의학박사 학위논문

Obesity mechanism after hypothalamic damage: Cohort analysis of neuroimaging, psychological, cognitive, and clinical phenotyping data

시상하부 비만의 메커니즘에 대한 다차원 표현형 분석

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이미우

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Graduate School of Medicine
Seoul National University
Biomedical Sciences Major

Miwoo Lee

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위 원 장

부위원장

위 원

위 원

위 원

Abstract

Miwoo Lee
Biomedical Sciences Major
Graduate School of Medicine
Seoul National University

Objective: The hypothalamus regulates energy homeostasis, and its damage results in severe obesity. I aimed to develop a novel method of hypothalamic volume measurement and investigate the multifaceted characteristics of hypothalamic obesity through two studies for craniopharyngioma patients' cohort.

Methods: (Study 1) I included 78 patients with adult-onset CP who underwent surgical resection. Postoperative HT volume was measured using T1- and T2-weighted magnetic resonance imaging (MRI) with a slice thickness of 3 mm, and corrected for temporal lobe volume. (Study 2) I performed multidimensional analyses of brain structure/function and psychological and behavioral phenotypes in 29 CP patients (craniopharyngioma) and 31 controls (non-functional pituitary adenoma). Patients underwent structural and functional magnetic resonance imaging and completed self-reports and cognitive tasks.

Results: (Study 1) The corrected postoperative HT volume measured using T1- and T2-weighted images was significantly correlated. However, HT volume was overestimated using T1-weighted images owing to obscured MR signals of the thalamus in patients with severe HT damage. Therefore, I used T2-weighted images to evaluate their clinical implications in 72 patients with available medical data. Postoperative HT volume was negatively associated with preoperative body weight and preoperative tumor volume. In the subgroup analysis of CP patients who underwent primary surgery (n=56), pre- and postoperative body weights were negatively associated with HT volume. (Study 2) The CP patients showed significantly higher postoperative weight gain than controls. The CP group also showed significant hypothalamic damage and lower neural activation in the left caudate nucleus in response to food images. The CP group had significantly higher food inattention, lower satiety, and higher restrained eating behavior. Within the CP group, eating behavior scores and attention related features was associated with activation in the food cognition and reward areas such as fusiform gyrus, orbitofrontal cortex and amygdala.

Conclusion: Adult-onset CP patients showed negative associations between postoperative HT volume and preoperative/postoperative

body weight. Various phenotyping results suggest that hypothalamic damage contributes to weight gain by altering the brain response, attention, satiety, and eating behaviors. These studies propose novel neuro-psycho-behavioral mechanisms targeted for patients with hypothalamic obesity.

Keyword: Obesity, fMRI, Attention, Craniopharyngioma, Hypothalamic obesity

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List of Abbreviation

AVOVA: Analysis of variance

CP: Craniopharyngioma

fMRI: Functional magnetic resonance imaging

HD: Hypothalamic damage

HO: Hypothalamic obesity

HT: Hypothalamus

LSD: Least significant difference

MRI: Magnetic resonance imaging

MPRAGE: Magnetization prepared rapid gradient echo

NFPA: Non-functioning pituitary adenoma

PACS: Picture archiving and communication system

ROI: Region of interest

T: Tesla

TE: Times to echo

TR: Times to repeat

Introduction

Hypothalamic damage and obesity

The hypothalamus is the primary site for the regulation of energy homeostasis. Given the critical function of the hypothalamus, damage to the hypothalamus may lead to several detrimental effects. For example, hypothalamic obesity (HO) is a form of obesity caused by structural damage in the hypothalamus [1–3]. HO occurs in approximately half of the patients who have undergone surgical removal of tumors near the hypothalamus, such as craniopharyngioma. Hypothalamic obesity is the most concerning complication and is often developed despite the adequate replacement of pituitary hormone deficiencies [3, 4]. Moreover, it is associated with severe sequelae and negatively impacts the quality of life [5].

Hypothalamic injury, particularly in the regions that regulate appetite and balance energy metabolism, is considered to play a major role in the development of postoperative weight gain in CP patients [4]. Patients with HO commonly exhibit hyperphagia, reduced energy expenditure, low resting metabolic rate, and low physical activity [5–7]. Dysregulation of circadian rhythm and

reduced sympathetic tone are also suggested as possible factors for the development of HO [8, 9].

Structural damage of hypothalamus

Based on the pathophysiological mechanisms associated with HO, the occurrence and degree of this condition inevitably depend on the damaged hypothalamic region. The ventromedial hypothalamus (HT) is the most crucial territory for the development of HO and includes two major nuclei, the arcuate nucleus and paraventricular nucleus [10]. The arcuate nucleus regulates appetite, in which agouti related protein and neuropeptide Y increases appetite, whereas proopiomelanocortin neurons decrease appetite [11]. Thus, hypothalamic injury, particularly involving the ventromedial hypothalamus, can lead to dysregulation of appetite, which contributes to the development of HO. Disruption of the posterior hypothalamic nuclei, including the dorsomedial nucleus, ventromedial nucleus, and dorsal hypothalamic area nucleus, has been suggested as a crucial factor for the occurrence of HO. Rather than regulating appetite, these nuclei mainly mediate leptin-induced energy expenditure and sympathetic activation related to locomotion and thermogenesis [12].

To date, several studies have attempted to analyze

hypothalamic damage in CP patients to predict HO. Roth et al. developed a novel hypothalamic lesion scoring system that covers hypothalamic areas critical to energy homeostasis[13]. This approach scores the affected lesions using anatomical landmarks in both sagittal and coronal views, not measuring HT volume. The study showed that although anterior and medial hypothalamic injuries were commonly observed in patients with HO, the most robust weight gain was observed in patients with disruptions in the posterior hypothalamus. However, the sample size of the study was small (41 CP patients) and all patients had childhood-onset CP. Fjalldal et al. used a manual segmentation method to measure HT volume involving 3T magnetic resonance imaging (MRI) and showed negative associations of HT volume with fat mass and leptin [14]. However, this study also included only patients with childhood onset CP, with a median age of 22 years after the initial diagnosis.

Abnormal eating behavior and psychologies

Previous studies have shown that hypothalamic obesity is associated with abnormal eating behavior and psychologies [6-8]. For example, pathological eating behaviors (e.g., higher eating restraint scores, snacking, night eating, and altered attitudes toward food) have been

reported among patients with hypothalamic obesity [7, 9, 15]. Psychological abnormalities (e.g., sleepiness, mood, and personality) have been reported to be the leading cause of abnormal eating behaviors [15]. However, these studies were conducted to examine pathological eating behaviors and psychological characteristics independently. This lack of integration between behavioral and psychological characteristics may limit the comprehensive and integrated understanding of hypothalamic obesity. (Figure 1)

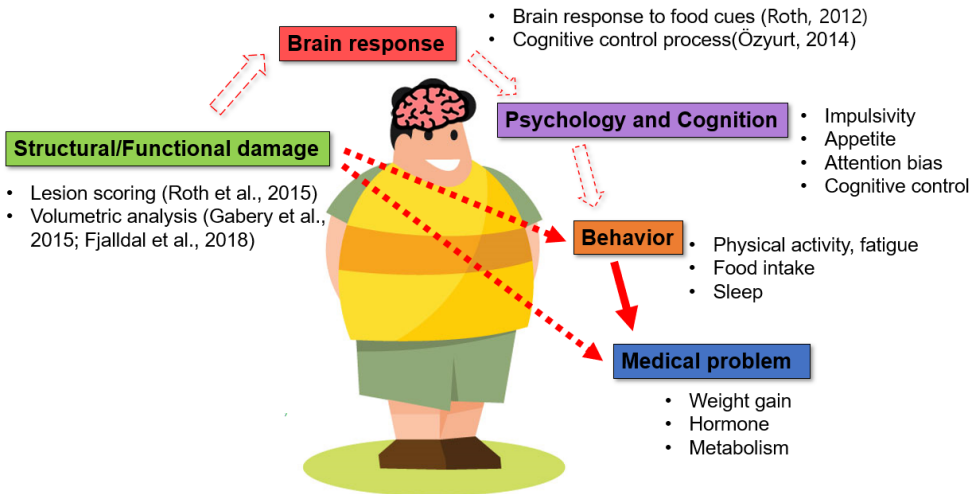

Figure 1. Partial studies of hypothalamic obesity to date

Research purpose

Study 1:

I aimed to evaluate hypothalamic damage in adult CP patients using HT volume measurements. To better evaluate hypothalamic damage, I first developed a method for HT volume measurements using T2-weighted MR images and compared its performance with that of T1-weighted MR images. Based on HT volume data using T2-weighted MR images, I further analyzed the associations between the postoperative HT volume and clinical parameters in adult CP patients.

Study 2:

Furthermore, the direct mechanism linking hypothalamic damage to abnormal eating behavior is thought to involve neural circuit malfunctions related to eating [5, 16]. This suggests that examinations of neural function as well as psychological/behavioral assessments in patients with hypothalamic obesity may be required. Indeed, a few functional magnetic resonance imaging (fMRI) studies have investigated altered brain activation in patients with hypothalamic obesity [17, 18]. However, these studies did not focus on food or obesity-related fMRI mechanisms of hypothalamic obesity through multiple-dimension analyses, including hypothalamic structural damage, whole-brain response to food, food-related cognition, food-related psychology, eating behaviors, and weight gain. I hypothesized that hypothalamic damage could alter brain functions for satiety, food attention, and inhibitory control, which could result in unhealthy behavior and weight gain.

Methods

Study 1

Development of individually tailored HT volumetric method

I included 78 (42 male and 36 female) adult-onset CP patients (aged ≥ 18 years) who underwent surgical resection at Seoul National University Hospital (SNUH) between 2012 and 2017. Two independent raters manually segmented the HT area using the freehand option of the SNUH PACS(Picture Archiving and Communication System) program (INFINITT Co. Ltd, South Korea). Rater 1 (M.L.) was a well-trained neuroimaging analyst. Rater 2 (Y.H.K.)[①] was an expert neurosurgeon who conducted all surgical resections.

Method 1: conventional method (n=62)

Rater 1 evaluated the HT volume in 62 subjects. Two to five slices (3 mm thickness) were taken for HT volumetric analysis, from the slice where optic tract splits from optic chiasm to just before the slice where the mammillary body is visible, from postoperative T1-weighted MR images (Discovery 750w 3.0 Tesla scanner, General

① Professor Yong Hwy Kim, Department of Neurosurgery, SNUH

Electronics Company) at the last follow-up. T1-weighted MR images were obtained using the following parameters: Slice number=15, TR=416.7 ms, TE=11 ms, flip angle=90, voxel size=0.4 x 0.5 x 3 mm^3 , slice thickness= 3 mm, and matrix= 320 x 256. Rater 1 manually segmented the HT area by established boundaries of HT: the lateral edge of the optic tract, third ventricle, optic chiasm, and mammillary body [14, 19]. Lateral border of hypothalamus defined as a linear line was drawn connecting upper edge of third ventricle and lateral edge of optic tract. The raw HT volume (left and right separately, mm^3) of each subject "I" was calculated as follows: Average segmented area of slices (mm^2) x slice number of "I" x inter-slice space (slice thickness, mm). **Figure 2** shows an example of HT volume measurements using T1-weighted MR images.

