33)	2693.64 (473.26)	0.893
R Hippocampus (mm^3)	2978.96 (310.16)	2956.29 (351.91)	0.908
L Amygdala (mm^3)	925.64 (190.33)	874.74 (208.64)	0.142
R Amygdala (mm^3)	942.37 (161.10)	847.45 (195.27)	**0.027***
L Nucleus Accumbens (mm^3)	475.43 (63.55)	487.62 (78.97)	0.355
R Nucleus Accumbens (mm^3)	345.57 (61.13)	390.77 (79.96)	**0.043***

Note: Values are presented as mean (SD) for continuous and proportions for categorical variables.
Group comparisons were made using MANCOVA.
*Significant differences at $p \leq 0.05$ level.
Subcortical volumes were adjusted for age.
Abbreviations: L; left, R; right

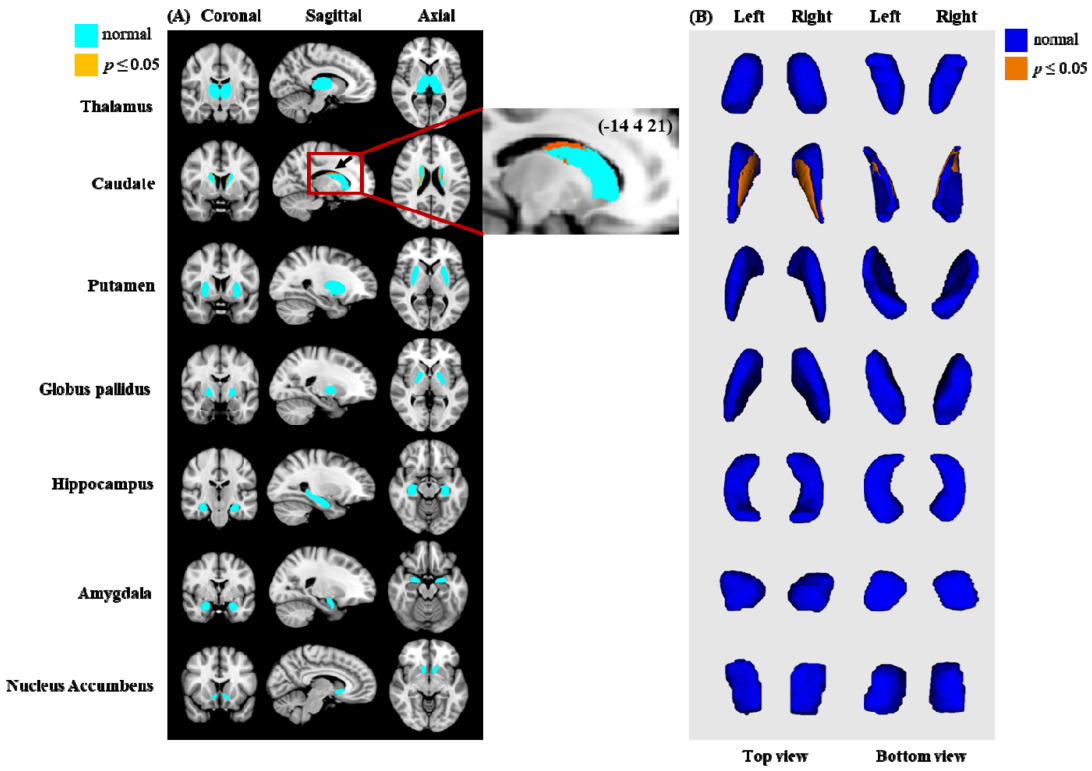

Fig. 3. (Color online) Subcortical surface alterations between groups adjusted for age. (A) Coronal, sagittal and axial views of the results of Vertex Analysis. Region in orange represent the specific location where volumetric change occurred. (B) 3D rendering of the results of Vertex Analysis. Orange regions represent the locations where volumetric change occurred.

compared to healthy controls. None of the other subcortical regions differed significantly between groups.

3.4. Correlation analysis

Correlation coefficients between subcortical structural

Table 3. Correlation coefficients between subcortical structures and age.

Subcortical structure	Obese		Control	
	r	p	r	p
L Thalamus	–0.369	0.100	–0.039	0.914
R Thalamus	–0.368	0.100	–0.085	0.815
L Caudate	–0.236	0.302	–0.275	0.442
R Caudate	–0.406	0.068	–0.294	0.410
L Putamen	0.073	0.754	–0.366	0.298
R Putamen	0.026	0.910	–0.601	0.066
L Globus Pallidus	–0.189	0.412	0.343	0.331
R Globus Pallidus	–0.056	0.810	–0.199	0.581
L Hippocampus	–0.134	0.561	0.251	0.484
R Hippocampus	–0.117	0.613	0.085	0.816
L Amygdala	–0.477	0.029*	0.180	0.618
R Amygdala	–0.474	0.030*	–0.367	0.297
L Nucleus Accumbens	–0.326	0.149	–0.073	0.840
R Nucleus Accumbens	–0.356	0.111	–0.464	0.176

Note: *Significant differences at $p \leq 0.05$ level.
Abbreviations: L; left, R; right

volumes and age in obese and healthy control groups are presented in Table 3 and Fig. 4. The volumes of the left amygdala (r = –0.477, p = 0.029) and right amygdala (r = –0.474, p = 0.030) significantly correlated with age in obese patients. None of the other subcortical structures correlated significantly with age in control groups.

