Obesity THE OBESITY SOCIETY **WILEY**

Cerebral ^{18}F-fluorodeoxyglucose metabolism alteration of reward- and motivation-related regions in groups of different BMI classifications

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Abstract

Objective: This study explored the relationship between BMI and regional cerebral glucose metabolism and explicitly detected regions with significant differences in cerebral metabolism using positron emission tomography (PET)/magnetic resonance imaging in the resting state.

Methods: Corresponding PET images acquired from 220 participants were sorted into four groups according to Asian BMI standards: underweight, normal weight, overweight, and obesity. Pearson correlation coefficient analysis was performed to assess the association between BMI and standard uptake value. The regional cerebral glucose metabolism was measured in the fasted state. The PET images were analyzed using statistical parameter maps. One-way ANOVA was used to explore differences in the standard uptake value as an indicator of regional cerebral glucose metabolism.

Results: This study found that lower cerebral glucose metabolism in reward- and motivation-related regions was accompanied by more severe obesity and that regional cerebral glucose metabolism activities were negatively correlated with BMI. In addition, more severe obesity was accompanied by a larger range of areas with significant differences independent of current dietary status.

Conclusions: These findings suggest that the reward and motivation circuits may be a factor regulating energy balance and influencing the degree of obesity.

Yu-Jie Duan, Mou-Xiong Zheng, Jia-Jia Wu and Jie Ma contributed equally to this work and share first authorship.

INTRODUCTION

Obesity, a chronic low-grade inflammatory disorder [1], can produce various direct and indirect effects, leading to the dysfunction of multiple tissues and organs, including the pancreas, liver, muscle, cardiovascular system, and brain; such dysfunction can eventually result in a diverse set of health-related and life-threatening complications [2]. With the global overweight/obesity phenomenon still developing, the number of affected individuals has reached 2 billion, accounting for ∼30% of the world's population [3].

A key problem when seeking to manage obesity involves confronting the abundance of highly processed, readily available food, as regular consumption of such foods makes it challenging for individuals to maintain a healthy weight. In addition, obesity is also a major worldwide challenge in modern society and medicine.

Neuroscience can play a crucial role in analyzing the physiological and pathological mechanisms of dietary behavior regulation, thereby paving the way toward personalized treatment. Some eating behaviors beyond homeostatic regulation are pivotal to the human diet [4]. Even though the pathway beyond homeostasis is advantageous in environments with food scarcity and/or poor access, this mechanism is now a burden in a modern society where food is abundant and continuously available [5]. Craving and overconsumption, the important behavioral traits of adults with obesity, are now considered a type of neurobehavioral disorder [6].

Numerous studies have shown that the association between reward and motivation circuits and diet is related to the pathophysiology of obesity [7, 8]. In a functional magnetic resonance imaging study that examined cerebral response to olfactory food and control cues, adults with and without obesity were given food-related or non-appetite odors, respectively. In that study, food-related odors activated reward- and motivation-related regions of the brain, including the ventral striatum and anterior cingulate. The hippocampi of adults with obesity were more activated [9].

Cue-reactivity tasks indicate that food cues can lead to disordered eating behavior in adults with obesity and can specifically activate the reward and motivation circuits. In addition, previous studies focused on the cerebral glucose metabolism in the resting state. A functional magnetic resonance imaging study of adults with obesity involving the frontal-mesolimbic network found that small-world properties were disrupted and that the global integration of functional brain networks was reduced [10]. A study that explored the correlation between cerebral metabolic activity and dopamine D2 receptor availability in adults with obesity reported that hypometabolism in the orbitofrontal cortex and anterior cingulate cortex was associated with low striatal dopamine D2 receptor availability [11]. Nevertheless, it can be speculated that, even in the resting state, the motivation and reward circuits of adults with obesity may still have some dysfunction.

However, other studies investigating cerebral glucose metabolism have yielded conflicting results. A study exploring the cerebral glucose metabolic correlates with different BMI levels in older adults indicated that high BMI was associated with increased brain metabolism in the orbitofrontal cortex in women [12]. Another study reported that

Study Importance

What is already known?
- Adults with overweight/obesity consume more calories and have a more difficult time feeling satiated.
- To date, studies have demonstrated that there are differences in reward- and motivation-related brain regions in response to visual and gustatory stimuli of palatable foods as compared with adults with normal weight, but the results are controversial. In addition, there is a lack of research on cerebral glucose metabolism comparison in the relevant regions of adults with varying levels of BMI in the resting state.