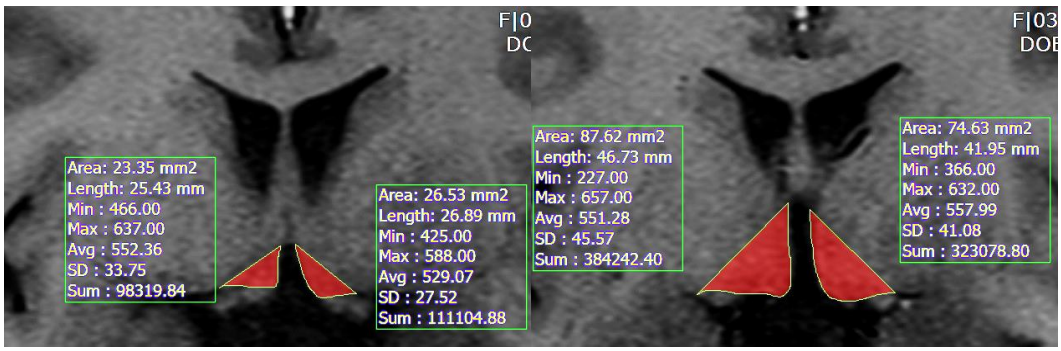

Figure 2. Example of method 1 (T1-weighted images)

Method 2: T2-based individually tailored method (n=78)

Method 2 was separately operated by rater 1 and 2. In patients with severely damaged HT, the optic tract is displaced outwardly owing to the large space of the third ventricle. In this situation, the HT volume can be distorted by the displacement of the optic tract location, which is detected on a T2-weighted image, but not on a T1-weighted image (**Figures 3A-3C**). To adjust the bias resulting from this, I adopted a new segmentation method using T2-weighted images instead of T1-weighted images. T2- weighted images were scanned using the following parameters: Slice number= 15, voxel size= 0.4 x 0.5 x 3 mm^3 , matrix= 320 x 256, slice thickness=3 mm, TR= 3000 ms, TE= 127.2 ms, and flip angle= 160. Medial ventral border of thalamus was visualized using T2-weighted image. For patients with minimal lateral distortion, who did not have any overlap between the lateral border of hypothalamus and medial ventral border of thalamus, conventional method was used to measure HT volume. However, for patient with more severe lateral distortion, there was substantial overlap between the lateral border of hypothalamus and medial ventral border of thalamus. For these patients with more severe lateral distortion, lateral border of hypothalamus was defined as a linear line from third ventricle upper

edge to medial ventral border of thalamus (leading to more medial position than lateral edge of optic tract). The lateral borderline was tailored to adjust the boundary of the thalamus for each patient. An example of an individually tailored method using T2-weighted images is shown in Figure 4.

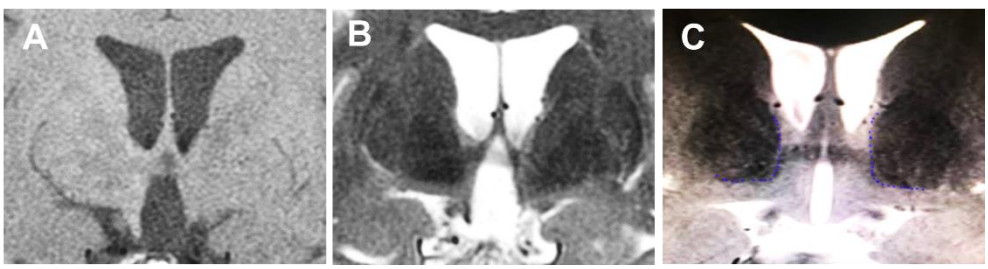

Figure 3. Example of T1 and T2 weighted MR image

(A) T1-weighted image with severely damaged HT (optic tract displacement is not observed).
(B) T2-weighted image with severely damaged HT (optic tract displacement is observed).
(C) T2-weighted image with normal HT.

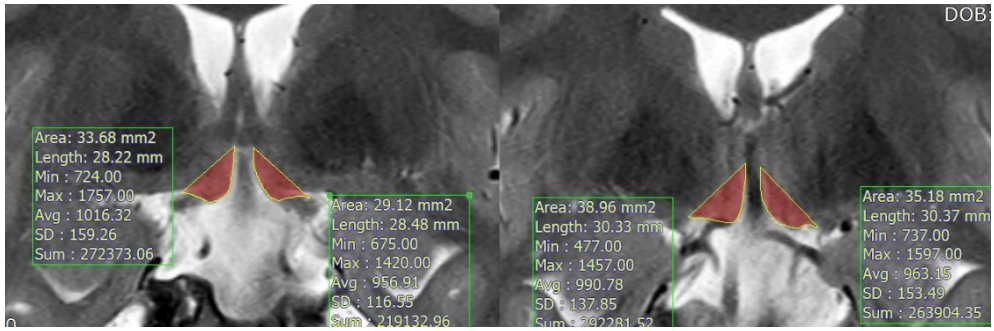

Figure 4. Example of individually tailored method

in T2-weighted images.

Whole brain correction

Three-dimensional segmental volume measurement of the temporal lobe was performed to adjust for whole brain size and brain atrophy (images of whole brain were unavailable). I measured temporal lobe volume to minimize changes in brain parenchymal volume resulting from hydrocephalus or mass effect. Temporal lobe volume has been reported to be associated with whole brain volume (15-17). The temporal horn was excluded from the measurements. The temporal lobe volume was calculated separately for each side by multiplying the segmented area by the number of slices and the inter-slice space. The corrected HT volume of each subject "I" was computed as follows: (right or left) corrected HT volume (i) = (right or left) HT volume raw (i)/(right or left) temporal lobe volume (i), where "HT volume raw (i)" is the raw value of HT and "temporal lobe volume (i)" s the temporal lobe of the subject "I" (Figure 5).

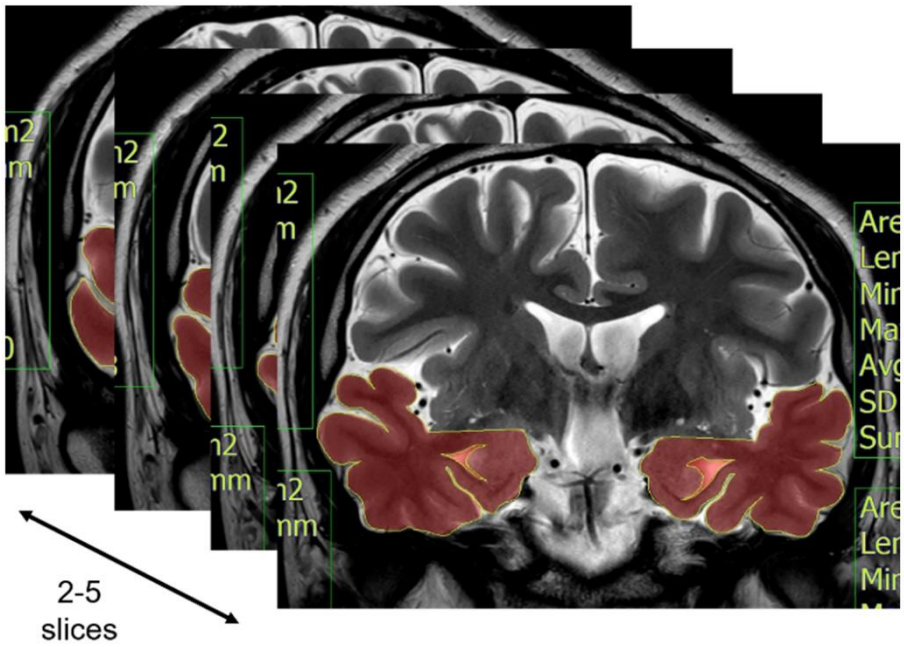

Figure 5. Example of temporal lobe segmentation
(temporal horn was excluded)

Correlation analysis between corrected postoperative HT volume and clinical parameters of study subjects

Among the 78 adult CP patients, 6 patients were excluded from the analysis owing to lack of data on postoperative body weight or hormone replacement therapy. I collected pre- and postoperative height and body weight data measured at the time when MRI was performed for HT volume measurements. The time point at which the postoperative MRI was performed was individualized. Follow-up duration was determined by the interval between the pre- and postoperative weight measurements. I reviewed the medical records on the postoperative steroid hormone replacement and calculated the equivalent steroid dose of hydrocortisone to adjust for differences in the glucocorticoid potency between steroids. Pre and postoperative subjective hypothalamic symptoms were assessed including sleeping disturbance, hyperphagia, and psychosocial problems. The presence of visual impairment was also examined. To assess hormone deficiency, basal hormone and dynamic function tests were performed in all patients before surgery and at 3 months postoperatively.

Study 2

Participants

This study included 29 patients and 31 controls who underwent endoscopic transsphenoidal surgeries for craniopharyngioma (CP group) and non-functional pituitary adenoma (control group), respectively. All participants were pair-matched based on age, gender, preoperative BMI, and hormone function status. The exclusion criteria were as follows: age <19 years, on medications that could significantly influence weight gain (besides hormone therapy), psychiatric problems, severe postoperative complications (bleeding, infection, or pituitary apoplexy), metastasis, previous treatment history (surgery, gamma knife, or radiation therapy), and visual disturbances. This study was reviewed and approved by the Institutional Review Board of SNUH (IRB No.1710-096-895).

Procedures

Patients were asked to arrive at the MRI center an hour before the MRI scan began. First, patients were asked to complete nine Korean standardized questionnaires. Then, patients underwent a routine follow-up structure MRI sequence. This was followed by an fMRI scan during the food image presentation. After finishing the MRI/fMRI scan, they were instructed to complete the Go/NoGo and dot-probe tasks (Figure 6).

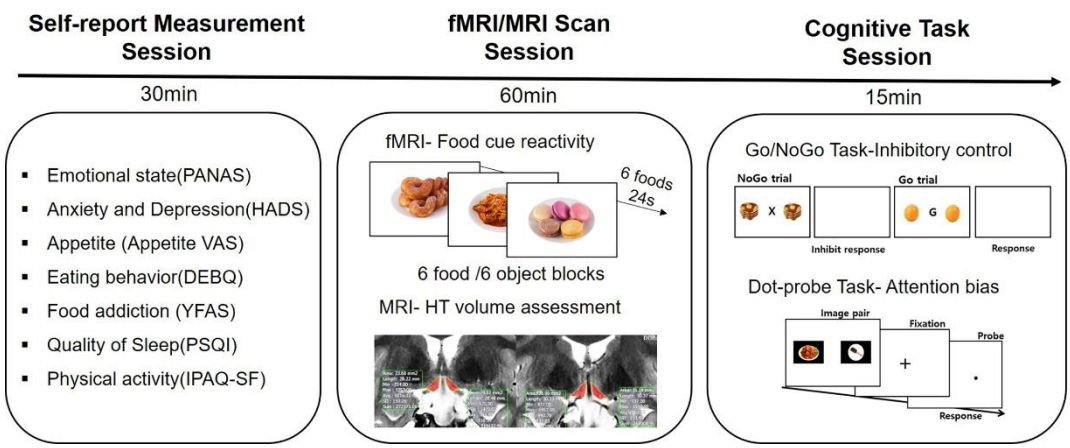

Figure 6. Study 2 design

Psychological measurements

I used the following self-reported measurements for the psychological and behavioral assessments: Appetite visual analog scale (VAS) [20, 21] for the appetite and internal state, Positive and Negative Affect Scale (PANAS) [22, 23] for the current affect state, Hospital Anxiety and Depression Scale (HADS) [24, 25] for pathological mood disorders, Dutch Eating Behavior Questionnaire (DEBQ) [26, 27] and Yale Food Addiction Scale (YFAS) [28, 29] for eating behavior, and International Physical Activity Questionnaire Short Form (IPAQ-SF) [30, 31] and Pittsburgh Sleep Quality Index (PSQI) [32, 33] for other eating-associated behaviors. All questionnaires were used validated Korean version.

Individually tailored hypothalamus volumetric method

I assessed the volume of the damaged hypothalamus (absolute volume of the hypothalamus) on a T2-weighted MR image [slice number= 15, voxel size = 0.4 × 0.5 × 3 mm^3 , matrix= 320 × 256, slice thickness = 3 mm, TR() = 3,000 ms, TE= 127.2 ms, flip angle= 160]. I manually segmented the hypothalamus area using the freehand option of the SNUH PACS program (INFINITT Co. Ltd., South Korea), based on study 1 [34]. I modified the lateral border of the optic tract to adjust the thalamus boundary for each patient in T2-weighted MR images to exclude thalamus areas from hypothalamic volume measurements [method 2 in study 1]. The intracranial volume was calculated from the segmentation function of the magnetization-prepared rapid gradient echo (MPRAGE) sequence using the CAT12 (a Computational Anatomy Toolbox for SPM) [35](**Figure 7**) for whole-brain correction. To adjust for individual head size differences, I calculated the relative hypothalamus volume by dividing the hypothalamus volume by the intracranial volume. Using total intracranial volume for whole brain correction is a method used in previous researches[14, 19, 36, 37].