4. Discussion

In this study, the volumetric differences of subcortical gray matter structure between obese patients and healthy controls with normal weight were studied. The imaging analysis found significant group differences in subcortical brain regions modulating food intake behavior such as the caudate, nucleus accumbens, and amygdala. Compared to healthy controls, obese patients had reduced subcortical GMV in the right caudate and right nucleus accumbens and enlarged volume in the right amygdala. Moreover, FIRST surface-based vertex-wise shape analysis showed bilateral caudate volume alterations when comparing obese patients to healthy controls. Within the field of 3T MRI, the current study suggests that vertex analysis which is based on the stereotactic of the brain could provide precise regional alterations of the subcortical gray matter.

Segmentations of the subcortical gray matter structures were generated using the FIRST algorithms. FIRST automatically yields information on the volumes of the segmented brain regions as well as the locations on the surfaces of the segmentations where volumetric change occurred. The segmentation is based on the outline and configuration models constructed from 336 manually segmented images using Gaussian presumption combined with Bayesian probabilistic access [27]. Measuring brain volume is useful for identifying neurophysiological changes in obese patients and for studying the correlations of characteristics in diseases such as BMI [28]. The development of automation-based software allows determination of subcortical brain volumes without manual input [29].

In addition, we found the local alterations in the bilateral caudate in obese group compared to healthy control group using vertex analysis. Vertex-based analysis is used to calculate the regional changes in structural morphology over groups [18]. This tool provides a local and direct determination of stereoscopic differences that does not depend on tissue division or random smoothing area. Also, this application enables the conductions of normal

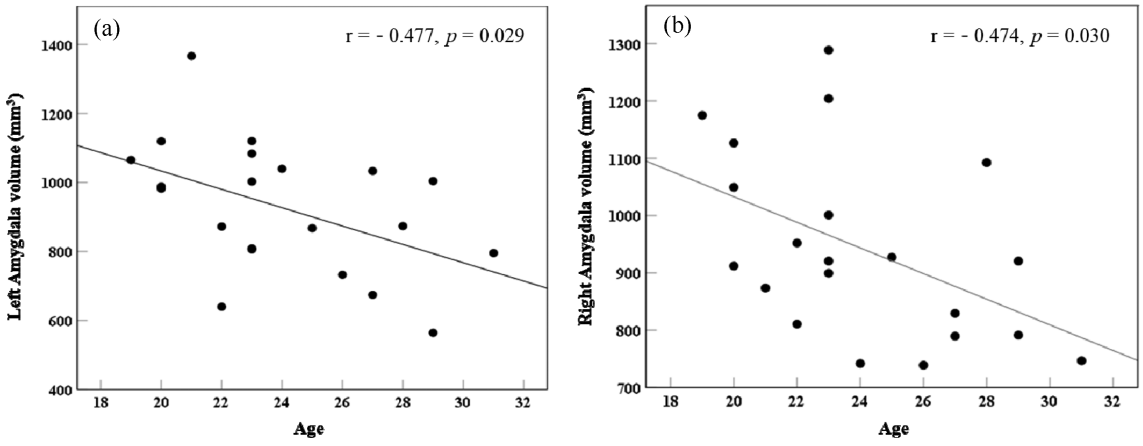

Fig. 4. Scatter plot of the correlations between normalized subcortical gray matter volume and age in obese group. (A) Negative correlation between left amygdala and age, Pearson's (r = –0.477, p = 0.029); (B) negative correlation between right amygdala and age, Pearson's (r = –0.474, p = 0.030).

and pathological variability in the brain. Vertex-based analysis illustrates the junction shape and outward form of the model to investigate the structural boundary. Therefore, it gives the potential to detect localized changes more accurately [24]. It is important to analyze the shape differences to identify the exact anatomical location change. Knowing regional shape differences is helpful in interpreting the results of anatomical discoveries [30].

Previous neuroimaging studies have shown that the volume of caudate nucleus decreased in obese youth [31] when compared to adolescents with normal weight. Lower GMV were also found in the caudate and thalamus in the adolescents with type 2 diabetes [32]. In a similar vein to these studies, we found subcortical gray matter reductions in right caudate and right accumbens of obese subjects. The function of the caudate has been linked to supporting the design and execution of strategies and behavior requested for accomplishing complicated goals [33]. Robinson *et al*. [34] showed that each part of the caudate nucleus has a different function: behavioral filtering of structures involved in cognitive function, emotion regulation and networks is mostly localized to the caudate nucleus head region, while perception ability is localized to the caudate body region [35].