What does this study add?
- Lower cerebral glucose metabolism in reward- and motivation-related regions, accompanied by more severe obesity, and regional cerebral glucose metabolism activities were negatively correlated with BMI.
- More severe obesity was accompanied by a larger range of brain regions with significant differences, independent of dietary status.

How might these results change the direction of research or the focus of clinical practice?
- These results provide a new direction for the nonsurgical treatment of obesity and a possible intervention target for the correction of brain imbalance using noninvasive electromagnetic therapeutic therapy. Furthermore, the current study lays a foundation for future research at the level of the brain network and even of the whole brain for establishing a machine learning model in the field of obesity.

global cerebral glucose metabolism in adults with severe obesity was significantly higher during hyperinsulinemic-euglycemic clamp, especially in the right caudate nucleus [13]. Therefore, cerebral reward- and motivation-related circuits that regulate food intake seem to play a central role in diet [4], and these changes may lead to differences in eating behavior and, ultimately, weight gain. There is also a lack of positron emission tomography/magnetic resonance (PET/MR) imaging studies exploring the potential neural mechanisms of obesity. PET/MR imaging can shorten the scanning time, protect the patient from exposure to additional ionizing radiation, and reduce inaccuracies and information loss during the registration process [14]. It also provides early evidence for the simultaneous detection of changes in synaptic function, neurochemistry, activity, and brain networks [15], and it is considered to be an ideal tool for in-depth studies of the human brain [16]. Furthermore, to our knowledge, no study has conducted a comprehensive and detailed examination specifically of cerebral glucose

metabolism in reward and motivation circuits to focus on the development of dysfunction in brain regions as BMI increases. Finally, there is a lack of relevant research on Asian individuals with obesity in the direction we focus on. Based on the previous views, we believe that it is necessary to conduct the current study.

The current study included healthy adults without metabolic or chronic diseases that may cause obesity or emaciation. By excluding adults with such disorders, we were able to rigorously analyze the underlying neural mechanisms of adults with different BMI levels. The current study had a relatively large sample size, which made the findings more credible. Moreover, given the unique advantages of PET/MR imaging, we applied this technology to explore differences between adults. In this way, we can better explore the relatively more realistic situation of brain activity. Finally, in the current study, all adults were sorted into four groups: underweight, normal weight, overweight, and obesity, which made the classification more robust. The present study aimed to examine the changing trend between cerebral glucose metabolism and BMI in reward- and motivation-related brain regions using ^{18}F-fluorodeoxyglucose-PET/MR imaging in the resting state. A secondary aim was to explore whether the reward- and motivation-related brain regions were different between groups of adults with underweight, overweight, or obesity compared with groups of adults with a normal weight and whether irregular cerebral glucose metabolism progressed as weight gained.

According to the relevant literature, the regions of interest (ROIs) we extracted from the reward circuit (i.e., the amygdala, nucleus accumbens, orbitofrontal cortex, and ventral pallidum) and from related regions considered to be involved in motivational processes (i.e., the anterior cingulate cortex, caudate nucleus, hippocampus, hypothalamus, insula, and prefrontal cortex) have been reported to be closely related to the reward and motivation mechanism [17–20].

METHODS

Participants

The current retrospective study, which was conducted in accordance with the Helsinki Declaration and its later amendments, was approved by the Medical Ethics Committee of Yueyang Hospital. The data for all participants were filtered through the Universal Medical Imaging Diagnostic Center, Shanghai, China, between January 2016 and December 2020. A total of 220 participants were retrospectively enrolled in the study (96 men and 124 women; mean [SD] age 49.0 [9.0] years), with 55 participants per group. The definition of BMI is considered as the weight in kilograms divided by the height in meters squared, and the classification is as follows: underweight when BMI < 18.5; normal weight when BMI = 18.5 to 22.9; overweight when BMI = 23.0-27.5; and obesity when BMI ≥ 27.5 [21]. The group of adults with normal weight was treated as the control, and the other three groups were

compared. A χ^2 test was performed to identify whether there were significant differences in sex and smoking status. One-way ANOVA was performed to identify significant differences in age, height, body weight, BMI, and blood sugar. Intergroup differences in demographic characteristics are presented in Table 1.

Inclusion criteria

Volunteers were selected if they were the following: 1) were currently without any metabolic or chronic diseases that may cause obesity or emaciation such as diabetes, cardiovascular disease, or cancer; 2) had a stable body weight for the last 3 months, were not on a diet, and were not athletes.

Exclusionary criteria

Volunteers were ineligible if they were the following: 1) had any history of psychiatric or neurological condition; 2) were currently on psychoactive drugs; 3) had a history of loss of consciousness or major head injury; and 4) were currently ill with any eating disorder that could potentially affect appetite or weight.

