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Cortical gray matter structural changes in obese on 3T MRI

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SUMMARY

Background: Obesity is associated with imbalanced energy intake and expenditure. Many studies have been conducted on obesity and brain morphometric structural changes. However, the findings have been inconsistent and the exact relationships between obesity and brain structural changes are unclear. We aimed to examine the structural alterations of cortical gray matter between obese patients and healthy controls with normal weight. Methods: 21 obese patients (age=24.05 ± 3.41 years; body mass index [BMI]=29.81 ± 3.89 kg/m^2) were age-matched with 17 healthy controls (age=25.65 ± 4.29 years; [BMI]=22.46 ± 1.43 kg/m^2). High-resolution T1-weighted MPRAGE 3D scans were acquired on a 3T MRI scanner. FreeSurfer and FSL-FIRST were used to examine cortical thickness, surface area, and volume. Results: The obese patients exhibited increased and decreased cortical structural brain alterations in frontal, parietal, temporal, and occipital cortex area summarize the article's main findings. Our results suggest that morphological changes of brain structures can lead to functional variations that worsen food intake behavior. Conclusions: The current study presents the association between obesity and structural brain differences in several cortical gray matter regions involved in food intake regulation. Therefore, we believe that alterations in brain structure could be neuronal markers in understanding how obesity develops.

Keywords: Obesity; Cortical thickness; Cortical surface area; Cortical volume

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INTRODUCTION

Obesity is one of the major public health issues with rates nearly tripling over the past three decades. In 2016, 39% of adults aged 18 years and over were overweight and 13% were obese [1]. The increasing emergence of obesity is associated with multiple morbidities, including an type 2 diabetes [2], hypertension [3], cardiovascular disease [4], and cancer [5].

When energy intake exceeds a person's energy expenditure, excess energy contributes to weight gain [6]. Obesity results from changes in homeostasis and sybaritic food intake behavior resulting from changes in the plasticity of cortical and subcortical brain structures [7]. Therefore, unnatural eating habits are an important factor in defining obesity as a disease [8]. Food intake is modulated by various cognitive influences such as celebratory representation, environmental situations, and emotional and compensatory characteristics [9]. Studies have shown that structural differences in the brain may cause a more likelihood of obesity, but it is also likely that the condition of obesity itself can change the brain due to development of physiological control disorders [10].

A number of studies have reported that increased body mass index (BMI) is related to the increased cortical thickness and that there was a significant positive correlation between visceral fat ratio and cortical thickness throughout the brain [11,12]. In contrast, other studies showed that increasing BMI was associated with cortical thinning in the left inferior temporal and the inferior parietal cortex and increasing visceral adipose tissue was related to cortical thinning in the left fusiform gyrus, the right inferior temporal and mid-insular [13]. BMI showed a negative correlation with cortical thickness in the left lateral occipital cortex and right ventromedial prefrontal cortex area [10].

Studies that assessed gray matter volume (GMV) in obese subjects found that obese subjects showed enlarged left putamen which correlated with increasing BMI and enlarged amygdala and hippocampus [8,14]. Studies also showed that the higher waist-hip ratio and waist circumference, the lower the total brain volume (TBV) and GMV [15]. Previous studies that compared lean subjects and obese individuals showed that obese individuals had significant lower gray matter density in the postcentral gyrus, frontal operculum, putamen, middle frontal gyrus [16], left dorsolateral prefrontal cortex [17], ventral diencephalon, and brainstem than those of lean subjects [7].

A number of studies have suggested the relationships between obesity and morphology of the brain area. However, the results of previous research are diverse and consistent results on regional brain changes in obesity have not been established. The purpose of this study was to examine the structural differences of the cortical gray matter (e.g., cortical thickness, surface area, and volume) between obese patients and healthy controls. We hypothesized that obese patients would exhibit regional cortical structural alterations in brain areas which are involved in food intake behavior regulation.

