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ORIGINAL RESEARCH

Cerebral glucose metabolism differs according to future weight change

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Abstract

The brain is known to play a central role in controlling the desire to eat. We aimed to evaluate the brain regions that might have a long-term effect on eating behavior and weight changes. We utilized the data of cognitively normal subjects who are examined by several neurologic tests, and followed-up for 36 months from Alzheimer's Disease Neuroimaging Initiative (ADNI) database, and investigated to search the brain regions that are associated with future weight change. The weight of each subject was measured on each visit at baseline (W0), 36 (W36) months after brain ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET). Percentage (%) change of weight was calculated as follows: [(W36–W0)/W0]*100. We classified each subject's change into one of three categories: weight loss, stable, and weight gain. Dynamic 3-dimensional scans of six 5-min frames were acquired 30 mins after injection of 185 MBq of FDG. Image analysis was done using Statistical Parametric Mapping 12. Ninety-six subjects were included in this study (male 54, female 42). Subjects with future weight gain showed hypometabolism in left cerebellum compared with those with future weight loss & stable. Percentage change of weight was positively associated with brain metabolism in right insula, and right caudate nucleus. In conclusion, subjects with future weight gain showed hypometabolism in left cerebellum, and percentage change of weight was positively associated with brain metabolism in right insula, and right caudate nucleus. This study raises the possibility that the brain glucose metabolism precedes the future weight change.

Keywords Cerebral cortex · Fluorodeoxyglucose F18 · Body weight

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Introduction

Worldwide, the number of obese subjects is constantly increasing and is one of the major problems of public health in the twenty-first century. Obesity is not only a cosmetic concern, but it can induce a series of chronic metabolic disease, such as cardiovascular disease, diabetes, dyslipidemia, hypertension and nonalcoholic fatty liver (Eisenstein et al. 2015; Flegal et al. 1998). Thus, it is importance to understand the neural mechanism underlying the behavioral regulation of energy balance.

Obesity results from an energy imbalance, which is an energy intake chronically exceeding energy expenditure (Pak et al. 2018). The brain is known to play a central role in controlling the desire to eat (Pak et al. 2018). Although several factors contribute to weight gain, motivation and reward is considered central components in regulating eating behavior. There is a neuroanatomical correlation between taste and olfaction, which are known as a primary reinforcers of food intake (Small et al. 1999; Zald and Pardo 2000; Kinomura et al. 1994; Small et al. 2001). Using positron emission tomography (PET), increased activity of middle insula was observed in response to taste stimulation of hungry obese subjects (Tataranni and DelParigi 2003). In addition, cerebellum play a role not only in controlling and coordinating motor movements, but also helping to generate an integrated and coordinated somatic-visceral response in feeding behavior (Zhu and Wang 2008). Functional neuroimaging techniques, such as PET and functional magnetic resonance imaging (fMRI) enables to search for brain regions involved in the regulation of eating behaviors and in the pathophysiology of obesity (Tataranni and DelParigi 2003). Stimulation with taste and smell has been shown that limbic regions such as the amygdala, insula, orbitofrontal cortex, cingulate cortex and basal forebrain have a role in eating behavior (Zatorre et al. 1992; Tataranni and DelParigi 2003).

Although obesity comes from a chronic state of energy imbalance, previous studies have focused on investigating brain regions involved in food stimulus. Therefore, we aimed to evaluate the brain regions that might have a long-term effect on eating behavior and weight changes. In this study, we downloaded the data of cognitively normal subjects who are examined by several neurologic tests, and followed-up for 36 months from Alzheimer's Disease Neuroimaging Initiative (ADNI) database, and investigated to search the brain regions that are associated with future weight change.

Materials and methods

Subjects

Data used in the preparation of this article were obtained from ADNI database. Cognitively normal subjects from ADNI database without signs of depression, mild cognitive impairment, or dementia were included in this study. Subjects