Image acquisition

Corresponding PET images were collected using a Biograph mMR (Siemens Healthineers, Erlangen, Germany) from all participants sorted into four groups: underweight, normal weight, overweight, and obesity. The participants were required to fast for at least 6 hours prior to their morning PET imaging session; each participant was asked to lie supine for the PET scanner, with the head placed in the vacuum cushion and fixed to reduce any head movement.

Before scanning, blood glucose levels were measured to ensure that there was no hyperglycemia (>150 mg/dL). On average, the participants received 3.7 MBq/kg of ^{18}F-fluorodeoxyglucose as a slow bolus intravenous injection. The entire scanning procedure lasted 40 to 50 minutes; PET/MR imaging data sets were acquired in five bed positions from the head to the midthigh, each taking 3 minutes. Three-dimensional image reconstruction was actualized using an attenuation-weighted ordered-subset expectation–maximization iterative reconstruction with three iterations and 21 subsets, and a Gaussian filter with a 4.0-mm full width half maximum. The slice thickness of the image was 2.03 mm, and the matrix size of the acquired image was 172×172. The resulting transverse and axial spatial resolution for the system was 4.17 mm. With a dual-echo spoiled-gradient echo sequence with Dixon fat and water separation in breath hold, the MR scans were acquired for MR-based attenuation correction, echo time 1 = 1.23 milliseconds, echo time 2 = 2.46 milliseconds, repetition time = 3.6 milliseconds, and flip angle = 10°.

TABLE 1 Intergroup differences of demographic characteristics and clinical variables

	Underweight (*n* = 55)	Normal weight (*n* = 55)	Overweight (*n* = 55)	Obesity (*n* = 55)	F/χ^2	*p* value
Male, *n* (%)	18 (32.7%)	24 (43.6%)	28 (50.9%)	26 (47.3%)	4.140	0.247
Age range (y)	31-87	45-50	40-50	31-82		
Age (y), mean ± SD	48.4 ± 11.0	46.0 ± 6.6	45.2 ± 3.1	48.5 ± 12.2	1.834	0.142
Height (cm), mean ± SD	164.1 ± 6.8	164.6 ± 7.9	166.7 ± 8.2	166.5 ± 8.8	1.530	0.208
Body weight (kg), mean ± SD	47.1 ± 4.7	58.3 ± 6.1	74.1 ± 7.5	88.6 ± 10.8	313.987	<0.001
BMI, mean ± SD	17.6 ± 1.0	21.2 ± 1.1	26.6 ± 1.2	31.9 ± 2.0	1153.067	< 0.001
Bg (mmol/L), mean ± SD	5.3 ± 1.5	5.2 ± 0.2	5.2 ± 0.2	5.5 ± 0.9	1.855	0.138
Smoking, *n* (%)	5 (9.1%)	4 (7.3%)	10 (18.2%)	8 (14.5%)	3.842	0.279

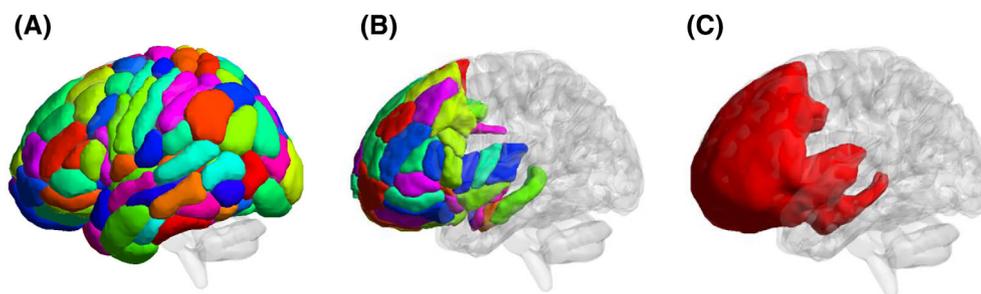Abbreviation: Bg, blood sugar.

FIGURE 1 Parcellation scheme of the human brain in the Brainnetome Atlas. (**A**) The human brain in the Brainnetome Atlas. (**B**) A full list of predefined ROIs. (**C**) An anatomical mask with a full list of predefined ROIs. ROI, region of interest [Color figure can be viewed at wileyonlinelibrary.com]

Image processing

Upon data collection, all images were preprocessed using Statistical Parametric Mapping 12 (SPM12)-based routines (http://www.fil.ion. ucl.ac.uk/spm/software/spm12) (SPM, RRID: SCR_007037) on MATLAB 2013b platform (MathWorks, Inc., Natick, Massachusetts) (MATLAB, RRID: SCR_001622). During the preprocessing operations, all PET images were eligible, and no participants were excluded from subsequent analyses.