MATERIALS AND METHODS

Subjects

Thirty-eight male subjects, 21 with obese (age=24.05 ± 3.41 years; body mass index [BMI]=29.81 ± 3.89 kg/m^2) and 17 healthy controls with normal weight (age=25.65 ± 4.29 years; [BMI]=22.46 ± 1.43 kg/m^2) 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. Subjects with neurological abnormalities, history of psychiatric illnesses, illicit drug dependence or alcohol abuse were excluded from this study. This study was approved by the Institutional Review Board (IRB) by College of Medicine Chungbuk National University in Cheongju, Korea. All subjects provided written informed consent after detailed instructions of the study.

MRI acquisition

Brain imaging data were acquired on a 3T MR scanner (Achieva 3.0T TX, Philips Medical Systems, Eindhoven, Netherlands). A 32-channel receive-only phased array head coil was used for receiving. Structural images were acquired using a high-resolution T1-weighted three-dimensional (3D) magnetization prepared rapid gradient echo (MPRAGE) with the following parameters: repetition time (TR)=7 ms, echo time (TE)=3 ms, flip angle=9º, slice thickness=1.2 mm, field of view (FOV)=256 mmx 256 mm, and matrix=243.

Image processing

T1-weighted MR images were converted from DICOM to NIFTI files using MRIcron software (http://www.cabiatl.com/micro/mricron/index.html, accessed on 19 August 2008) [18] and processed using FreeSurfer image analysis suite (v6.0.0, http://surfer.nmr.mgh.harvard.edu/, accessed on 1 January 2017). The entire process is completely automated. The detailed pipeline for FreeSurfer is described on the web page. Briefly, T1-weighted MR images were linearly registered to the Talairach space, B_1 bias field corrected and skull stripped. Images were segmented into the gray-white matter and reconstructions of cortical surface models were identified using gray-white boundary surface and pial surface. The regions on the cortical surface, as well as subcortical brain structures, were labeled by nonlinear registration of the cortical surface of a subject with a stereotaxic atlas. FreeSurfer output was visually checked to ensure accuracy and image quality.

Statistical analysis

Group differences in age, BMI, GMV, white matter volume, TBV were analyzed with one-way ANOVA using IBM® SPSS® Statistics (version 23). The statistical threshold was set at $p<0.05$.

Group cortical analysis was performed to compare cortical thickness, cortical surface area, and cortical volume between groups. Statistical maps were generated using general linear models (GLM) in FreeSurfer's statistical tool QDEC (Query, Design, Estimate, Contrast), including age as a nuisance factor. The significant threshold was set at voxel-wise $p<0.01$ and cluster-wise $p<0.05$, Monte Carlo correction with 10,000 iterations for multiple comparisons. Data were smoothed with a Gaussian 10 mm full-width-at-half-maximum (FWHM) kernel to enhance the variability between subjects [19].

RESULTS

Demographic and clinical characteristics are presented in **Tab.1**. The obese patients and healthy controls differed significantly in terms of BMI (obesity patients=29.81 ± 3.89; healthy controls=22.46 ± 1.43; $p<0.001$). There were no significant group differences in age ($p=0.208$), GMV ($p=0.177$), white matter volume ($p=0.848$) and total brain volume ($p=0.356$).

Examples of cortical thickness differences between obese patients and healthy controls, after controlling age, are shown in **Fig. 1**. Thirty-five clusters of thinner regions and eight clusters of thicker regions were observed in obese patients ($p<0.01$). Representations of these regions are shown in **Tab. 2**.

Compared with the healthy controls controlling for age, the obese patients showed significant larger cortical surface area ($p<0.01$) in the left superior temporal, postcentral, isthmus cingulate, and precuneus. Also, obese patients showed the reduced cortical surface area in the left pars opercularis and right temporal pole (see **Fig. 2.** and **Tab. 3**).

After controlling age, there were cortical volume increases in obese patients in the left postcentral, superior temporal, postcentral, medial orbitofrontal, isthmus cingulate, bankssts and right paracentral, lingual, and bankssts. Cortical volume reductions were observed in the left pars opercularis, rostral middle frontal, lateral occipital and right postcentral, superior parietal, rostral middle frontal, middle temporal, inferior temporal, and lateral occipital in obese patients compared to healthy controls with significant threshold of ($p<0.01$, see **Fig. 3.** and **Tab. 4.**).