The nucleus accumbens has been known to be an important element of the reward system and for regulates various cognitive processes including hedonic influence and crave of food [36]. Caudate and nucleus accumbens are recognized as the key regions regulating food intake through central reward circuits. It is known that improper regulation of reward circuitry in the brain induces obesity [37]. Subjects with obesity were found to be influenced by change in fiber thickness of caudate and accumbens node, which indicates that there is an association between reward network and white matter volume [36]. Previous PET study documented that because obese subjects tend to have increased sensitivity to external food stimuli, it is likely that stimulus-response acquisition becomes dysfunctional in obese subjects. The imbalance of the brain circuit and reduced cognitive control are the distinct features of the obesity [12]. Morphological changes can cause a functional modification in the brain. Therefore, alteration of the body weight can lead to changes in the organization of the reward system, causing morphological changes [37]. However, the mechanism of changes in brain connectivity and volume associated with obesity is not yet clear.

The amygdala is an important area for controlling appetite. It is a complicated neural system that contributes to the evaluation of food [13]. The amygdala shows cognitive inhibition during food stimulation in the male subjects and plays a part in the limbic system for handling the memory of emotional responses related establishment of conditioned responses [38]. GMV of the amygdala has been suggested to be greater in obese [13]. Regional brain activation has shown to correlate with global brain volume [39] so it is reasonable that that reduced regional brain volume is associated with defective function [15].

Obesity has been linked with dysregulation of eating, reduced volume of cortical gray matter, and degraded performance on cognitive evaluation [40]. Obesity itself is related to structural changes in the brain particularly in the deficit of global and regional brain volume as well as white matter integrity [41]. Reduced brain volume is likely due to inadequate metabolic supply. In particular, the decrease of gray matter or neurons could be illustrated by energy shortage due to the fact that neurons are one of the most energy-demanding cells [42]. The deformations may result from a number of causes, including cellular loss, atrophy of neuronal dendritic arbors, demyelination, reduction in somatic size, or loss of afferent input [43]. In rodents, it has been shown that increased neuronal excitability is associated with reductions in dendritic intricacy [44].

BMI has been suggested to be related to the volume of gray matter in the medial orbitofrontal cortex, hypothalamus, and the left putamen. It has previously been reported that the structural differences related to obesity may reflect the elevated signaling from adipose tissue to the brain, rather than a consequence of altered ingestive behavior [45]. There are also relationships between change in BMI and either volume of specific brain regions or regional lesion loads. Specific regional brain volume associations with obesity and whole brain volume, cerebrospinal fluid (CSF), total, and temporal white matter, and the hippocampus were observed [41]. Lower GMV were found in the medial prefrontal cortex, frontal pole, anterior cingulate, nucus, and caudate as BMI percentile increased [46].

Driscoll *et al*. [41] showed that both age and obesity are linked to improper brain structural alterations. We found that the volume of the bilateral amygdala showed a correlation with the age obese. The volume of the bilateral amygdala showed a negative correlation with age in obese subjects, but not in the healthy control group. The amygdala regulates the sense of taste, which is assumed to guide eating behavior [47]. A neuroimaging study have identified physiological aging of deep gray matter through the measuring of quantitative magnetic resonance parameters sensitive to complementary tissue features [48]. None of the other subcortical structures and clinical characteristics correlated significantly in obese and healthy

control groups. These results suggest that obese men might have volumetric alterations in the subcortical brain region with variations depending on the subjects age.

Our research was limited by several features. First, in the current study, we only recruited male subjects. The previous study examined sex-related differences in obesity and suggested that men and women may have different fundamental neural mechanisms [37]. Differences in both hedonic and homeostatic regulation systems may show a varying tendencies in eating behavior [45]. Second, the relatively small sample size limits complex statistical analyses. In this study, only ten healthy control participants were studied. A higher number of sample size would increase statistical significance of this experiment. Third, the assessments of cognitive functioning were not conducted. The cognitive function is an important for variations in food intake behavior. Dominik *et al*. [18] investigated brain circuit abnormalities and associated cognitive dysfunctions with likelihood of developing anorexia nervosa, an eating disorder characterized by aberrant eating behavior and inappropriately low body weight. Therefore, cognitive performance may be important in regulating food behavior in obese subjects and could have influenced out results. Further studies are required to expand our knowledge of the interactions between subcortical brain regions and obesity.

5. Conclusion

The main findings of this study shows that obese patients had significantly smaller normalized volume of subcortical gray matter including right caudate and right nucleus accumbens and significantly enlarged volume of right amygdala when compared to healthy controls. Moreover, vertex-wise shape analysis showed bilateral caudate volume alterations in obese groups. Additionally, we found significant negative correlations in the bilateral amygdala volume with age in obese groups. These results suggest the evidence of the morphological alterations of subcortical structures involved in reward system in obese patients. Future research will be necessary to clarify the specific connection between structural alteration of the reward network and food intake behavior.

Acknowledgements

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