The raw Digital Imaging and Communications in Medicine (DICOM) format of the PET images was converted into Neuroimaging Informatics Technology Initiative (NIFTI) format using ImageJ software (NIH, Bethesda, Maryland). Subsequently, each participant's image was reoriented so that the origin approximated the anterior commissure and the orientation was approximated to the Montreal Neurological Institute (MNI) space. Head movement was corrected by realigning the reconstructed PET images. The PET images were then spatially normalized to the MNI standardized space (https://brainmap. org/training/BrettTransform.html). Finally, the images were smoothed using a Gaussian kernel of 8 mm (full width at half maximum).

A mask (value one within the mask and zero out of the mask) consisted of 80 regions that were related to reward and motivation as ROIs: amygdala, nucleus accumbens, orbitofrontal cortex, pallidum, anterior cingulate cortex, caudate, putamen, hippocampus, hypothalamus, insula, and prefrontal cortex [20, 21]. The predefined ROIs were extracted from the preprocessed PET images in the standard stereotactic space. We delineated the ROIs using a template from the human Brainnetome Atlas (http://atlas.brainnetome.org), thereby avoiding the subjectivity inherent in manual ROI drawing. A mask consisting of predefined ROIs was created using image calculator fslmaths (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Fslutils; Figure 1).

Intergroup differences of standard uptake value

The raw data were preprocessed, and the mask's standard uptake value (SUV) was calculated. The SUV is an indicator of glucose metabolism and is the standard for reporting glucose metabolism in PET images. It is regarded as a common index for clinicians to quantify activity in a particular region of the image because of its good clinical value. The calculation method expresses cerebral glucose metabolism as the ratio of the mean cerebral glucose metabolism of the mask to that of the whole brain.

The SUV of each group was calculated with the BMI of the groups with underweight, normal weight, overweight, and obesity, respectively. We then investigated the relationship between BMI and regional cerebral glucose metabolism using ANOVA to calculate the difference in SUV as an indicator of regional cerebral glucose metabolism and the BMI of each group with a level of significance of 0.05, and then we conducted the least significant difference post-test between every two groups if the data were in accordance with homogeneity of variance. Two-tailed *p* < 0.05 was regarded as significant.

Correlation

The correlation between SUV and BMI was analyzed using the statistical package SPSS Statistics V24 (IBM Corp., Armonk, New York) (IBM SPSS Statistics, RRID: SCR_019096). The association between BMI and SUV was assessed using the Pearson correlation coefficient. The relationship between BMI and SUV within each classified group was also calculated using Pearson correlation. Two-tailed $p < 0.05$ was regarded as significant.

Voxel-based analysis

Within the mask, analyses were performed using SPM12 to assess the activation of each participant. One-way ANOVA was performed on the individual normalized PET images, with BMI as a between-subjects factor. The mean cerebral glucose metabolism of the whole brain was included as a covariate of no interest in the intergroup analyses. Significant clusters of the main effect of the group were reported and then binarized to a new mask. A two-sample t test was used to identify the differences in the groups with underweight, overweight, and obesity compared with the group of adults with normal weight. A statistical comparison was performed within the boundary of the mask generated for the second time. To decrease type I errors, the corrected significance level was set at $p < 0.05$, with a false discovery rate correction and a more stringent clusterwise threshold of $k = 30$ voxels as the minimal cluster size.

RESULTS

Participants

As indicated in Table 1, there were no intergroup differences in sex ($\chi^2 = 4.140$, $p = 0.247$), smoking ($\chi^2 = 3.842$, $p = 0.279$), age ($F = 1.834$, $p = 0.142$), height ($F = 1.530$, $p = 0.208$), or blood sugar level ($F = 1.855$, $p = 0.138$). There were intergroup differences in body weight ($F = 313.987$, $p < 0.001$) and BMI ($F = 1153.067$, $p < 0.001$). The participants in all groups were matched for sex and age.