DISCUSSION

In the present study, structural brain alterations in the cortical gray matter between obese patients and healthy controls with normal weight were studied. Using FreeSurfer,

Tab. 1. Demographic and clinical characteristics between obese patients and healthy controls.

Characteristic	Obese patients (N=21)	Healthy controls (N=17)	*p*-value
Age (year)	24.05 (3.41)	25.65 (4.29)	0.208
Body Mass Index (kg/m^2)	29.81 (3.89)	22.46 (1.43)	<0.001*
Gray Matter volume (cm^3)	825.09 (38.12)	809.40 (30.55)	0.177
White Matter volume (cm^3)	702.38 (31.37)	700.21 (37.99)	0.848
Total Brain volume (cm^3)	1527.47 (55.58)	1509.61 (62.10)	0.356

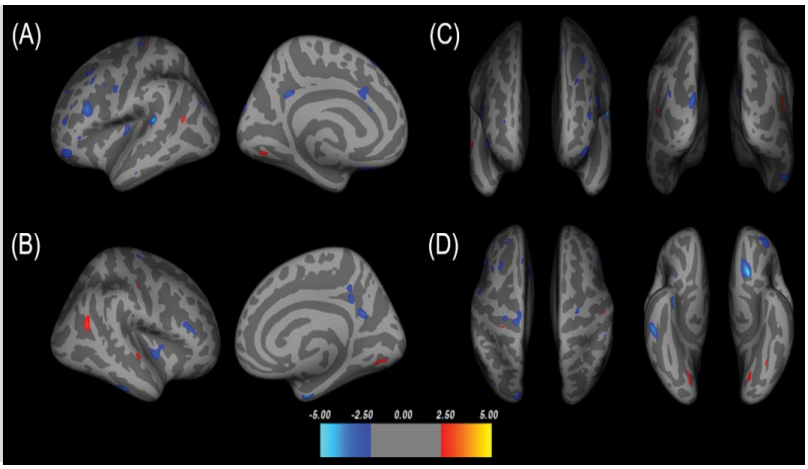

Fig.1. Group comparison of cortical thickness differences between obese patients (N=20) and healthy controls (N=17) after controlling for age. Significant threshold was set to $p<0.01$ (uncorrected). **(A)** Left lateral and medial, **(B)** Right lateral and medial, **(C)** Anterior and posterior and **(D)** Superior and inferior views. Areas are color-coded according to significance level (*t*-statistic), with blue-light blue representing thinning and red-yellow representing thickening (color scale shows –log (10) *p*-value) in obese compared to control. Light gray shading represents gyral and dark gray sulci. The quantitative measurements of each region are shown in Table 2.

Tab. 2. Clusters of significant differences in cortical thickness in obese patients compared to healthy controls.