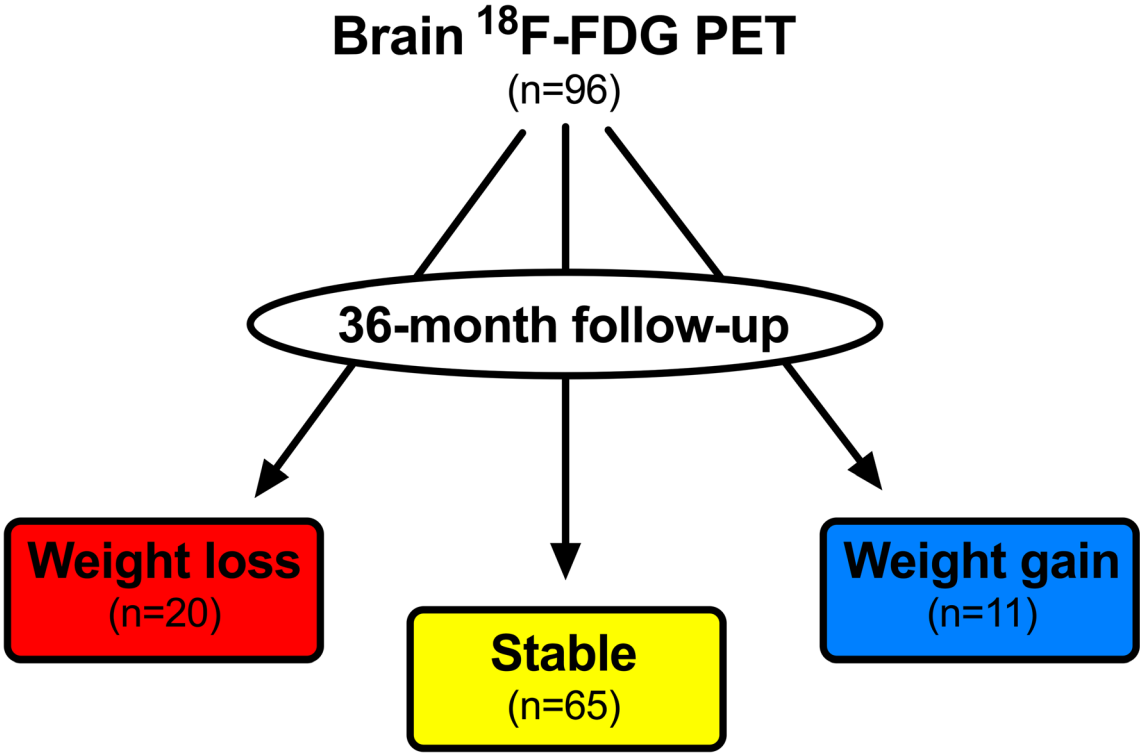

Fig. 1 Study protocol

Table 1 Subjects' characteristics

	Weight loss & Stable ($n = 85$)	Weight gain ($n = 11$)	p
Sex (Male/Female)	49/36	5/6	0.4431
Age	75.3 ± 5.6	74.2 ± 5.2	0.4375
W0 (kg)	75.9 ± 14	73.1 ± 11.5	0.4242
W36 (kg)	73.7 ± 13.5	81.8 ± 11.4	0.0739
Percentage change of weight (%)	−2.8 ± 4.5	12.1 ± 4.1	<0.0001
ADAS11	6.5 ± 3.0	6.8 ± 2.5	0.5257
MMSE	29.0 ± 1.0	28.8 ± 2.0	0.3239

*ADAS, Alzheimer's Disease Assessment Scale-Cog test; MMSE, The Mini Mental State Examination

underwent brain ^{18}F-Fluorodeoxyglucose (FDG) PET at baseline, and followed up for 36 months. In addition, neurologic tests of Alzheimer's Disease Assessment Scale-Cog test (ADAS11), and the Mini Mental State Examination (MMSE) were done for each subject. Detailed information on participant recruitment, inclusion/exclusion criteria are provided on the ADNI website (http://adni.loni.usc.edu/). The study was approved by local institutional review boards of all participating sites, and written informed consent was obtained. Study protocols are shown in Fig. 1.

Weight change

The weight of each subject was measured on each visit at baseline (W0), 36 (W36) months after brain ^{18}F-FDG PET. Percentage change of weight (%) was calculated as follows: [(W36–W0)/W0]*100. We classified each subject's change into one of three categories: weight loss (decrease of 5% or more since the baseline measurement), stable (change of less than 5% since the baseline measurement), and weight gain (increase of 5% or more since the baseline measurement) .