Intergroup differences of SUV

As indicated in Figure 2, a trend was observed between mean regional cerebral glucose metabolism and BMI. The SUV, as an indicator of regional cerebral glucose metabolism, conformed to the tests of normality using the Shapiro–Wilk test ($p = 0.839$) and homogeneity of variance ($p = 0.272$). A significant group effect was also observed ($df = 3$, $F = 3.655$, $p = 0.013$). According to the least significant difference post-test, there was a significant difference in the comparison of groups of adults with obesity and
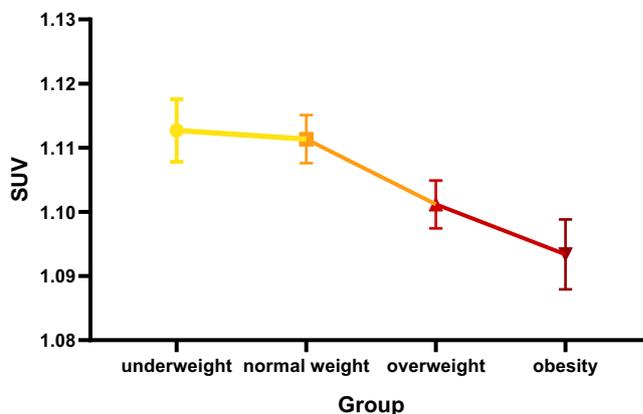

FIGURE 2 The changing trend in mean of SUV for each group (±SEM) over BMI. As BMI increased, the mean of SUV for each group decreased. SUV, standard uptake value [Color figure can be viewed at wileyonlinelibrary.com]

those with normal weight ($p = 0.013$), but no significant difference was observed in the comparison of groups of adults with underweight and normal weight and the comparison of groups of adults with overweight and normal weight ($p = 0.787$, $p = 0.079$, respectively).

Correlation

In assessing the relationship between the BMI and SUV measurements derived from ^{18}F-fluorodeoxyglucose-PET/MR imaging, BMI was observed to be correlated with SUV as indicated by the analysis of bivariate correlation with Pearson between the BMI and SUV; specifically, the results were negatively correlated ($r = -0.215$; $p = 0.001$). The relationship between BMI and SUV within each classified group was not significant.

Voxel-based analysis

Comparison of groups of adults with underweight and normal weight

No brain regions showed a significant difference in regional cerebral glucose metabolism in the underweight group compared with the normal weight group (Table 2).

Comparison of groups of adults with overweight and normal weight

The cluster size, peak t value, and peak MNI coordinates of the regions are shown in Table 2 and Figure 3. The results revealed that, compared with the group of individuals with normal weight, the group of individuals with overweight presented a significant

TABLE 2 Significant differences in the brain regions

Cluster	Cluster size	Group	Extent	Cluster centroid MNI coordinates			t value
				x	y	z	
		Underweight vs. normal weight					
		None					
		Overweight vs. normal weight					
(N)Cluster_1	44	Inferior frontal gyrus_R_6_4 (rostral area 45)	24	51	48	−6	−3.952
(N)Cluster_2	44	Superior frontal gyrus_R_7_6 (medial area 9)	22	3	45	42	−3.651
(N)Cluster_3	35	Basal ganglia_L_6_2 (globus pallidus)	35	−21	0	6	−3.904
		Obesity vs. normal weight					
(N)Cluster_1	637	Inferior frontal gyrus_L_6_1 (dorsal area 44)	79	−45	12	27	−3.717
		Insular gyrus_L_6_6 (dorsal dysgranular insula)	43	−42	0	0	−4.337
		Orbital gyrus_L_6_2 (orbital area 12/47)	19	−39	54	−15	−3.473
(N)Cluster_2	451	Superior frontal gyrus_L_7_6 (medial area 9)	73	0	42	48	−3.885
		Superior frontal gyrus_R_7_1 (medial area 8)	40	6	24	63	−3.267
		Cingulate gyrus _R_7_3 (pregenual area 32)	37	6	39	24	−3.625
(N)Cluster_3	406	Orbital gyrus_R_6_3 (lateral area 11)	85	30	33	−21	−3.576
		Middle frontal gyrus_R_7_4 (ventral area 9/46)	80	51	42	18	−3.844
		Orbital gyrus_R_6_2 (orbital area 12/47)	62	51	45	−12	−3.798
(N)Cluster_4	238	Basal ganglia_L_6_1 (ventral caudate)	79	−6	6	12	−3.683
		Orbital gyrus_L_6_5 (area 13)	56	−3	9	−15	−3.326
(N)Cluster_5	91	Superior frontal gyrus_L_7_2 (dorsolateral area 8)	40	−21	18	45	−3.023
(N)Cluster_6	46	Middle frontal gyrus_R_7_2 (inferior frontal junction)	45	36	9	33	−3.156
(N)Cluster_7	43	Middle frontal gyrus_R_7_3 (area 46)	39	30	57	6	−2.331
(N)Cluster_8	31	Hippocampus_L_2_1 (rostral hippocampus)	31	−15	−12	−24	−2.802