	Max *t*-statistic	Size (mm^2)	Talairach Coordinates			N vertices	Anatomical Regions
			X	Y	Z		
Obese>Control	2.7141	113.23	41.9	-57.7	16.7	249	R inferior parietal
	2.6828	34.72	-44.5	-61	11.9	71	L inferior parietal
	2.4766	35.78	63.5	-10.7	-1.7	90	R superior temporal
	2.3338	93.39	-16.5	-73.6	-9.7	106	L lingual
	2.2591	17.76	47.9	-18	41.6	37	R postcentral
	2.1979	121.44	18.2	-72.3	-6.4	125	R lingual
	2.1726	20.18	-27.9	-30.5	60.1	42	L postcentral
	2.1217	17.15	-32.5	-61.1	-15.5	24	L fusiform
Obese<Control	-5.2037	114.06	-53.3	-36.9	10.3	248	L superior temporal
	-5.0148	185.28	-15.6	20	-16.9	440	L lateral orbitofrontal
	-3.9973	58.85	25.6	-2.9	-34.5	146	R entorhinal
	-3.9391	186.87	56.2	-30.4	-26.9	299	R inferior temporal
	-3.6392	197.32	-39.5	22.8	20.2	364	L rostral middle frontal
	-3.3098	201.81	-11.7	-94.8	20.4	259	L lateral occipital
	-3.215	151.6	35.4	-12.5	-5.2	369	R insula
	-3.2074	63.77	-9.7	-49	29.3	141	L isthmus cingulate
	-3.1925	223.97	-35.4	44.3	-10.6	322	L pars orbitalis
	-3.1829	88.37	4.6	-58.7	21	183	R precuneus
	-2.9156	156.77	-13.2	-27.6	65.5	363	L precentral
	-2.882	47.14	12.2	-44.6	31.4	129	R isthmus cingulate
	-2.7613	44.78	-23.8	-23.5	57.8	99	L precentral
	-2.7126	70.44	-6	19	28.6	157	L caudal anterior cingulate
	-2.7032	40.29	-55.3	-0.5	35.6	105	L precentral
	-2.6532	127.39	44.4	29.7	12.4	217	R rostral middle frontal
	-2.5902	98.69	-33.3	-20.5	5.6	211	L insula
	-2.5663	74.59	-31.3	18.6	44.1	120	L caudal middle frontal
	-2.434	42.56	29.6	-17.9	68.6	99	R precentral
	-2.3584	17.63	-44.7	30.8	-1.7	31	L pars triangularis
	-2.3494	48.96	-37.9	46.1	12	70	L rostral middle frontal
	-2.3286	38.31	-39.3	21.5	40	67	L caudal middle frontal
	-2.3101	41.04	6.8	-44.5	40.6	104	R precuneus
	-2.2898	29.47	-38.8	-81.5	24.6	46	L inferior parietal
	-2.2448	4.61	-5.8	25.1	17.2	12	L caudal anterior cingulate
	-2.2244	42	-24	39.4	32.3	63	L rostral middle frontal
	-2.1218	14.09	25.1	52.7	8.9	19	R rostral middle frontal
	-2.1206	12.69	49.2	-36.2	45.8	26	R supramarginal
	-2.1086	17.33	-7	28.8	54.8	32	L superior frontal
	-2.0969	12.27	-40.9	38.8	23.1	19	L rostral middle frontal
	-2.088	4.1	28.5	12.3	-15.7	13	R insula
	-2.0466	6.19	-61.1	-17.4	-22.7	8	L middle temporal
	-2.039	4.51	-36.6	1.1	33.5	10	L caudal middle frontal
	-2.025	1.9	55.8	4.9	14.2	4	R precentral
	-2.0164	2.23	37.9	-16	-28.8	4	R fusiform

*Positive *t*-values indicate thickening and negative values indicate thinning. X/Y/Z represent Talairach Coordinates in millimeters. N vertices are vertex number at maximum. Results are shown with a threshold of $p<0.01$. Group comparisons including age as nuisance factor. L, left; R, right.

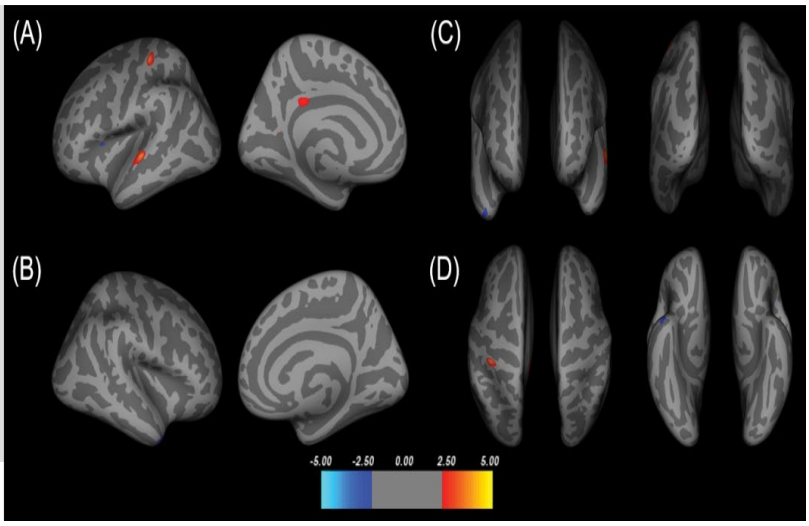

Fig.2. Group comparison of cortical surface area differences between obese patients (N=20) and healthy controls (N=17) after controlling for age. Significant threshold was set to $p<0.01$ (uncorrected). **(A)** Left lateral and medial, **(B)** Right lateral and medial, **(C)** Anterior and posterior and **(D)** Superior and inferior views. Areas are color-coded according to significance level (*t*-statistic), with blue-light blue representing thinning and red-yellow representing thickening (color scale shows –log (10) *p*-value) in obese compared to control. Light gray shading represents gyral and dark gray sulci. The quantitative measurements of each region are shown in Table 3.