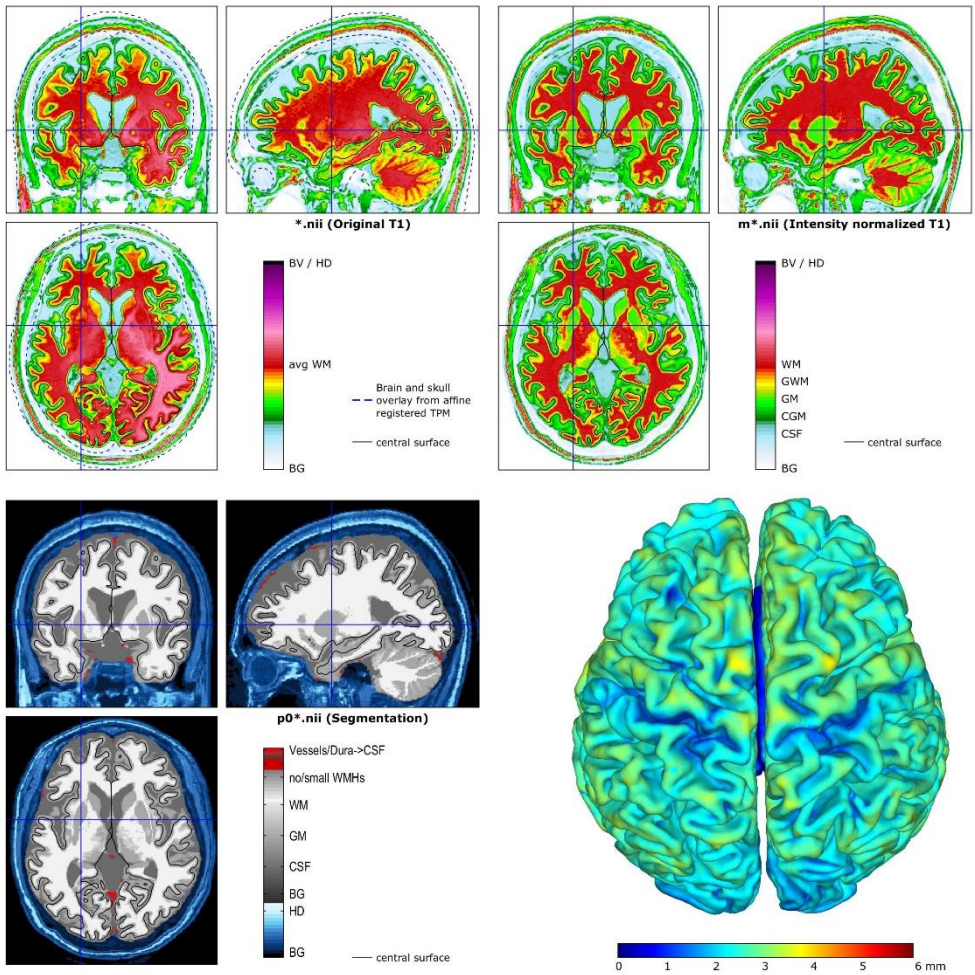

Figure 7. Example of total intracranial volume measuring in CAT12

Functional MRI

Image acquisition

I collected the imaging data on a 3.0-T scanner (SIEMENS MAGNETOM TrioTim syngo MR B17, Germany) using a 32-channel sensitivity encoding head coil. I used an MPRAGE sequence (192 contiguous sagittal slices with TR = 2,100 ms, echo time = 3.74 ms, flip angle = 10, voxel size = 0.9 × 0.9 × 1 mm^3 , and matrix = 256 × 256) to obtain a high-resolution 3-D volume image. fMRI data were obtained (198 volumes with TR = 2,000 ms) with T2-weighted single-shot echo planar imaging sequences. Each participant was axially scanned using the following parameters: voxel size = 3.4 × 3.4 × 3.4 mm^3 , slice number = 38 (interleaved), matrix = 80 × 80, slice thickness = 3.4 mm, slice gap = 0 mm, TR = 2,000 ms, TE = 30 ms, and FOV = 240 × 240.

Food image perception task

I used pictures of palatable food stimuli [38] and non-food object stimuli for the in-scanner visual perception task (45 images each). I presented the task on a projector screen using the E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA). The palatable food images and non-food object images were presented in a block design format during the two experimental runs. The two runs were counterbalanced. Each run consisted of six (food blocks and object blocks, three each) blocks comprising 24 s. Six individual images for 4 s from the list of 15 stimuli were randomly presented in each block. Each block was separated by 8 s. Moreover, each run began with a blank screen comprising a fixation cross for 16 s (see Figure 8).

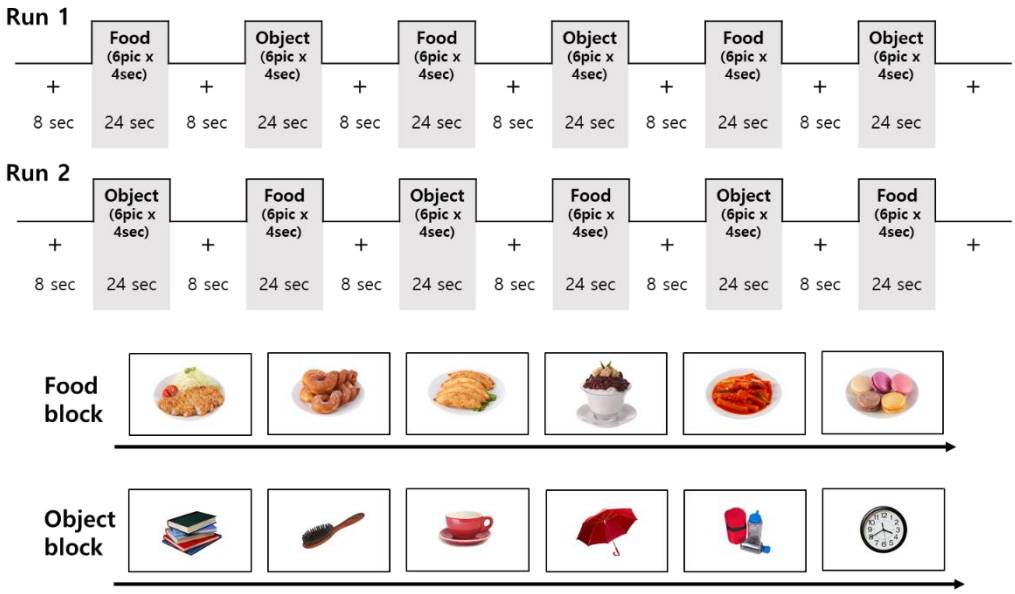

Figure 8. Food image perception task

fMRI data analyses

I preprocessed and analyzed the whole-brain functional images using the SPM12 software package (Wellcome Department of Imaging Neuroscience, London, United Kingdom). They were run in MATLAB 9.4.0 (R2018a, The MathWorks Inc., Natick, MA, USA). The functional images were slice time-corrected, realigned, and co-registered. They were then spatially normalized to the standard Montreal Neurological Institute brain template. These images were smoothened using an isotropic Gaussian kernel with a 6-mm complete width at half maximum. Moreover, I used Artifact Detection Tools(http://www.nitrc.org/projects/artifact_detect) for detecting the outliers. Single scans identified as invalid outliers were removed from the subsequent analysis.

Subject-level analyses included the following two regressors per model: visual exposure to food images and object images. Head motion parameters and outliers were also included in the model as covariates to control the effects of motion and outliers. For each subject, I calculated the following contrast image for each subject: food vs. object. Group-level analyses were conducted using two-sample t-tests to compare group differences in neural activation in response to food images (vs. object images). I reported on the fMRI

results with a significance level of P = 0.005 (uncorrected) and a cluster extent threshold of k = 30 contiguous voxels, as recommended by previous studies [39, 40]. Food-related regions of interest (ROIs) included the bilateral amygdala, caudate, putamen, fusiform, insula, nucleus accumbens, and orbitofrontal cortex [41-43]. I defined the ROIs using Automated Anatomical Labeling 3. However, the ROI for the nucleus accumbens was defined by the Harvard-Oxford Subcortical Structural Atlas. The MarsBaR toolbox[②] was run in Matlab 9.4.0 (R2018a; The MathWorks Inc.,Natick, MA, USA) to extract the mean beta values from the clusters, showing significant group differences from the whole-brain *t*-tests.

fMRI analysis is an objective method of analysis that leaves less potential for analyst bias because it follows a set procedure and is the same for all subjects.

[②] http://marsbar.sourceforge.net/

Cognitive tasks

All computerized cognitive tasks were prepared using PsychoPy3.0 and run on a 15-inch Dell laptop. All food image stimuli used in the tasks were selected from the food image set for Koreans [38].

Go/NoGo task

I implemented the Go/NoGo task protocol postulated by Jasinska et al. [44], which is modified to include flanker food distractors, which eventually facilitated an assessment of the efficiency of inhibitory control in the presence of food images. I included 90 palatable food images for the distracters. The Go/NoGo task measures the efficiency of response inhibition or inhibitory control [45], as indexed by the number of false alarms on NoGo trials (i.e., commission error rate). A higher rate of false alarms indicates a greater deficit in inhibitory control. I measured the lapse of attention to cue by the number of no responses in the Go trials (omission error rate). A higher rate of error in the Go trial indicated a greater deficit in attention. Reaction time indicates response/attention bias. I included food distracter trials to maximize the number of false alarms committed per category. The participants

observed a target letter in the middle of the screen, flanked by two identical food distracter images. I instructed them to press the space bar for all letters except the letter X (Go trials, 66% of all trials) and to inhibit their response for the letter X (NoGo trials, 33% of all trials). The Go targets included the letters G, Q, and O. Each trial consisted of a target stimulus and two flanker food distractors presented for 500 ms, followed by a white screen presented for 1,000 ms. The total response limit was 1,500 ms. After the instructions and following eight practice trials, the participants completed three runs of tasks each consisting of 90 trials (60 Go trials and 30 NoGo trials), for a total of 270 trials (180 Go trials and 90 NoGo trials, respectively). The instructions emphasized on both speed and accuracy. The order of trials was randomized across the three blocks for each participant. All participants were provided with the same food distracter images (see Figure 9).

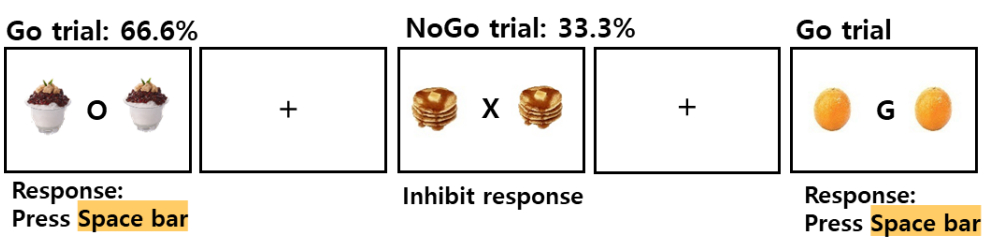

Figure 9. Go/NoGo task

Dot-probe task

I employed a food visual image-specific dot-probe task to assess the attentional bias to food. I obtained 104 and 56 food and non-food object pictures, respectively, for the stimuli. There were 168 experimental trials that comprised the following in picture pairs from each category: 56 food/object (congruent trial), 56 food/object (incongruent trial), 28 food/food (neutral), and 28 object/object (neutral). Their order of presentation was randomized for each participant, with a restriction on the immediate repetition of the preceding pair. The fixation was presented for 500 ms in each trial, followed by a separation of the pairs for 1,000 ms. Moreover, one picture each was presented left and right to the central point. Immediately following an offset of the picture pair, a small dot appeared in place of one of the two pictures, in line with previous research using the dot-probe procedure [46-49]. Each picture within the pair was likely equal to fall in either the left or the right position on the computer screen. Furthermore, the dot was equally likely to replace either the food (congruent trial) or the object (incongruent trial) picture. Differences in the reaction time of each type of trial are indexed as the attention bias, initial attentional orientation (i.e., attention orienting), and disengagement of attention from the visual cue (i.e., attention disengagement) [46, 50]. The

participants were instructed to fix their eyes on the cross at the center of the screen every time it appeared. Furthermore, I asked them to rapidly and accurately indicate the point where the dot appeared by pressing either a left('E') or right('P') response key on the keyboard. The computer recorded the response time to the nearest millisecond and the number of errors. The participants were provided a break for 30 s, halfway through the trial (see Figure 10).