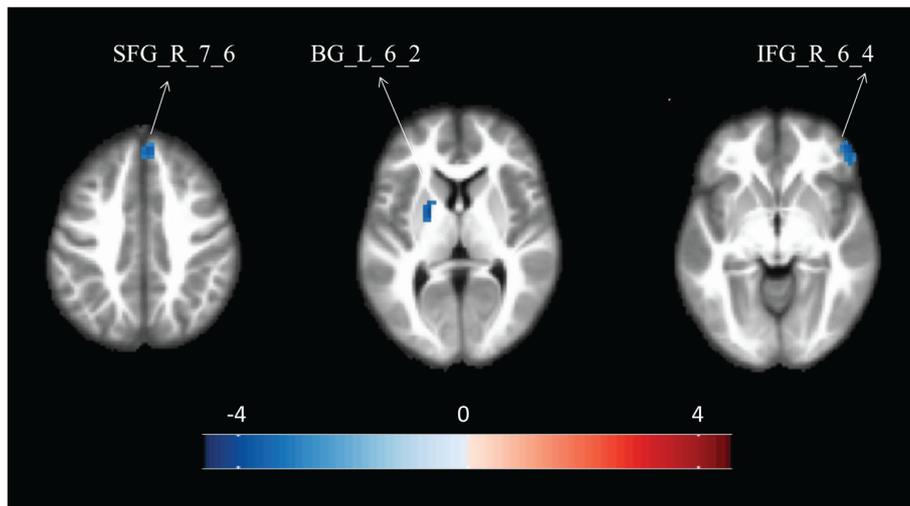Abbreviations: MNI, Montreal Neurological Institute; N, negative.

FIGURE 3 ANCOVA between the groups of adults with overweight and normal weight. BG, basal ganglia; IFG, inferior frontal gyrus; SFG, superior frontal gyrus [Color figure can be viewed at wileyonlinelibrary.com]

decrease in the inferior frontal gyrus_R_6_4 (rostral area 45), superior frontal gyrus_R_7_6 (medial area 9), and basal ganglia_L_6_2 (globus pallidus). No brain regions showed increased cerebral glucose metabolism in the group with overweight compared with the normal weight group.

Comparison of groups of adults with obesity and normal weight

The cluster size, peak t value, and peak MNI coordinates of the regions are shown in Table 2 and Figure 4. Compared with the group of adults
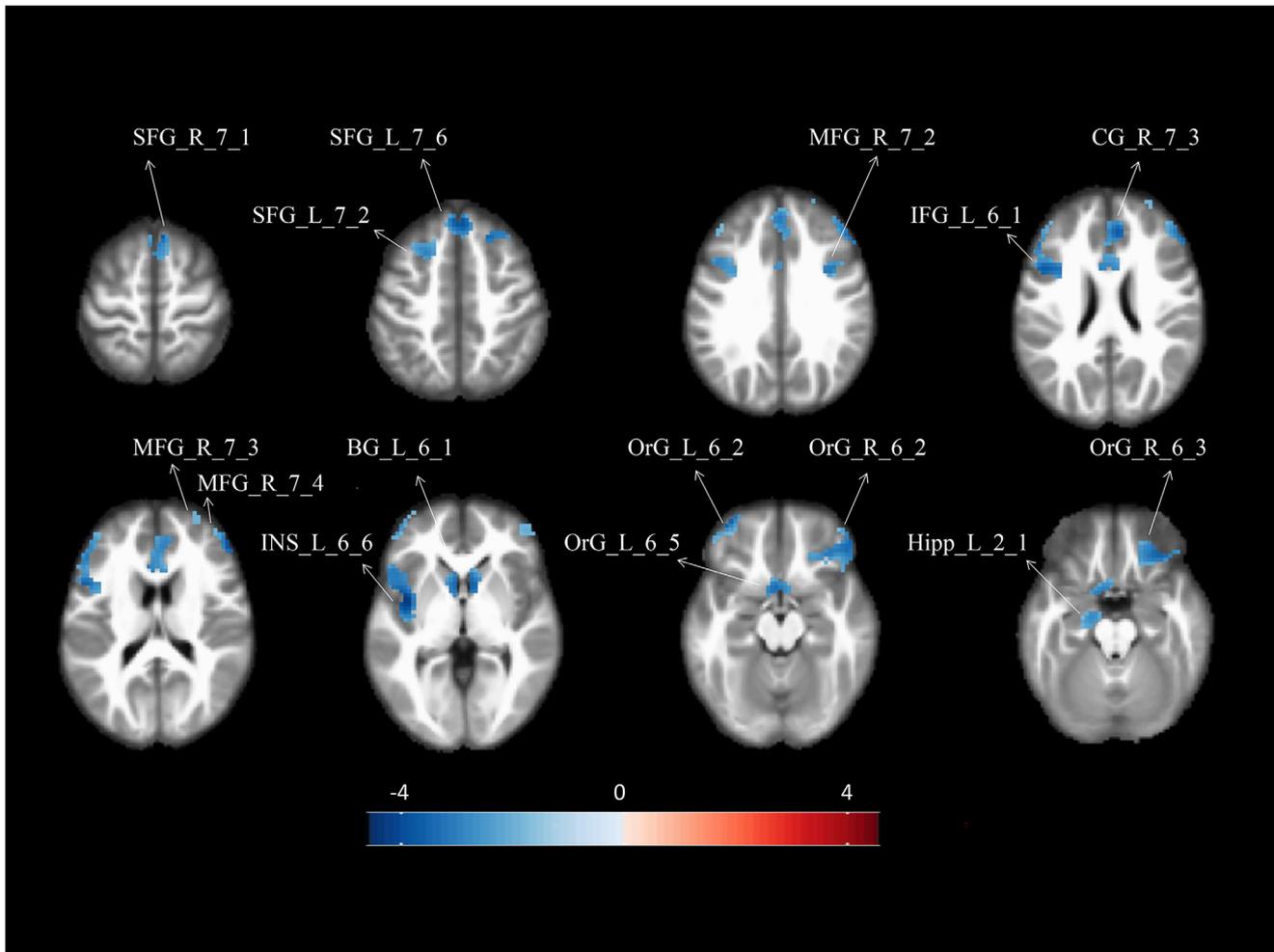
FIGURE 4 ANCOVA between the groups of adults with obesity and normal weight. BG, basal ganglia; CG, cingulate gyrus; Hipp, hippocampus; IFG, inferior frontal gyrus; INS, insular gyrus; MFG, middle frontal gyrus; OrG, orbital gyrus; SFG, superior frontal gyrus [Color figure can be viewed at wileyonlinelibrary.com]