Image acquisition and analysis

Dynamic 3-dimensional scans of six 5-min frames were acquired 30 mins after injection of 185 MBq of FDG. Data were spatially normalized in Montreal Neurological Institute (MNI) atlas, and smoothed with 8 mm FWHM. A two-sample unpaired t-test was used to compare subjects of weight gain and others with age and sex as covariates. Regression analysis was done between cerebral glucose metabolism (CMRglu) and percentage change of weight with age and sex as covariates in all subjects. Results were displayed at a significance threshold of uncorrected $p < 0.001$ and minimum cluster size of 50 contiguous voxels. Image analysis was done using Statistical Parametric Mapping 12 (https://www.fil.ion.ucl.ac.uk/spm/, Wellcome Trust Centre for Neuroimaging, UK) implemented on Matlab R2016b (MathWorks, USA). Coordinates of local maxima were converted from MNI atlas to Talairach space, and labeled using the Talairach Client v2.4.3 (http://www.talairach.org/). Region-of-interest (ROI)-based analysis was done to validate the association between the percentage change of weight and standardized uptake value ratio (SUVR) of ROI. ROIs of right insula and right caudate nucleus from automated anatomical labeling (AAL) template were defined, and the mean uptake from each ROI was extracted. The mean uptake of each ROI was scaled to the global mean value of each individual, and defined as SUVR.

Statistical analysis

Normality was assessed using the D'Agostino & Pearson normality test. Mann-Whitney test was used to compare subjects of weight gain with others. Regression analysis was used to examine the relationship between percentage change of weight and SUVR of each ROI after adjustment with age and sex. Statistical analysis was done by Prism (v7.0d, GraphPad Software Inc., La Jolla, CA, USA), and MedCalc software package (v12.6.0.0, MedCalc, Mariakerke, Belgium).

Table 2 Comparison between subjects with future weight loss & stable vs weight gain

	Cluster extent (voxels)	Structure	Talairach coordinates			Brodmann area	p (uncorrected)	T
			x	y	z			
Weight loss & Stable > Weight gain	68	Cerebellum, left	−23.7	−43.6	−18.0	*	<0.001	3.43
			−29.7	−38.2	−26.6	*	0.001	3.39
Weight loss & Stable < Weight gain	*							