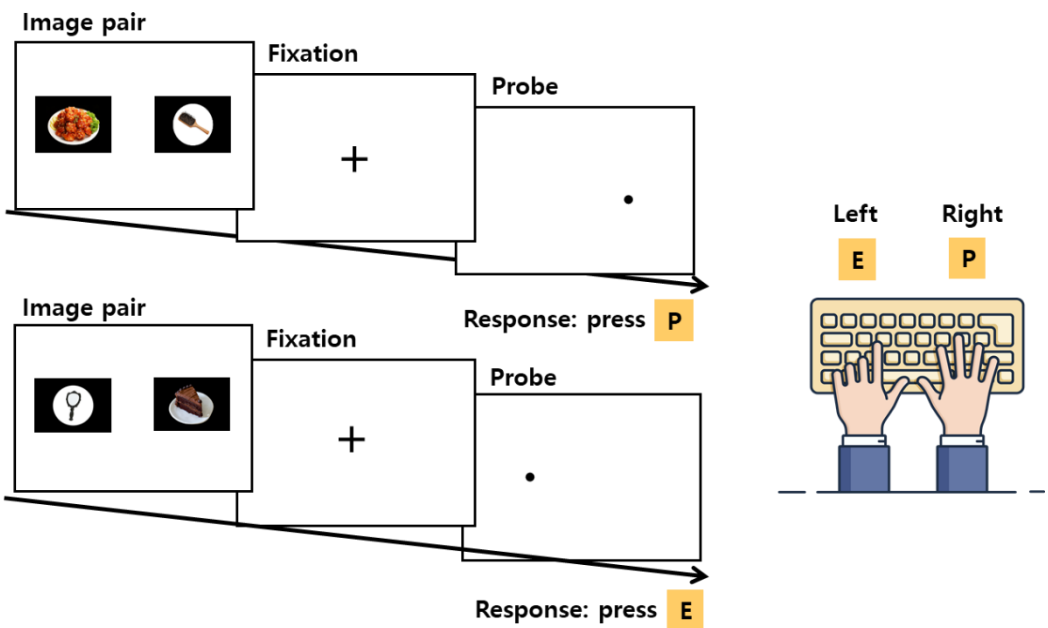

Figure 10. Dot-probe task

Statistics

I analyzed the psychological, behavioral, and anthropometric data using the SPSS Statistics software (version 25, Armonk, NY, USA). The P-values are from an unpaired, two-sample t-test that compared patients in the CP group to those in the control group. I conducted independent sample t-tests to compare the percentage of damaged hypothalamus volume and the mean volume of each group. The t-value represents the difference between the sample mean and the population mean, standardized by the standard deviation of the sample. The correlation between all anthropometric, psychological, and behavioral data and the ROI beta values was assessed using the Pearson product-moment correlation coefficient (two-tailed, $P < 0.05$).

Results

Study 1

Validation of the Individually Tailored HT Volumetric Method

I aimed to validate the performance and efficacy of the newly developed individually tailored HT volumetric method by comparing systematic bias and outliers between methods. Validation of the individually tailored HT volumetric method developed in the present study is shown in **Figure 11**. The corrected HT volume between method 1 and method 2 conducted by rater 1 was significantly correlated (r=0.51 [95% CI 0.32 to 0.67], P<0.01; **Figure 11A**), which suggests a good concordance and robustness between methods. The Bland– Altman plot revealed the relationship between the differences and the magnitude of the two measurement methods to identify any systematic bias and outliers. Systematic bias was observed between method 1 and method 2 of rater 1 (**Figure 11B**). The difference between method 1 and method 2 showed a significantly negative correlation with the magnitude of HT volume using method 1 (r=–0.84 [95% CI −0.91 to −0.72, P<0.01), which shows that there was a significant difference between methods in

patients with smaller HT volumes. No significant outliers were observed. There was a significant correlation between the two raters' HT volume assessment using method 2 (r=0.93 [95% CI 0.88 to 0.97], P<0.01; **Figure 11C**). Intraclass correlation (ICC) between the raters was reliable (ICC [2,1] = 0.92 (95% CI 0.88 to 0.95), P<0.01). The Bland-Altman plot showed that there was a minimal systematic bias between raters 1 and 2 using method 2 (r=- 0.15 [95% CI -0.32 to 0.12, P=0.22; **Figure 11D**). The variance of inter-rater difference was limited to an acceptable range (+0.02 to -0.02). Significant outliers were not observed. The individually tailored method (method 2) was superior to method 1 with respect to systematic bias, especially in cases of severe hypothalamic damage.

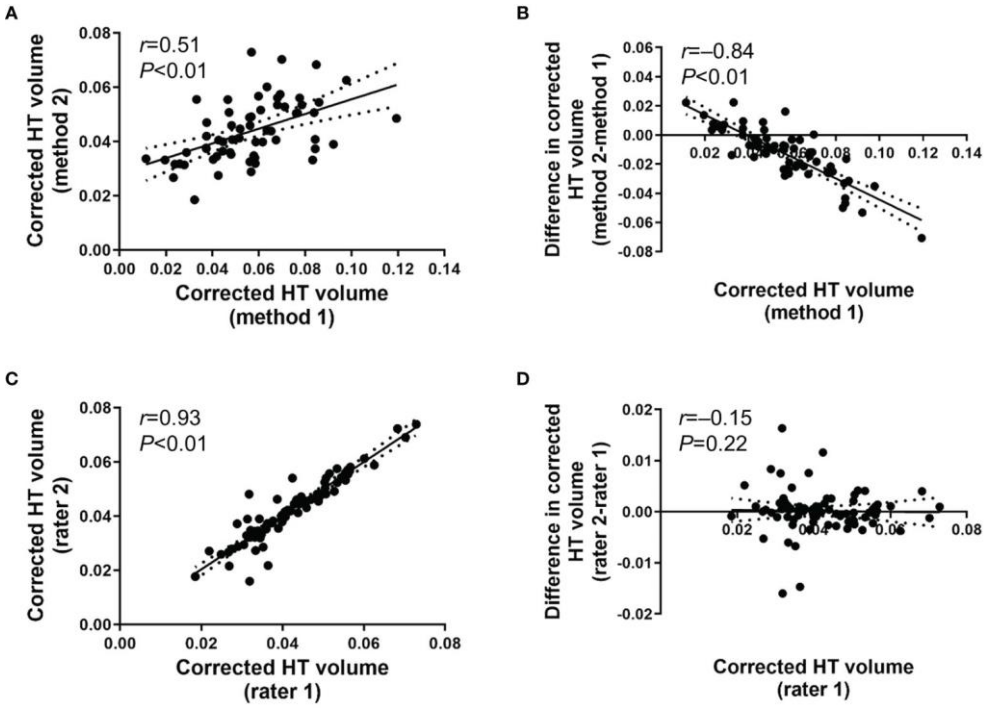

Figure 11. Scatter plot: method validation

Clinical Characteristics of Subjects

Baseline characteristics of the study subjects included in the correlation analysis are shown in Table 1 (n=72). The mean age was 46.8 ± 14.8 years, and male patients were dominant (56.9%). The mean pre- and postoperative body weights were 69.1 ± 13.0 kg and 72.0 ± 13.0 kg, respectively. The mean pre- and postoperative body mass indices (BMIs) were 25.3 and 25.9 kg/m2, respectively. I categorized patients based on the postoperative BMI according to underweight, normal, overweight, and obesity using the definition of obesity for Asians (18). The prevalence of obesity (≥25 kg/m²) was 62.5% (45/72), and that of obesity or overweight (≥23 kg/m²) was 87.5% (63/72). Only 12.5% (9/72) of the subjects were classified as normal weight (18.5–22.9 kg/m²), and none of the subjects were underweight (<18.5 kg/m²). Therefore, considering the high prevalence of HO in the present study, the power of this study is considered appropriate. During a median follow-up duration of 764 days (interquartile range 479–1724), the mean body weight change was 3.0 kg and mean BMI change was 1.3 kg/m² (both P<0.01). The percentage changes in body weight and BMI were both 4.4%. The preoperative tumor volume was 4.6 (interquartile range 2.1–10.5) cm^3 . With respect to HT volume, I used corrected postoperative HT volume from rater 1, and that was 0.042 ± 0.011 after adjusting for

temporal lobe volume. Sixteen patients (22.2%) had a history of surgery and/or irradiation. Pre- and postoperative pituitary hormone deficiencies were observed in 76.3% and 93.0% of the patients, respectively. The median duration of steroid replacement therapy was 719 days (interquartile range 232-1456) with a median daily steroid (hydrocortisone) dose of 12.9 mg (interquartile range 10.9-15.3). Postoperative diabetes insipidus was reported in 62 patients (86.1%). Two patients required postoperative ventroperitoneal drainages due to uncontrolled hydrocephalus occurring before surgery.

Table 1. Baseline characteristics of study 1 subjects

Variables	***n*=72**
Age (years)	46.8 ± 14.8
Male, *n* (%)	41 (56.9)
Preoperative height (cm)	164.0 ± 9.6
Preoperative body weight (kg)	69.1 ± 13.0
Preoperative BMI (kg/m^2)	25.3 (22.7–27.2)
Postoperative body weight (kg)	72.0 ± 13.0
Postoperative BMI (kg/m^2)	25.9 (23.9–28.3)
Follow-up duration (days)	764 (479–1724)
Body weight change (kg)	3.0 (-0.9–6.2)
% body weight change (%)	4.4 (-1.1–10.1)
BMI change (kg)	1.3 (-0.3–2.4)
% BMI change (%)	4.4 (-1.1–10.0)
Previous history of surgery or irradiation for craniopharyngioma	16 (22.2)
Duration of steroid replacement (days)	719 (232–1456)
Daily steroid dose (mg/day) [a]	12.9 (10.9–15.3)
Cumulative steroid dose (mg)[a]	7295 (2962–12309)
Preoperative tumor volume (cm^3)	4.6 (2.1–10.5)
Postoperative corrected hypothalamic volume[b]	0.042 ± 0.011
Preoperative visual disturbance, n (%)	52 (72.2)
Postoperative visual disturbance status	
Aggravation	4 (5.6)
No change	14 (19.4)
Improvement	50 (69.4)
Non-applicable	4 (5.6)
Preoperative hormone deficiency	
0	17 (24.6)
1	16 (22.2)
2	8 (11.1)
3	1 (1.4)
4	30 (41.7)
Postoperative hormone deficiency	
0	5 (6.9)
1	3 (4.2)
2	0 (0.0)
3	0 (0.0)
4	64 (88.9)
Postoperative diabetes insipidus, *n* (%)	62 (86.1)
Preoperative hypothalamic symptom, *n* (%)	25 (34.7)
Postoperative hypothalamic symptom, *n* (%)	9 (12.5)

a Hydrocortisone−equivalent dose of steroid.

b Corrected hypothalamic volume = measured hypothalamic volume/temporal lobe volume.

Correlation analysis between corrected postoperative HT volume and clinical parameters of subjects

I observed a significant negative association between the corrected postoperative HT volume and preoperative body weight (r=–0.25 [95% CI −0.45 to −0.04], P=0.04) (Table 2A).

However, there were no associations between postoperative HT volume and postoperative body weight, body weight change, or percentage body weight change. I performed sensitivity analysis using BMI and changes in BMI. No associations were also observed regarding pre− and postoperative BMI, BMI change, or percentage BMI change (data not shown). The corrected postoperative HT volume showed a significant negative correlation with preoperative tumor volume (r=–0.26 [95% CI −0.40 to −0.15], P=0.03). Postoperative daily steroid dose (r=–0.32 [95% CI −0.49 to −0.06], P=0.01) and hypothalamic symptoms (r=–0.25 [95% CI −0.45 to −0.02], P=0.04) were also negatively associated with postoperative HT volume.