Tab. 3. Demographic and clinical characteristics between obese patients and healthy controls.

	Max *t*-statistic	Size (mm^2)	X	Y	Z	N vertices	Anatomical Regions
Obese>Control	4.0068	192.82	-62.9	-17.8	-0.9	520	L superior temporal
	3.7039	155.73	-43.1	-29.5	61.8	395	L postcentral
	2.4997	69.86	-6.7	-35.5	28.9	171	L isthmus cingulate
	2.036	2.84	-14.5	-57.1	10.2	8	L precuneus
Obese<Control	-2.2619	13.8	-32	15.7	13.3	35	L pars opercularis
	-2.2145	96.29	41.5	12.6	-37.2	140	R temporal pole

*Positive *t*-values indicate thickening and negative values indicate thinning. X/Y/Z represent Talairach Coordinates in millimeters. N vertices are vertex number at maximum. Results are shown with a threshold of $p<0.01$. Group comparisons including age as nuisance factor. L, left; R, right.

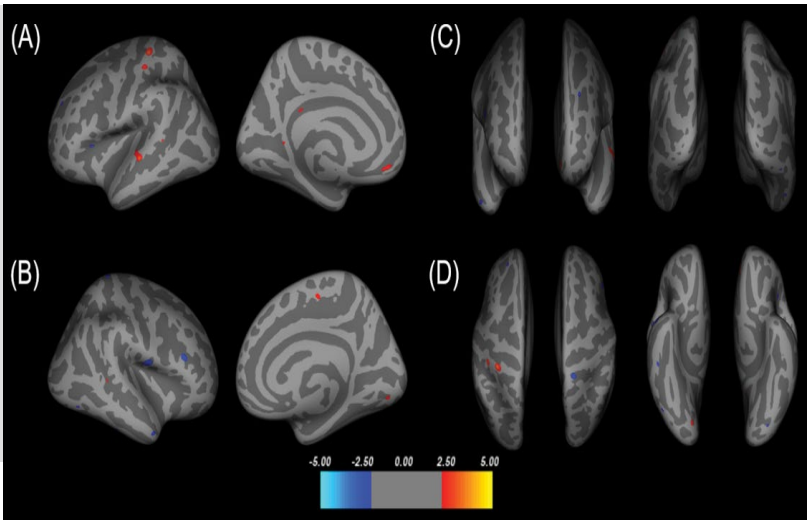

Fig.3. Group comparison of cortical volume differences between obese patients (N=20) and healthy controls (N=17) after controlling for age. Significant threshold was set to p<0.01 (uncorrected). (A) Left lateral and medial, (B) Right lateral and medial, (C) Anterior and posterior and (D) Superior and inferior views. Areas are color-coded according to significance level (t-statistic), with blue-light blue representing thinning and red-yellow representing thickening (color scale shows –log (10) p-value) in obese compared to control. Light gray shading represents gyral and dark gray sulci. The quantitative measurements of each region are shown in Table 4.

a surface-based cortical brain measurement application, we analyzed cortical thickness, cortical surface area, and cortical volume between groups. We found that several cortical regions including frontal, parietal, temporal, and occipital cortex were altered in obese patients. These results show evidence of the structural brain alterations that occur within obese subjects.