with normal weight, the group of adults with obesity showed significantly lower cerebral glucose metabolism in the regions of inferior frontal gyrus_L_6_1 (dorsal area 44), insular gyrus_L_6_6 (dorsal dysgranular insula), orbital gyrus_L_6_2 (orbital area 12/47), superior frontal gyrus_L_7_6 (medial area 9), superior frontal gyrus_R_7_1 (medial area 8), cingulate gyrus _R_7_3 (pregenual area 32), orbital gyrus_R_6_3 (lateral area 11), middle frontal gyrus_R_7_4 (ventral area 9/46), orbital gyrus_R_6_2 (orbital area 12/47), basal ganglia_L_6_1 (ventral caudate), orbital gyrus_L_6_5 (area 13), superior frontal gyrus_L_7_2 (dorsolateral area 8), middle frontal gyrus_R_7_2 (inferior frontal junction), middle frontal gyrus_R_7_3 (area 46), and hippocampus_L_2_1 (rostral hippocampus). No brain regions showed higher cerebral glucose metabolism in the group of adults with obesity than in the normal weight group.

DISCUSSION

The current study assessed regional cerebral metabolism activity during the resting state to identify the association in reward- and motivation-related regions in adults with overweight and obesity

compared with adults with normal weight. We have shown that a decrease in regional cerebral glucose metabolism was observed in the participants with overweight and obesity. SUV, as an indicator of cerebral glucose metabolism, was negatively correlated with BMI for those adults with overweight or obesity. We observed that the higher the degree of obesity, the lower the energy metabolism of the reward and motivation circuits. These results are consistent with the previous evidence. Reductions in cerebral glucose metabolism in adults with obesity have been reported in metabolic activity in the reward- and motivation-related regions [11, 22]. Further studies have also shown that there are differences in regional cerebral metabolic activity and poor dopamine signaling in adults with substance abuse disorders and obesity compared with non-drug-using and normal weight adults [23]. Therefore, we concluded that there is an association between higher BMI and more severe eating disorders in adults with overweight or obesity. We also concluded that the cerebral glucose metabolism was decreased, so it might be difficult to reach a sufficient threshold to trigger a negative feedback system.