To exclude the effect of pre−existing hypothalamic damage caused by prior surgery or radiation for CP, I performed a subgroup analysis in patients who underwent primary surgery for CP (n=56) (Table 2B). Pre− and postoperative body weights exhibited significant

negative associations with the corrected postoperative HT volume (r=–0.30 [95% CI −0.53 to −0.03], P=0.03 and r=–0.29 [95% CI −0.53 to −0.02], P=0.03, respectively) (Figure 12A, B). Preoperative tumor volume also showed a negative association with postoperative HT volume (r=–0.36 [95% CI −0.53 to −0.25], P=0.01). However, I did not observe any significant associations between HT volume and body weight change and percentage body weight change. In addition, there were no associations between HT volume and pre− and postoperative BMI, BMI change, or percentage BMI change. Negative correlations between the corrected postoperative HT volume, daily steroid dose, and postoperative hypothalamic symptoms that were previously observed in all subjects were not present in this subgroup analysis.

Additionally, I performed adjusted multiple linear regression analysis to evaluate the independent association of HT volume with postoperative body weight after adjusting for preoperative body weight, duration of days between surgery and MRI/body weight measurement, preoperative tumor volume, and daily steroid dose. However, I did not find a significant association in the analysis in all patients (n=72; b=0.02, P=0.72) as well as in those who underwent primary surgery (n=56; b=−0.10, P=0.92).

I underwent sensitivity analysis using HT volume without

temporal lobe volume normalization. In all patients (n=72), body weight change and percentage body weight change were positively associated with HT volume (r=0.36 [95% CI 0.18 to 0.52], P<0.01 and r=0.33 [95% CI 0.15 to 0.50], P<0.01). BMI change and percentage BMI change were also positively associated with HT volume (r=0.34 [95% CI 0.16 to 0.50], P<0.01 and r=0.33 [95% CI 0.15 to 0.50], P<0.01). Similar trends were observed in those who underwent primary surgery for CP (n=56). Body weight change and percentage body weight change were positively associated with HT volume (r=0.40 [95%CI 0.19 to 0.57], P<0.01 and r=0.35 [95% CI 0.14 to 0.54], P<0.01). BMI change and percentage BMI change were also associated with HT volume (r=0.39 [95% CI 0.19 to 0.56], P<0.01 and r=0.36 [95% CI 0.14 to 0.54], P<0.01). However, HT volume did not show significant associations with tumor volume, steroid replacement, or hypothalamic symptoms in both groups (data not shown). These findings support the need for temporal lobe volume normalization to accurately assess individual HT volume.

Table 2. Descriptive statistics and correlation matrix between corrected postoperative hypothalamic volume and clinical parameters

	Corrected HT volume	Preop Bwt	Postop Bwt	Bwt change	% Bwt change	Preop tumor volume	Duration of steroid	Daily steroid dose[a]	Postop hormone deficiency	Postop hypothalamic symptoms
(A) All patients (*n*=72)										
Corrected HT volume	1	–0.25[b]	-0.22	0.10	0.13	-0.26[b]	-0.01	-0.32[b]	-0.07	-0.25[b]
Preop Bwt	–0.25[b]	1	0.91	-0.35[b]	-0.43[b]	0.09	-0.11	0.05	0.13	0.13
Postop Bwt	–0.22	0.91[b]	1	0.07	-0.02	0.09	-0.13	0.13	0.13	0.15
Bwt change	0.10	-0.35[b]	0.07	1	0.98	-0.01	-0.03	0.17	-0.01	0.04
% Bwt change	0.13	-0.43[b]	-0.02	0.98[b]	1	-0.03	0.00	0.12	-0.00	0.01
Preop tumor volume	–0.26[b]	0.09	0.09	-0.01	-0.03	1	0.10	-0.00	0.13	0.12
Duration of steroid	–0.01	-1.11	-0.13	-0.03	0.01	0.10	1	-0.24[b]	0.27[b]	-0.11
Daily steroid dose[a]	–0.32[b]	0.05	0.13	0.17	0.12	0.00	-0.24[b]	1	-0.01	0.13
Postop hormone deficiency	–0.07	0.13	0.13	-0.01	-0.01	0.13	0.27[b]	-0.01	1	0.10
Postop hypothalamic Sx	–0.25[b]	0.13	0.15	0.04	0.01	0.12	-0.11	0.13	0.10	1
(B) Patients who underwent primary surgery for CP (*n*=56)										
Corrected HT volume	1	–0.30[b]	-0.29[b]	0.07	0.10	-0.36[b]	-0.13	-0.18	-0.04	-0.13
Preop Bwt	–0.30[b]	1	0.90[b]	-0.34[b]	-0.43[b]	0.14	-0.14	0.20	0.13	0.29[b]
Postop Bwt	–0.29[b]	0.90[b]	1	0.10	-0.01	0.13	-0.14	0.33[b]	0.14	0.32[b]
Bwt change	0.07	-0.34[b]	0.10	1	0.98[b]	-0.04	0.03	0.25	0.01	0.02
% Bwt change	0.10	-0.43[b]	-0.00	0.98[b]	1	-0.06	0.07	0.16	0.01	-0.02
Preop tumor volume	–0.36[b]	0.14	0.13	-0.04	-0.06	1	0.14	0.11	0.16	0.11
Duration of steroid	–0.13	-0.14	-0.14	0.03	0.07	0.14	1	-0.14	0.30[b]	-0.01
Daily steroid dose[a]	–0.18	0.20	0.33[b]	0.25	0.16	0.11	-0.14	1	-0.12	0.11
Postop hormone deficiency	–0.04	0.13	0.14	0.01	0.13	0.16	0.30[b]	-0.12	1	0.10
Postop hypothalamic Sx	–0.13	0.29[b]	0.32[b]	0.02	-0.02	0.11	-0.01	0.11	0.1	1

HT, hypothalamus; Preop, preoperative; postop, postoperative; Bwt, body weight; Sx, symptom.
a Hydrocortisone-equivalent dose of steroid.
b Correlation is significant at the 0.05 level (two-tailed

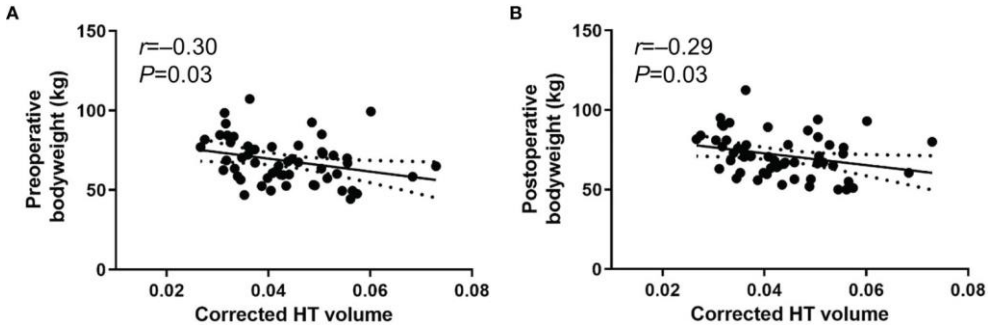

Figure 12. Scatter plots between body weight and corrected postoperative HT volume using method 2 from rater 1

Study 2

Demographic and clinical characteristics

Sixty-one participants completed the entire study procedure. Two patients failed to complete the fMRI scan due to a problem with the fMRI projector. I successfully collected the fMRI data of 55 of the 59 eligible patients (93%), and the data of four patients were excluded due to a technical issue of data transfer (N = 3) and poor vision (N = 1). I excluded the data of two patients in the Go/NoGo task [one outlier (error rate > 30%) and one missing data].

The demographic and clinical characteristics of the study participants are shown in Table 3. There were no differences in age, preoperative weight, and preoperative BMI between the CP group (craniopharyngioma, n = 29) and the control group (non-functional pituitary adenoma, n = 31). There was a significant difference in the Mueller grading [51] and follow-up duration (the period between surgery and participation in this study).

Table 3. Demographic and clinical characteristics of study 2

	CP (n=29)	Control (n=31)	*P*-value
Age[1]	48.00 ± 12.77	48.77 ± 13.10	.818
Sex, Male, n (%)	16 (55.2)	16 (51.6)	.782
Follow-up duration(month)[2]	40.67 ± 25.87	23.16 ± 20.18	.005*
Initial tumor size(mm[3])	10509.37± 16859.68	7021.55 ± 4129.23	.269
Pre-operative body weight	67.54 ± 12.70	70.5 ± 13.30	.383
Post-operative body weight	72.85 ± 17.60	71.08 ± 15.00	.675
Pre-operative BMI	25.06 ± 3.24	25.23 ± 3.14	.836
Post-operative BMI[3]	26.88 ± 4.32	25.38 ± 3.54	.145
Mueller grading, n (%)			
0	5 (17.2)	25 (80.6)	
1	9 (31.0)	5 (16.1)	.000*
2	15 (51.7)	1(3.2)	

Note. Data are expressed as mean ± SD or n (%).
CP group: Craniopharyngioma, Control group: Non-functioning pituitary adenoma. *P*-value presented relate to unpaired, 2-sample Student's t test comparing hypothalamic damage group with control group. Chi-square *P*-value presented for sex and Mueller grading.

[1] Age when our patients participated in this study
[2] Period between surgery and participation in this study
[3] BMI when our patients participated in this study

Weight change

Patients in the CP group gained greater postoperative weight compared with the control group. There was a 7.23% increase in postoperative weight in the CP group, while only a 0.63% increase was observed in the control group (t (58) = 3.02, P = 0.004, Figure 13D). A total of 51.72% of CP patients (15 of 29) had a weight gain greater than 5%, and 31.03% of CP patients (9 of 29) had a weight gain greater than 10% after the surgery.

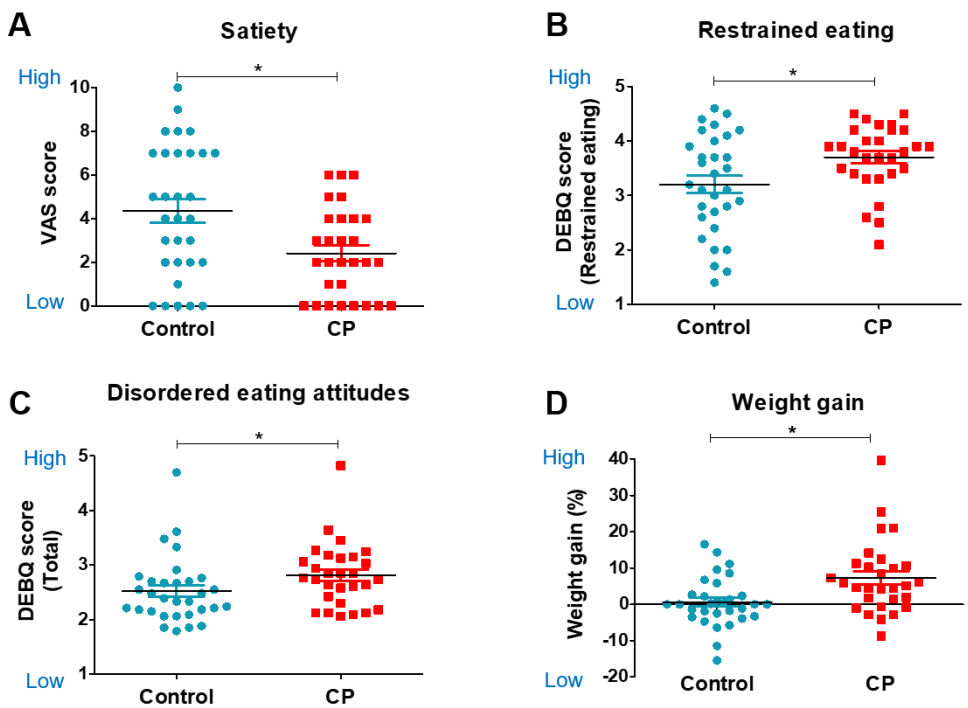

Figure 13. Food-related psychology, eating behavior, and weight change

Structural MRI: The degree of hypothalamic damage

The CP group showed a significantly lower absolute volume of the hypothalamus (667.63 *vs.* 782.54, $t(58) = -2.351$, $P < 0.05$) and relative volume of the hypothalamus (hypothalamic volume percentage; [hypothalamus volume/total intracranial volume] * 100), indicating significant hypothalamic damage, compared with the control (0.0460 *vs.*0.0534, $t(58) = -2.017$, $P < 0.05$, Table 4; Figure 14A).