Our results show that obese patients exhibit cortical thickening in the parietal, temporal, and occipital cortex in the bilateral hemisphere. In addition, cortical thinning was found in the frontal, parietal, temporal, and occipital cortex in the bilateral hemisphere and the right insula. Larger surface area was found in obese patients compared to healthy controls in the parietal, temporal, and occipital cortex in the left hemisphere. The decreased surface area in obese patients was observed in the left frontal cortex and right temporal cortex. Increased cortical volumes in obese patients were shown in the frontal, parietal, temporal, and occipital cortex in the left hemisphere and the frontal, temporal, and occipital cortex in the right hemisphere. Moreover, decreased cortical volumes include the frontal and occipital cortex in the left hemisphere and the frontal,

Tab. 4. Clusters of significant differences in cortical volume in obese patients compared to healthy controls.

	Max *t*-statistic	Size (mm^2)	X	Y	Z	N vertices	Anatomical Regions
Obese>Control	3.4062	78.18	-38.4	-31.1	65.4	236	L postcentral
	3.2085	127.01	-58.9	-20.5	-2.3	289	L superior temporal
	2.8765	47.07	-48.4	-25.3	55.8	112	L postcentral
	2.4903	29.6	-11.3	40.2	-11.2	59	L medial orbitofrontal
	2.2869	18.9	7.6	-16.9	50.2	37	R paracentral
	2.2072	49.47	11.9	-82.5	-9.6	38	R lingual
	2.0745	6.91	-15.2	-51.5	4.6	17	L isthmus cingulate
	2.062	6.54	44.9	-41.3	2.9	23	R bankssts
	2.0511	3.53	-9	-38.6	26.5	19	L isthmus cingulate
	2.0411	4.8	-53.5	-42.1	6.1	11	L bankssts
Obese<Control	-3.0252	104.62	52.4	-7	11.1	251	R postcentral
	-2.8471	52.21	16.9	-39.1	66.7	102	R superior parietal
	-2.7637	47.93	43.5	26	19.2	90	R rostral middle frontal
	-2.2506	28.75	51.4	5.8	-30.8	44	R middle temporal
	-2.2094	10.63	-33.6	23.2	11.1	32	L pars opercularis
	-2.178	14.46	50.2	-33.4	-24.3	22	R inferior temporal
	-2.1588	27.62	-24	41.2	29.5	36	L rostral middle frontal
	-2.0874	11.82	46.1	-65.9	-11.3	14	R lateral occipital
	-2.0598	7.77	-31.9	-81.5	-12.8	10	L lateral occipital

parietal, temporal, and occipital cortex in the right hemisphere.

In the previous studies on obesity, several mixed results have been published with both increased and decreased cortical structural brain alterations. Compared to normal-weight individuals, obese patients exhibited shrink in the frontal lobes, anterior cingulate gyrus, hippocampus, and thalamus [20]. The frontal lobe is involved in the neural circuitry regulating executive function, cognition, working memory, and impulse control [21]. The parietal cortex contributes to attention to learning, encoding, consolidating, and retrieving memory [22]. A review study suggests that the temporal lobe which includes two main structures (e.g., the amygdalae and the hippocampi) has been reported in the regulation of cognitive and sentimental functions connected to learning and memory [23]. Moreover, temporal lobe plays a central role in controlling food intake and body weight. Therefore, the dysregulation of the temporal lobe can cause functional disturbance in regulating hunger.

Previous research found that increasing BMI is connected to cortical thinning in left lateral occipital cortex and right ventromedial prefrontal cortex [10]. An fMRI study showed that viewing images of food stimulates the activation of the occipital gyrus [24]. It has been demonstrated that increased body weight correlated with GMV reductions in the occipital lobe [25]. The insular cortex is composed of three cytoarchitectonic domains (e.g., anterior ventral agranular, dorsal anterior dysgranular, and posterior granular) and is identified as the primary taste and gustation cortex [26]. The anterior insular cortex is known as the primary hub for processing cognition, emotion, and sensory stimulation and is responsible for the regulating appetite and energy balance [27]. Many of these studies reporting cortical structural alteration findings vary and the consistency as well as the accuracy of results are less clear-cut.