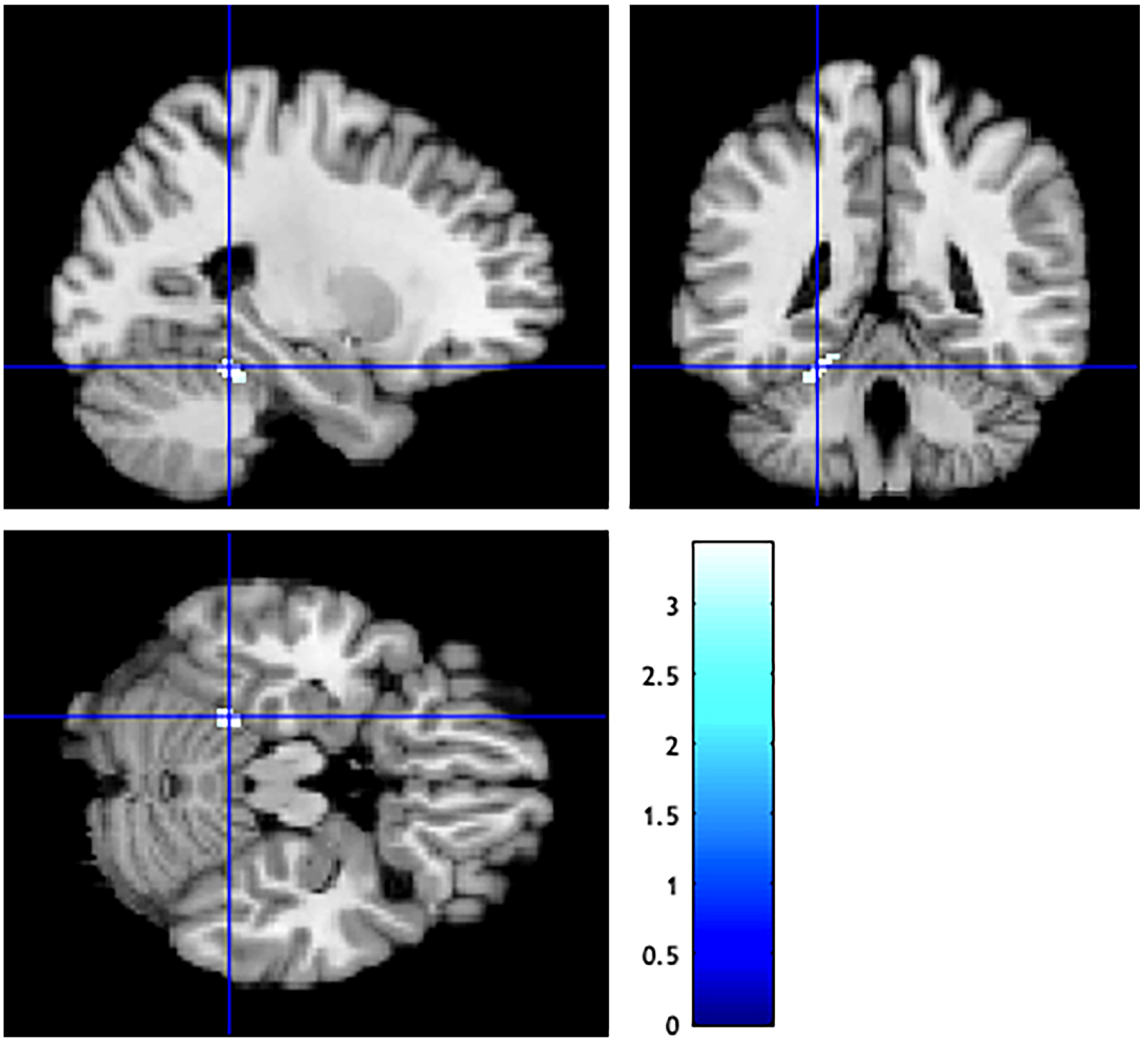

Fig. 2 Areas of hypometabolism in subjects with future weight gain: left cerebellum

Results

Ninety-six subjects were included in this study (male 54, female 42). The mean age was 75.1 ± 5.6 years. The mean W0, W36, and percentage change of weight were 75.6 ± 13.7, 74.6 ± 13.5 kg, and − 1.1 ± 6.5%, respectively. After 36 months follow-up, 11 subjects (11.5%) gained the weight, while 85 lost their weight or showed the stable weight change (88.5%). Sex ($p = 0.4431$), age ($p = 0.4375$), W0 ($p = 0.4242$), and W36 ($p = 0.0739$) were not different between subjects of weight gain and others. In addition, neurologic tests of ADAS11 ($p = 0.5257$), and MMSE ($p = 0.3239$) did not show any significant difference between subjects of weight gain and others (Table 1).

Subjects with future weight gain showed hypometabolism in left cerebellum compared with those with future weight loss & stable (x − 23.7; y − 43.6; z − 18.0, x − 29.7; y − 38.2; z − 26.6). No brain areas showed hypermetabolism in subjects with future weight gain after comparison with others (Table 2, Fig. 2). Percentage change of weight was positively associated with CMRglu in right insula (× 39.6; y − 21.8; z − 9.0, $p < 0.001$),

Table 3 Regression with Percentage change of weight

	Cluster extent (voxels)	Structure	Talairach coordinates			Brodmann area	p (uncorrected)	T
			x	y	z			
Positive	67	Insula, right	39.6	−21.8	−9.0	13	<0.001	3.42
		Caudate, right	37.6	−33.0	0	Caudate	0.001	3.40
Negative	*							