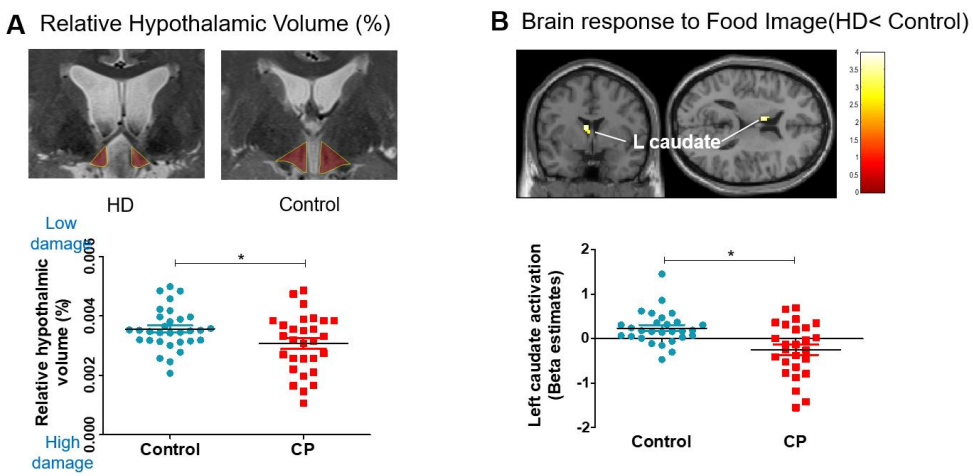

Figure 14. Hypothalamic damage and whole-brain response to food.

Scatter plots for relative hypothalamic volume and brain response difference in the CP and control groups.

Table 4. Group differences between CP and control group

Dimension	Phenotype	Variables	Hypothalamic Damage (n=29)	Control (n=31)	*P*-value
Hypothalamic Structure	Hypothalamic Damage	Absolute volume of hypothalmus (mm^3)	667.63 ±224.50	782.60± 148.92	**.022***
		Relative volume of hypothalamus (%)	0.0460 ± 0.01637	0.0534 ± 0.01085	**.043***
Food Related Cognition	Go/NoGo task				
	Inattention	Go RT (s)	0.50 ± 0.07	0.47 ± 0.06	.075
	attention	Go errors (%)	9.13 ± 8.11	4.09 ± 4.19	**.005***
	Inattention	NoGo errors (%)	8.02 ± 6.83	6.30 ± 4.93	.274
	Dot-probe task				
	Attention bias	RT difference (IT-CT) (ms)	-1.04 ± 18.39	3.00 ± 21.42	.437
	Attention orienting	RT difference (N - CT) (ms)	-1.64 ± 20.20	-0.03 ± 15.99	.733
	Attention disengagement	RT difference (IT-N) (ms)	0.60 ± 15.40	3.04 ± 25.18	.655
Food Related Psychology	Hunger	Visual Analog Scale	2.66 ± 2.59	2.68 ± 2.84	.975
	Satiety	Visual Analog Scale	2.41 ± 2.03	4.35 ± 3.01	**.005***
	Fullness	Visual Analog Scale	2.97 ± 2.47	4.35 ± 3.01	.303
	Prospective to eat	Visual Analog Scale	4.62 ± 2.01	4.26 ± 2.34	.523
	Tasty	Visual Analog Scale	1.76 ± 1.49	1.70 ± 1.77	.888
	Craving	Visual Analog Scale	2.52 ± 2.28	2.84 ± 2.85	.633
Eating Behavior	Disordered Eating Attitudes	DEBQ (total)	2.81 ± 0.58	2.52± 0.61	.064
	Restrained Eating	DEBQ_R	3.7 ±0.6	3.2± 0.91	**.016***
	Emotional Eating	DEBQ_Emo	1.98 ± 0.92	1.62± 0.86	.137
	External Eating	DEBQ_Ext	3.01 ± 0.71	3± 0.68	.969
	Food Addiction	YFAS	1.41 ± 1.24	1.29 ± 1.47	.727

Weight Change	Weight (%)	Body weight change (%)	7.24 ± 9.98	0.63 ± 6.77	**.004***
	Weight(kg)	Body weight change (kg)	5.31± 7.90	0.85 ± 4.66	**.006***
	5%>weight gain (n)	5%>weight gain, n (%)	15 (51.7)	7 (22.6)	.019*
	BMI	BMI change (%)	7.2 ± 9.99	0.58 ± 6.76	**.004***
Mental and Physical Health	Emotion	PANAS	0.56 ± 0.10	0.56 ± 0.10	.848
	Anxiety	HADS Anxiety	5.03 ± 2.82	6.06 ± 2.61	.147
	Depression	HADS Depression	7.31 ± 3.71	6.81 ± 2.88	.558
	Sleep Quality	PSQI (total)	8.07 ± 3.40	7.58 ± 3.88	.607
	Physical Activity	IPAQ-sf (total)	4673.85 ± 6773.40	3585.70 ± 4567.46	.492

Note. Data are expressed as mean ± SD or n (%).

RT: Reaction time,
IT: Incongruent trial,
CT: Congruent trial,
N: Neutral,
DEBQ: Dutch Eating Behavior Questionnaire,
DEBQ_R: DEBQ Restrained Eating,
DEBQ_Emo: DEBQ Emotional Eating,
DEBQ_Ext: DEBQ External Eating,
YFAS: Yale Food Addiction Scale,
PANAS: Positive and Negative Affect Schedule,
HADS: Hospital Anxiety and Depression Scale,
PSQI: Pittsburgh Sleep Quality Index,
IPAQ-sf: Physical Activity Questionnaire (IPAQ) – Short Form.

Functional MRI: brain response to food image

The whole-brain analysis revealed that the CP group showed significantly lower activation in the left caudate nucleus, which is associated with reward, emotion, and motivation function (Figure 14B) when they viewed food images (*vs.* object images). The CP group also showed significantly higher activation in the right occipital gyrus and inferior frontal gyrus in response to food images (*vs.* object images) compared with the control group (Table 5).

Table 5. Regions in which brain activation during food image perception was significantly different CP (n=26) and Control(n=28) group

	Cluster	Cluster size(k)	x	y	z	Z-value	Region	%	Voxel
CP>	1	51	26	-66	34	3.30	R Superior occipital gyrus	50.98	26
							R Middle occipital gyrus	37.25	19
	2	38	-40	30	16	3.30	L Inferior frontal gyrus, triangular part	100	38
	3	36	2	-78	-28	3.20	L Lobule VII of vermis	58.33	21
							L Crus II of cerebellar hemisphere	41.67	15
CP<	1	47	-6	2	14	3.86	L Caudate nucleus	38.3	18

Whole-brain analysis result table. Significance level: uncorrected $P<0.005$, k>30, presented voxel>5

Computerized tasks: food-related cognition

The CP group showed significantly higher food inattention (lapses of attention, omission error %; not responding to the go cue in the Go/NoGo task) than the control group (9.13 ± 8.11 *vs.* 4.09 ± 4.19, t (56) = 3.00, P = 0.004, **Figure 15A**). The CP group also showed a trend of higher food inattention (attention bias, reaction time to the go cue in the Go/NoGo task) than the control group (0.50 ± 0.07 *vs.* 0.47 ± 0.06, t (56) = 1.86, P = 0.075, **Figure 15B**). No significant group differences were observed in the performance of the dot-probe task.

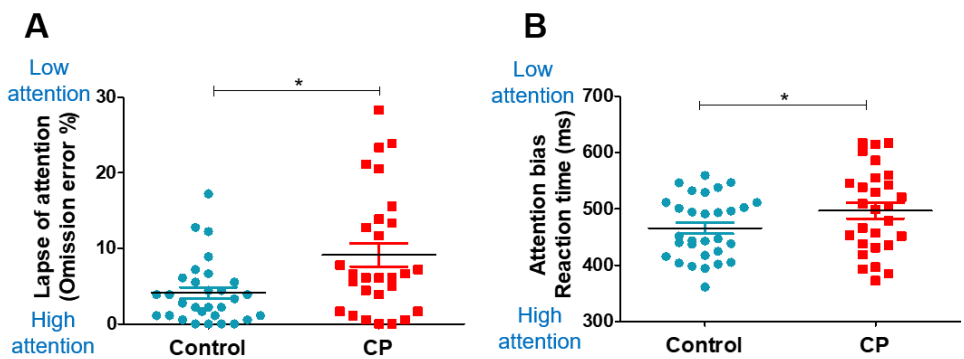

Figure 15. Food-related cognition

Scatter plots for Go/NoGo task results in HD group and Control group. Unpaired, 2-sample Student' s t test was used for comparing CP and control group

A. Group difference of omission error rate (missing response to Go tral)

B. Group difference of reaction time

Self-report assessments: food-related psychological characteristics

The CP group showed a lower satiety VAS score than the control group (2.41 ± 2.03 vs. 4.35 ± 3.01, t (58) = −2.91, P = 0.005, **Figure 13A**). There were no significant group differences in other psychological and cognitive measurements (**Table 4**). The CP group showed higher restrained eating behavior (restrained eating score from the DEBQ) than the control group (3.7 ± 0.6 vs. 3.2 ± 0.91, t (58) = 2.47, P = 0.02, **Figure 13B**). The CP group also showed a trend of higher unhealthy eating behavior (total score from the DEBQ) than the control group (2.81 ± 0.58 vs. 2.52 ± 0.61, t (58) = 1.89, P = 0.06, **Figure 13C**). There were no significant group differences in other psychological and cognitive measurements (**Table 4**).

Correlation analysis within the CP group

Since restrained eating was the major abnormal behavior observed in the CP group, further correlation analysis was performed within the CP group. Interestingly, higher restrained eating was significantly associated with lower activation in the left (r = −0.451, P = 0.021, **Figure 16A**) and right (r = −0.627, P = 0.001, **Figure 16A**) fusiform gyrus. Additionally, a higher disordered eating attitude was significantly associated with lower activation of the right orbitofrontal cortex (OFC) (r= −0.429, P= 0.029, **Figure 16B**). Right OFC activation was significantly related to the inhibitory control (commission error rate) (r= 0.439, P = 0.028, **Figure 16B**). Left hippocampus activation was significantly associated with both attention bias score (r= 0.598, P = 0.0001, **Figure 16C**) and attention orienting score (r= 0.446, P = 0.022, **Figure 16C**). Moreover, left hippocampus activation was negatively correlated with weight percent change (r= −0.452, P = 0.02, **Figure 16C**). Left amygdala activation was significantly associated with attention orienting score (r = 0.410, P = 0.038, **Figure 16D**). There is no statistically significant relationship between initial tumor size, age, and weight gain.