Moreover, we found that differences in the overweight group were mainly concentrated in reward-related regions of the brain and

that the group of adults with obesity showed more difference in brain regions associated with the reward circuit. Interestingly, we also found that most of the differences were focused on the circuit associated with motivation in the group of adults with obesity, which was not seen in the group with overweight. The regional range of differences in cerebral glucose metabolism increased with an increase in BMI, which was confirmed by discrepancies in the reward- and motivation-related brain regions in the current study. Therefore, we concluded that, as BMI increases, the irregular energy metabolism in reward and motivation circuits further increases, accompanied by a greater degree of eating disorders, contributing to long-term food seeking and intake and exhibiting less inhibitory control. In addition, because of the cerebral metabolic activity described in the resting state, excessive food-seeking in the brain is not necessarily constrained by a particular feeding state, so it is reasonable to think that this difference occurs profoundly in the brain, not just when food is seen or eaten. Physiological differences in the cerebral cortex may be closely related to the formation of differences in adults with obesity.

Food consumption depends on the interaction between homeostatic regulation and reward. Pertinent cortical and subcortical processing involves higher-order processes for acquiring pleasure [4]. Therefore, it has been hypothesized that food intake disorders in adults with obesity are a response to the dysfunctional mesolimbic reward system, which leads to overeating or ingestion of highly palatable and highly processed foods to compensate for this deficiency [24, 25]. Prior neuroimaging studies have also shown that adults with and without eating disorders responded differently to reward cues/receptivity [26, 27]. Accordingly, this is in line with research scholars' suggestions for compensatory overconsumption. Simply put, when the reward regulation and cognitive feedback system are unbalanced in response to external environmental stimuli (food and exercise), adults would try to stimulate the dull reward circuits by way of larger stimuli.

Furthermore, with the increase in BMI in our study, there were more motivation-related brain regions with a significant difference in addition to the increase in metabolic activity differences. This result represents a reflection of dysfunction in the self-regulation process in adults with obesity, and, thus, the lack of inhibition control over overeating in this population contributes to more severe obesity. We considered that the disruption in emotion regulation, self-control, and decision-making are important foundations for uncontrollable continuous eating to exacerbate further obesity. A relevant study showed that adults with overweight and obesity have higher impulsivity and insufficient functioning to process response inhibition [28]. A common characteristic of adults with obesity is excessive, compulsive overeating behavior, which is considered a manifestation of potential psychopathology [29]. For example, adults with obesity exhibit behavioral inhibition deficits and an immediate reward bias toward food rewards compared with adults with underweight [30]. In cases in which negative consequences are known, adults with obesity have difficulty correcting or inhibiting their own behavior. The lower motivational significance of negative behaviors toward overeating may lead to poorer decision making, as

adults with obesity behave in the delayed discount paradigm [31–33] and reduce their moderating effect on eating behaviors [34]. Furthermore, there is growing evidence that this process of compulsive behavior may function in the pathogenesis of overconsumption in adults with obesity [35].

Our findings highlight the role of reward and motivation circuits in the obesity process, and the results are consistent with our conjecture. However, in the present study, we were unable to conclusively determine the specific causes of the differences associated with reward and motivation. Whether this is due to the underdevelopment of innate reward and motivation circuits or insensitivity to the relevant regions due to overeating remains unexplained. The reward deficit theory of obesity suggests that it is precisely this reason that causes people to be affected differently by appetizing foods in the same dietary environment [24]. Genetics are generally considered to play an extremely important role in the occurrence and development of obesity. Several studies on obesity-related genes have demonstrated the role of genes in regulating food rewards. As an example, the A1 allele of the TaqIA restriction fragment length polymorphism was reported to be related to the dysfunctional dopamine signaling pathway in the striatum [36]. However, another theory is that the reduced response to food intake is due to the process of regularly eating pleasurable foods. This view is supported by animal models. High-fat diet-fed mice showed compulsive seeking of appetitive stimuli [37]. Another study reported gray matter remodeling in brain regions related to the reward circuits after weight loss [38]. We speculate that innate vulnerability increases the risk of uncontrolled eating. In addition, excessive intake of palatable foods subsequently causes blunted reward and motivation circuits, making it challenging to reach reward thresholds and inhibitory control difficulties. These possibly contribute to the eventual development of obesity. In addition, we consider that the causes of obesity are complex, so it is possible that the causes in different adults are not the same. The current research results are still controversial; therefore, the relevant results need to be further proved, and the mechanism of the brain's reward and motivation circuits in obesity needs to be studied in greater depth.⭕

CONFLICT OF INTEREST

The authors declared no conflict of interest.

CLINICAL TRIAL REGISTRATION

Chinese Clinical Trial Registry ChiCTR2000041020.

DATA AVAILABILITY STATEMENT

Individual deidentified data supporting the conclusions of this article will be made available by the authors without undue reservation.

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