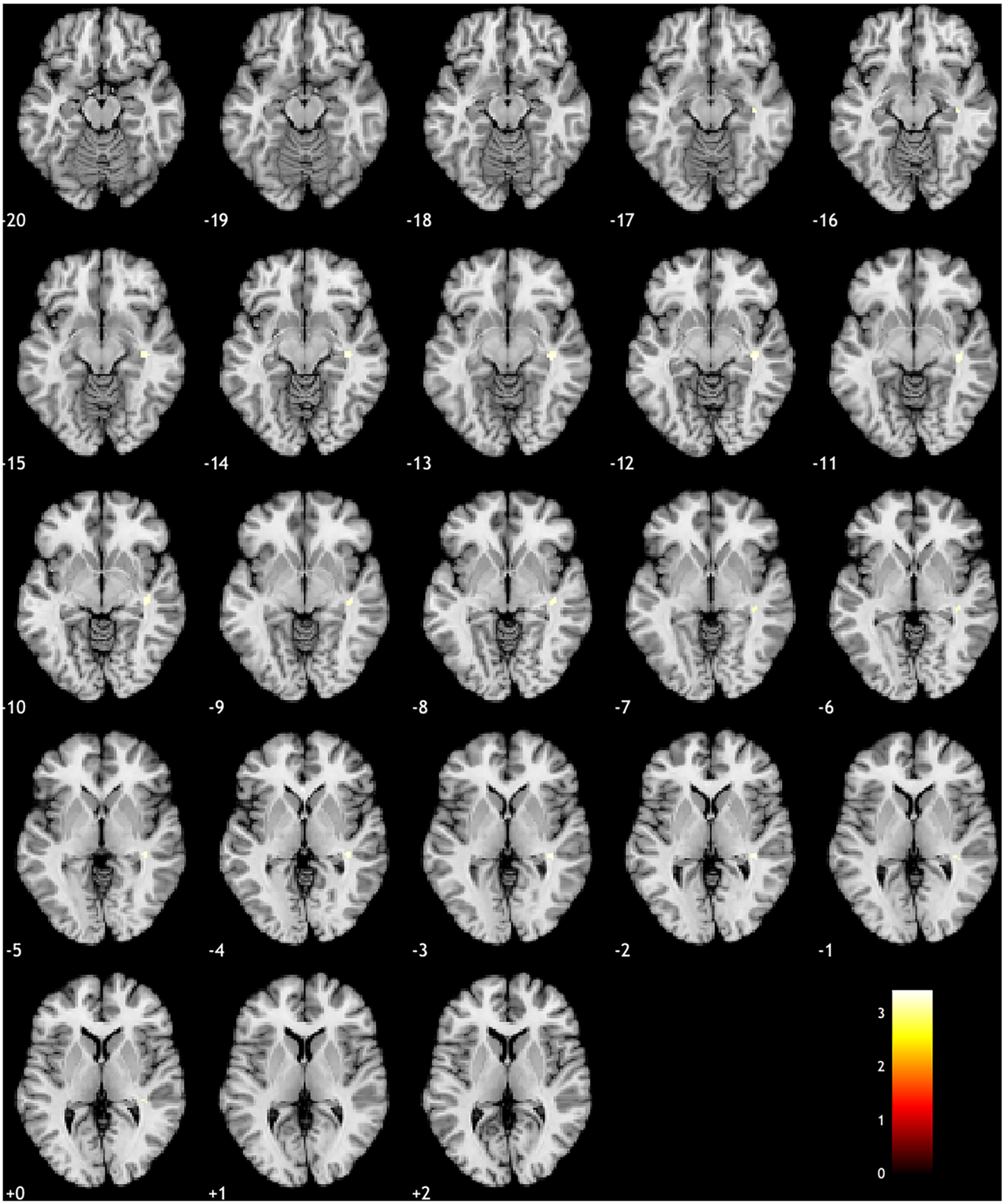

Fig. 3 Areas of positive correlation with percentage change of weight: right insula and right caudate nucleus

and right caudate nucleus (× 37.6; y − 33.0; z 0, $p = 0.001$). No significant area showed the negative association with percentage change of weight (Table 3, Fig. 3). In ROI-based analysis, SUVR of right insula was associated with percentage change of weight ($p = 0.0449$, coefficient 0.001284), however, that of right caudate nucleus was not ($p = 0.1280$, coefficient 0.002825) (Fig. 4).

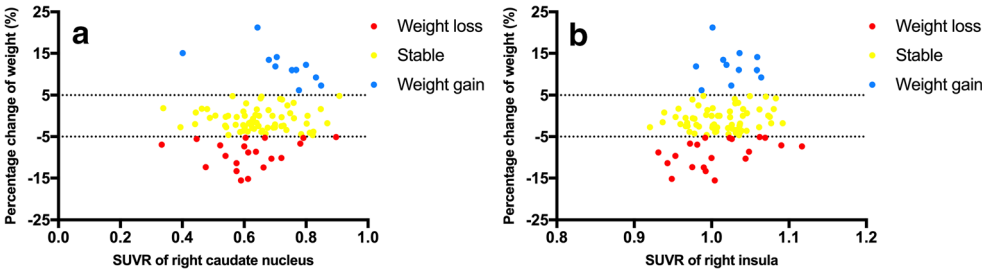

Fig. 4 Scatter plot of percentage change of weight and SUVR of right insula and right caudate nucleus

Discussion

In this study, the more future weight gain subjects had, the more activities in the right insula and right caudate were observed. In addition, subjects with future weight gain showed significantly decreased glucose metabolism in the cerebellum. However, there was no difference in the results of neurological tests. It provides the evidence that subjects who gain the weight in the future show the difference in baseline cerebral glucose metabolism before the weight changes.