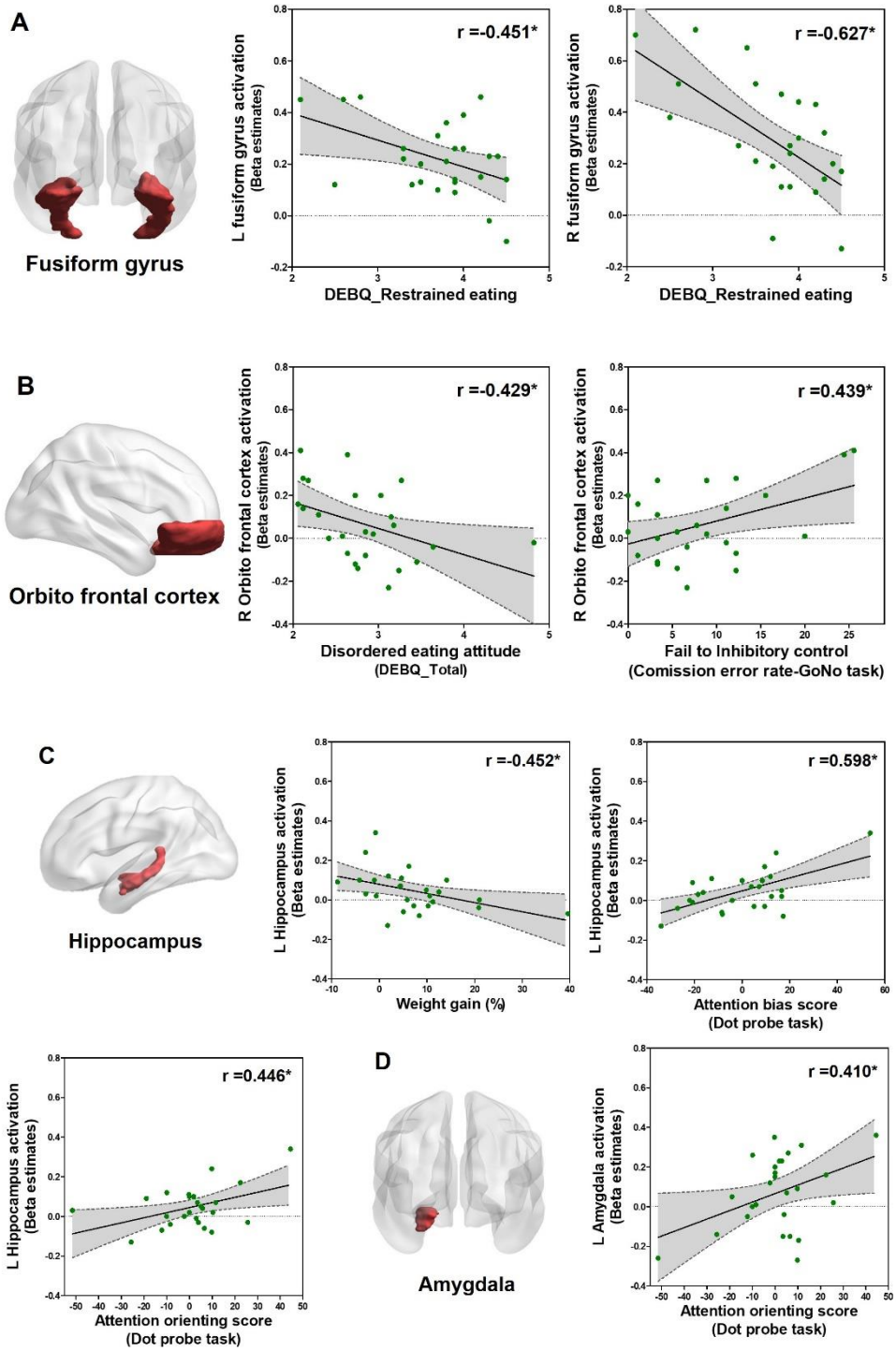

Figure 16. Correlation analysis within the CP group.

Correlations between eating behavior and the parameter of estimated beta value of ROIs within CP patients (n = 29)

Post-hoc analysis of CP with HO

Not all CP patients exhibited weight gain. Therefore, I performed a post-hoc analysis of those who experienced substantial weight gain (>5%) in the CP group (n=15, **Figure 17**). This condition is commonly referred as HO.

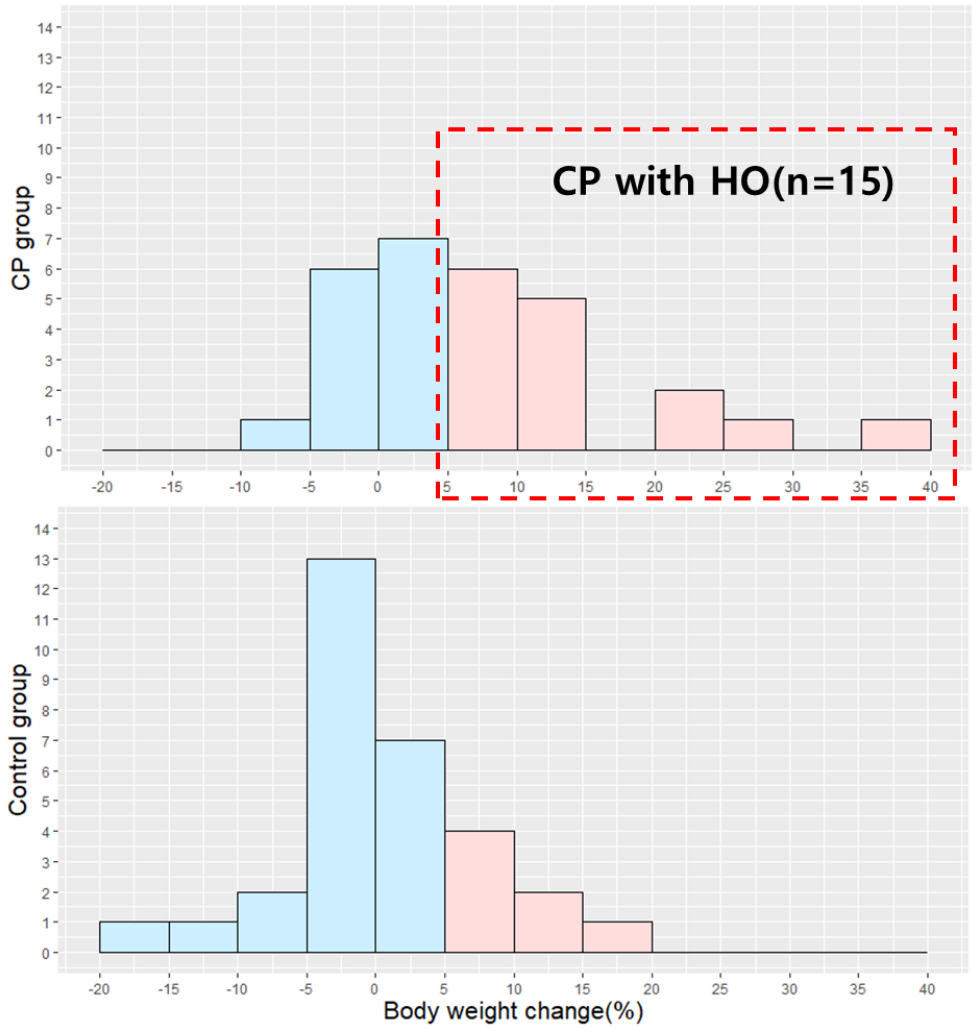

Figure 17. Body weight change histogram of patients

Association between psychological and cognitive dimensions in the HO group

I observed a significant negative correlation between the body weight change % and attention orienting score in the Dot-probe task among the CP patients and HO *(r=-0.655, P=<.01,* Figure 18A). The self-reported hunger VAS score was associated with a failure to inhibit control (Commission error % in the Go/NoGo task) (*r=-533, P<.05,* Figure 18B). Moreover, an independent-samples Mann-Whitney U test showed no significant difference(*P=.076*) regarding to food tolerance, which in turn is a subscale of the YFAS, but the two participants with food addiction tolerance both had lower hypothalamic volumes. (Figure 18C)

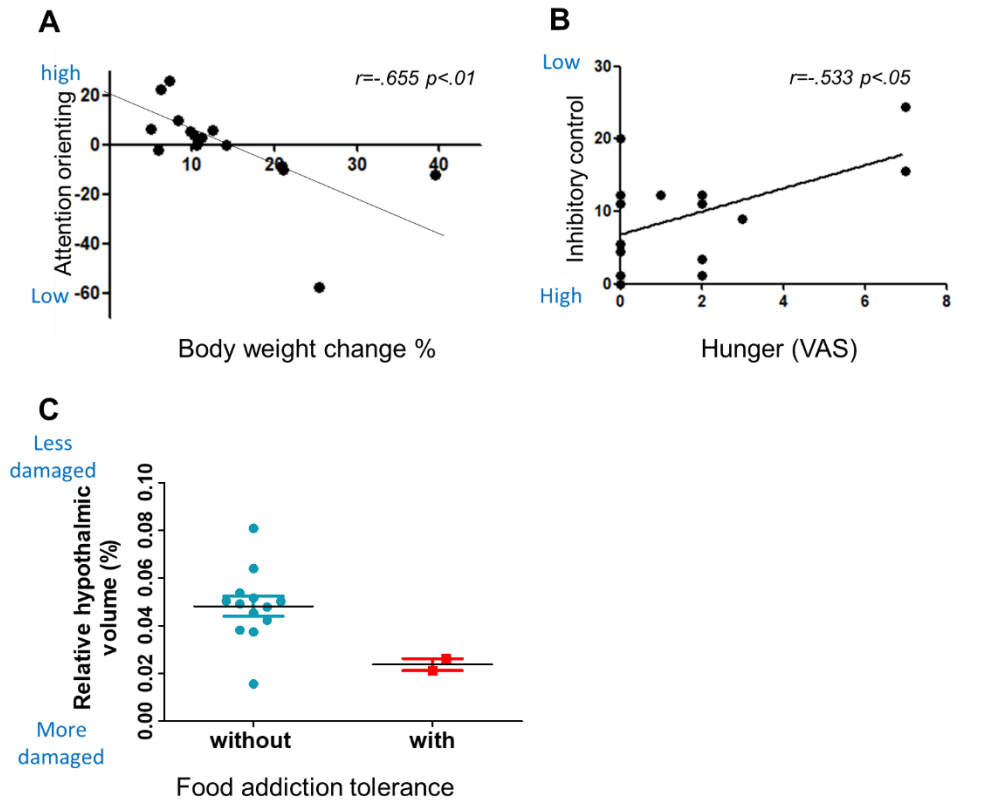

Figure 18. Cognitive phenotypes and HD extent are associated with pathologic weight gain and psychological phenotypes among HO patients

.

A: Attention orienting is calculated by mean of neutral trial reaction time (RT) – mean congruent trial reaction time (RT) in Dot-probe task.

B: Deficit of Inhibitory control is represented by higher commission error % in Go/NoGo task. Higher score of Y-axis means lower inhibitory control.

C: Degree of hypothalamic damage is represented by hypothalamus volume %. Less volume means more hypothalamic damage. Food addiction tolerance is one of subscales of Yale Food Addiction Scale.

ROI correlation with psychological dimensions in HO group

I analyzed the correlation between the activation level of food-related regions of interest (ROIs) and the psychological phenotypes on presenting food cues (**Figure 19**). The hunger VAS score was correlated with an activation of the left caudate nucleus (*r=.546, P<.05*). In contrast, the satiety VAS score was correlated with right amygdala activation. There were significant negative correlations between YFAS and the left amygdala *(r=-.553, P=.04)*, bilateral putamen *(r=-.599, P=.024 and r=.595, P=.025,* left and right, respectively), and bilateral orbitofrontal cortex *(r=-.639, P=.014* and *r=-.705, P=.005*, left and right, respectively).

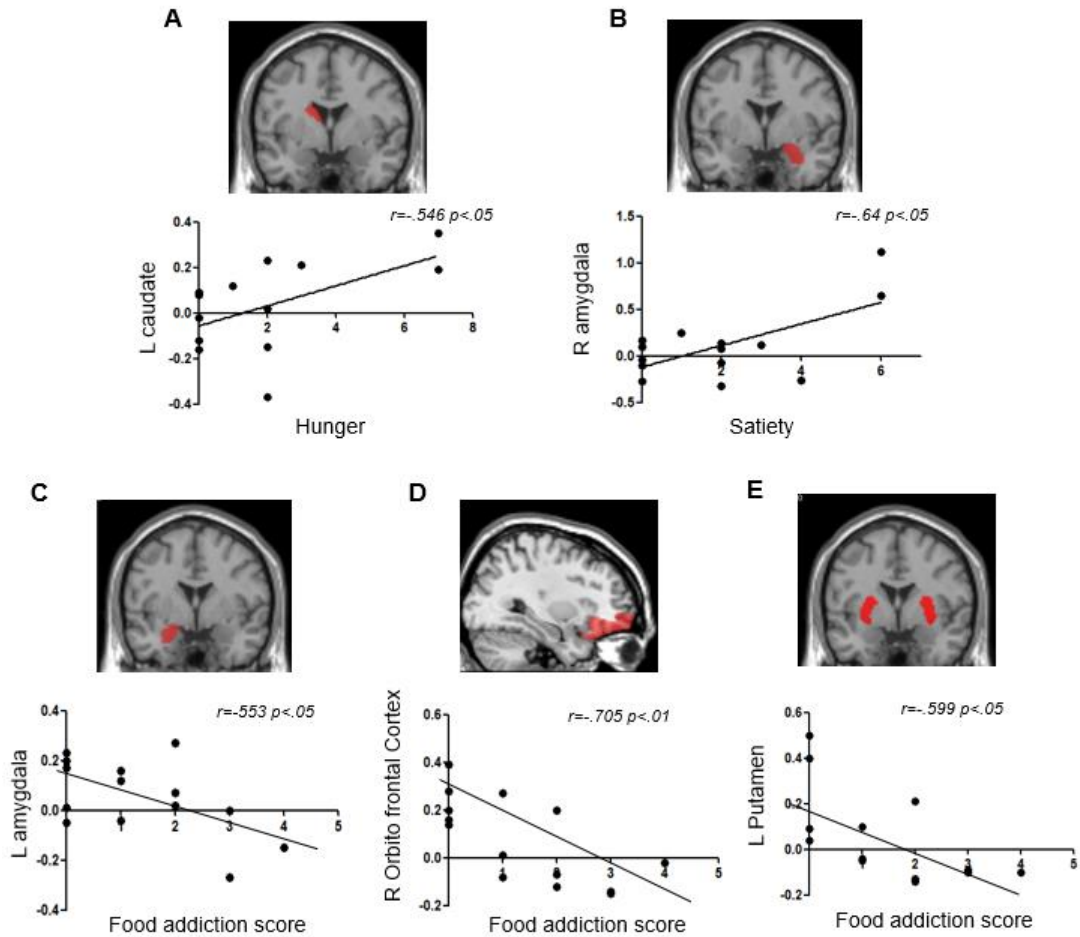

Figure 19. Reward related brain region activities are associated with psychological phenotypes related to food among HO patients.