Morphological cortical alterations are influenced by several factors. Cerebral cortex contains intermediate progenitor cells which are involved in neurogenesis and reflect laminar thickness, cortical surface area, gyral patterns [28]. The cerebral cortex also changes depending on the amount of myelination, cell size, dendritic spines, synaptic density [29], and neuronal circuits [30]. Surface area alterations of the cerebral cortex can indicate damages of white matter tracts due to atrophy of white matter fibers [31]. Taken together, changes in the cerebral cortex can indicate changes in neuron number and fundamental neuropathological support of obese patients.

Previous neuroimaging studies have shown smaller caudate volumes in adolescents with obesity [32,33]. In our previous study, we found subcortical GMV reductions in the bilateral caudate of obese groups compared to healthy controls [34]. The function of the caudate has been

linked to supporting the design and execution of strategies and behaviors requested for accomplishing complicated goals [35]. The caudate nucleus is concerned in behavioral and perceptual processes and forms networks that regulate cognitive function and emotion [36]. The caudate nucleus is also known as the key region regulating food intake through central reward circuits. It is known that improper regulation of reward circuitry in the brain induces obesity [37], it is possible that dysfunctional reward circuitry can be linked to changes in the size of the caudate nucleus. A previous positron emission tomography (PET) study documented that because obese subjects have increased sensitivity to external food stimuli, obese subjects had altered stimulus-response acquisition. The imbalance of the brain circuit and reduced cognitive control are the distinct features of obesity [38].

Obesity is associated with impaired eating control, reduced cortical gray matter volume, and poor performance cognitive evaluation [39]. Obesity itself is related to structural brain atrophy and deficiency of entire and specific regional brain volume and white matter integrity [40]. Reduced brain volume is likely due to inadequate metabolic provision. In particular, changes in gray matter or neurons can be caused by multiple factors such as insufficient energy supply particularly due to high energy demand of neurons [41], cellular change, demyelination and neuronal fiber loss with aging [42]. A study done on rats suggests that structural plasticity could be affected by the changes in dendritic morphology [43]. It is important to analyze the shape differences to identify the exact anatomical location changes. In addition, knowing regional shape differences is helpful in interpreting the results of anatomical discoveries [44]. Measuring brain volume is useful for identifying neurophysiological changes that occur due to obesity and linked to other factors such as BMI [45]. Additional studies regarding these factors will help the understanding of mechanisms between obesity and volume alterations. The mechanisms that obesity-related brain connection and volume alterations are still unclear.

Several limitations should be considered in this study. First, only male subjects were recruited. A previous study investigated gender-related differences in obesity, suggesting that men and women may have different underlying neural mechanisms [37]. Seconds, the relatively small sample size limits complex statistical analyses. A larger sample size would increase statistical significance of this study. Third, cognitive functioning was not evaluated. Cognitive function is important for changes in food intake behavior. The cognitive function is an important for variations in food intake behavior. Biezonski D, et al. [46] investigated brain circuit abnormalities and cognitive impairments in subjects with anorexia nervosa, an eating disorder associated with underweight and risky eating habits. Therefore, cognitive performance may be important in regulating food behavior in obese patients and may influence outcomes.

CONCLUSION

In conclusion, the present study demonstrates that obesity is related to structural brain abnormalities in cortical gray matter regions. Using a surface-based analysis, we observed distinct differences in cortical thickness, surface area, and volume in obese patients. The main findings of the current study show that compared to the healthy controls, obesity patients had a brain structure involved in food intake behavior controlling appetite. Therefore, we provide the evidence that cortical brain structures involved in food intake behavior are altered in obesity.

PATENTS

In conclusion, the present study demonstrates that obesity is related to structural brain abnormalities in cortical gray matter regions. Using a surface-based analysis, we observed distinct differences in cortical thickness, surface area, and volume in obese patients. The main findings of the current study show that compared to the healthy controls, obesity patients had a brain structure involved in food intake behavior controlling appetite. Therefore, we provide the evidence that cortical brain structures involved in food intake behavior are altered in obesity.

FUNDING

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INSTITUTIONAL REVIEW BOARD STATEMENT

This study protocol was approved by the University of Chungbuk Institutional Review Board (#CBNU-201506-BMSBBR-059-01), and informed consent was obtained from each patient.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Data is unavailable due to privacy or ethical restrictions.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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