Recently, neuroimaging studies using PET and fMRI have investigated the neuroanatomical correlation of various eating behaviors. Previous studies showed information about brain regions that are associated with the sensation of taste (Kinomura et al. 1994; Small et al. 1999, 2001), states of hunger (LaBar et al. 2001), distention stimuli of the proximal stomach (Vandenbergh et al. 2005), emotion regulation in feeding behavior (Steward et al. 2016), and olfactory stimuli (Zald and Pardo 1997, 2000). However, these studies did not explain the relationship between CMRglu and weight changes over time. Therefore, in this study we aimed to identify brain regions that preceded weight changes.

The insular cortex in the human brain lies deep within the lateral sulcus, almost surrounded by the groove of the circular sulcus and covered by the insular opercula. The insular cortex is known a variety of functions related to the integration of the autonomic response with feeding behaviors and response to food cues and stimuli. Especially, insular activation is correlated with the desire to eat as well as prospective food intake (Cornier et al. 2009). Insular cortex neurons are modulated during feeding behavior and can regulate feeding behaviors (Oliveira-Maia et al. 2012). Insular cortex of lean subjects was different from that of overweight subjects, which might explain the role of insular cortex as the regulation of body weight (Small 2009; Del Parigi et al. 2002). In addition, the left hemisphere of human brain is related with the specialization for language, and the right hemisphere has predominance for taste (Small et al. 1999). The caudate nucleus, especially the dorsal area, have been shown to play critical roles in ingestive behaviors, which significantly influences weight control (Nakamura and Ikuta 2017). This study showed that the activation of insula and caudate nucleus precedes the future weight gain.

Previous studies have shown that the cerebellum plays a critical role in motor control, learning (McCormick and Thompson 1984) and reflex adaptation (Robinson 1976). Although the exact mechanisms underlying the cerebellar regulation of food intake is still unclear, a few studies demonstrated that it is related to eating behaviors and weight change (Zhu and Wang 2008; Colombel et al. 2002). The cerebellum was found activated in response to gustatory or olfactory stimulation (Cerf-Ducastel and Murphy 2001; Sobel et al. 1998). And viewing of high-calorie instead of low-calorie foods yielded significant activation within the cerebellum (Killgore et al. 2003). Thus, the activated cerebellar regions may be directly involved in the integration of sensory and visceral signals, as well as affective activity associated with appetite and taste or olfaction during feeding. Gautier et al. reported that satiation in both obese and lean subjects produced significant decreases in regional cerebral blood flow (rCBF) in the cerebellum (Gautier et al. 2000, 2001). Moreover, rCBF decrease in the cerebellum were significantly greater in obese men than in lean men.

This study indicates that percentage change of weight was positively associated with CMRglu in right insula, which is consistent with its role as a primary gustatory cortex. These results suggest that more activation of insula drives subjects to eat more, resulting in weight gain.

There are several limitations in this study. First, our sample size was relatively small, which limits dividing subjects into training and validation sets. Second, as we adopted the threshold of uncorrected $p < 0.001$ with 50 voxels of cluster in voxel-based analysis, and $p < 0.05$ in ROI-based analysis, false positive results are main concerns and limitation of this study. Therefore, we will proceed prospective studies to investigate the association between cerebral glucose metabolism and future weight change to validate this result. Third, ADNI database was not primarily designed to determine the association between baseline brain glucose metabolism and future weight change. The primary goal of the ADNI is a prospective study to measure the progression of mild cognitive impairment and early Alzheimer's dementia. Thus, the participants in this study are old.

In conclusion, subjects with future weight gain showed hypometabolism in left cerebellum, and percentage change of weight was positively associated with CMRglu in right insula, and right caudate nucleus. This study raises the possibility that the change of brain glucose metabolism precedes the future weight change, drives to eat more.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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