Correlations between psychological phenotypes and parameter estimate beta value of ROIs within HO patients(n=14) using Pearson product moment correlation coefficient (2-tailed, $P < 0.05$).
Y-axis means the activation level of each ROI in food>object contrast. Hunger: hunger VAS score, Satiety: satiety VAS score, YFAS: Yale Food Addiction Scale total score.

Absence of significant fMRI findings in the HO group

Upon the application of a lenient threshold (uncorrected, $P<.005$, $k>30$), the whole-brain analysis revealed more activated regions, including the left superior temporal gyrus, left inferior frontal gyrus, bilateral rolandic operculum, left insula, left postcentral gyrus, right precentral gyrus, and left inferior temporal gyrus in the HO group (**Figure 20**). The right anterior cingulate cortex (ACC) and right superior frontal gyrus were less activated in the HO group, compared to others (**Table 6**). However, the whole-brain analysis revealed no significant differences in the brain regions between the groups, following the application of a stringent significance level of multiple comparison correction. Furthermore, I failed to observe significant correlation between the brain regions with weight gain or hypothalamic damage in the HO group.

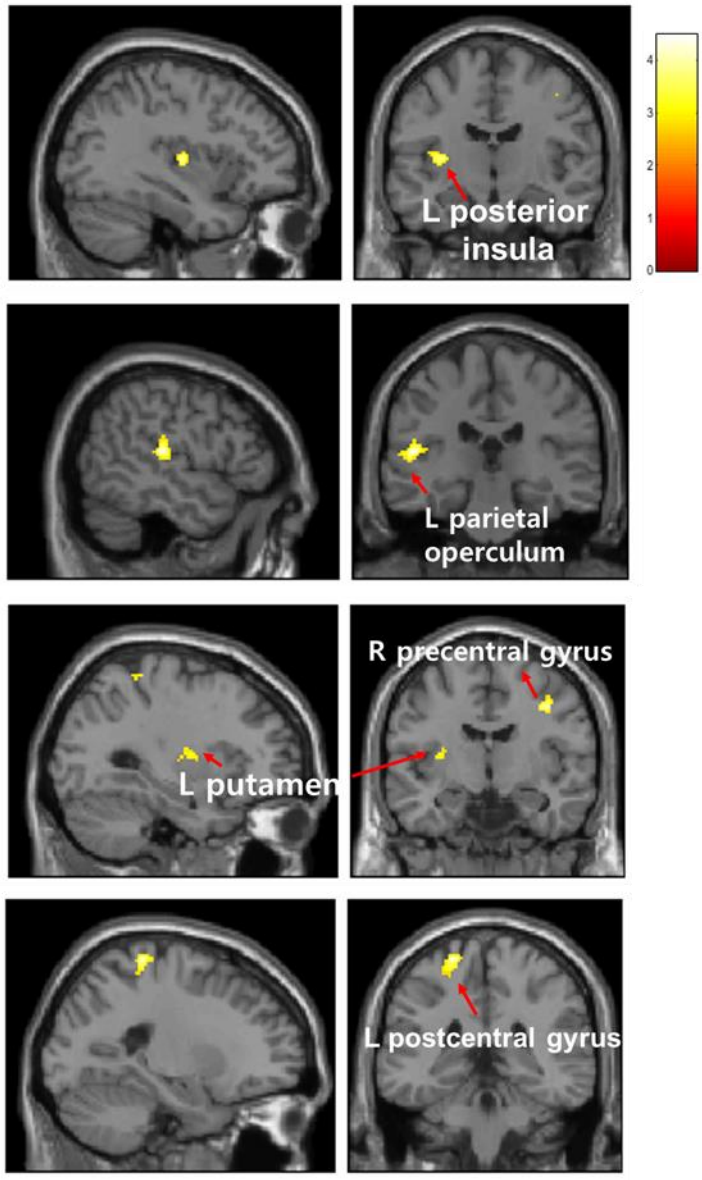

Figure 20. Brain regions activated in substantial weight gain HO group (n=14)

Table 6. fMRI cluster coordinate [HO(n=14) vs the others(n=40)]

	Cluster	Cluster size(k)	x	y	z	Z-value	Region	%	Voxel
HO>	1	176	-50	-26	12	4.10	L Superior temporal gyrus	65.34	115
							L Rolandic operculum	18.75	33
							L SupraMarginal gyrus	10.80	19
							L Postcentral gyrus	4.55	8
	2	113	-22	36	68	3.88	L Postcentral gyrus	92.92	105
	3	124	40	-8	42	3.82	R Precentral gyrus	65.32	81
	4	39	-54	-50	-8	3.82	L Inferior temporal gyrus	74.36	29
							L Middle temporal gyrus	25.64	10
	5	81	-36	-14	8	3.52	L Insula	45.68	37
							L Lenticular nucleus, Putamen	13.58	11
	6	33	26	-74	12	3.32	R Superior occipital gyrus	42.42	14
							R Calcarine	18.18	6
	7	34	-26	-84	10	3.25	L Middle occipital gyrus	76.47	26
	8	37	48	-18	22	3.23	R Rolandic operculum	62.16	23
	9	30	26	-66	32	3.22	R Superior occipital gyrus	86.67	26
	10	35	22	-78	0	3.09	R Lingual gyrus	91.43	32
	11	46	-38	22	24	3.18	L Inferior frontal gyrus	100	46
	12	31	-6	8	54	2.99	L Supplementary motor area	100	31
HO<	1	30	10	-34	-14	3.34	R Lobule III of cerebellar hemisphere	30	9
	2	50	14	44	4	3.27	R Anterior cingulate cortex	54	27
							R Superior frontal gyrus	46	23

Whole-brain analysis result table. Significance level: uncorrected $P<.005$, k>30, presented voxel>5

Post hoc analysis of HD

Hypothalamic volume and Muller grading

In whole patients, a Kruskal-Wallis test was performed to examine the difference in hypothalamic volume according to Muller grading. There was a significant difference in absolute and relative HT volume between groups (*H(2)=6.735, P=.034* and *H(2) =4.460, P=.015*). The post-hoc test showed that the grade 0 group had the largest HT volume, and there was no difference between grade 1 and 2(Table 7).

In CP patients, there was no significant difference in hypothalamic volume according to muller grading (0, 1, 2) in Kruskal-Wallis test. However, since there were only 5 participants in grade 0, I combined grade 0 and 1 (n=14). An independent sample t test was performed between the grade 0+1 group and the grade 2 group. There was no significant difference.

Table. 7. Kruskal-Wallis test results of whole patients

	Muller grading	N	*M*	*SD*	*H*	*P*	LSD
Absolute HT volume	0	30	791.25	163.37	6.735	.034*	0>2 0=1 1=2
	1	12	667.37	54.61			
	2	16	658.72	25.35			
Relative HT volume	0	30	0.0548	0.0120	8.368	.015*	0>1 1=2 0=2
	1	14	0.0429	0.0135			
	2	16	0.0497	0.0141			

LSD: Least significant difference

Muller grading and body weight gain

A Kruskal-Wallis test was performed to examine the difference in body weight change according to muller grading. There was a significant difference in body weight gain between the groups($H(2)=6.639,\ p=.036$). The post-hoc test showed the most body weight gain in the grade 2 group and no difference between grade 0 and 1.

In CP group, there is no significant body weight gain differences in muller grading group 0, 1 and 2 in Kruskal-Wallis test. An independent sample t-test was performed to determine the group difference between the grade 0+1 group and the grade 2 group (n=15). There was significantly more body weight gain in the grade 2 group compared to the grade 0+1 group (10.72% vs. 3.5%, $t(27)=2.058,\ P=0.49$).

HT volume and body weight gain

In the CP group, a one-way ANOVA analysis divided into four groups by quartiles of hypothalamic volume did not reveal any significant differences in body weight gain. An independent variable t-test divided the two groups by the median (0.470) hypothalamic volume in the CP group and found no significant difference.

Discussion

Study 1

Summary of the finding

I developed a novel method of HT volume measurement using T2-weighted MR images to evaluate the extent of hypothalamic damage in adult CP patients using an individually tailored segmentation method. In the present study, corrected postoperative HT volume was negatively associated with preoperative body weight, preoperative tumor volume, postoperative hypothalamic symptoms, and steroid daily dose in overall population. Of note, corrected postoperative HT volume was negatively associated with postoperative body weight as well as preoperative body weight and preoperative tumor volume in the primary surgery group, however, not with postoperative hypothalamic symptoms and steroid daily dose. I did not observe any significant correlations between the postoperative HT volume and postoperative weight gain parameters. In CP patients, a few studies have assessed HT damage; however, the study subjects were limited to patients with childhood- or adolescent onset CP [13, 14]. To the best of our knowledge, this is the first study to investigate HT volume measurements in adult-

onset CP patients.

Discussion

For HT volumetric assessments, previous studies mostly used established fixed landmarks and T1-weighted MR images. Several studies have attempted to evaluate HT volume manually [19, 52, 53] and semi-automatically [54-56]. Further optimized methods have been performed by reviewing descriptions of hypothalamic anatomy [54, 57] and criteria from other segmentation protocols [57-59]. For CP patients having severe structural damage, established fixed landmarks create critical problems as they are often severely distorted and displaced outwardly owing to a large space in the third ventricle. To overcome this limitation, I developed a novel individualized segmentation method using new landmarks, including the thalamus. However, T1-weighted MR images has a critical limitation as the MR image of the thalamus may be obscured [60], which could lead to overestimation of HT measurement by incorporating the thalamus. Indeed, our results demonstrate this problem of volume overestimation (**Figure 2**). To overcome this limitation, I adopted T2-weighted MR images which can be used to clearly visualize the thalamus. With this approach, the upper margin

of the HT was more accurate by avoiding the thalamus area. Furthermore, to precisely assess HT volume, I measured temporal lobe volume to correct the effect of whole brain size. Previous HT volumetric studies used specialized research setting for MR images with 0.5–1 mm slice thickness. This thin slice scan has better image quality and has been used for 3–dimentional reconstruction MR images. However, routine brain MRI for general clinical assessments usually does not use this thin thickness, including our hospital; MR images with 3 mm slice thickness are conventionally used in real–world clinical settings. Therefore, in the present study, I used MR images with 3 mm slice thickness. For wider usage of HT volume measurements, our new method may be more suitable for real world practice in terms of accuracy and accessibility.

Limitation

This study has several limitations. First, the median follow-up duration of our study was 2 years. Although excessive weight gain usually occurs in the first year after surgical resection of CP patients [8], HO is a long-term sequelae of CP; therefore, this interval may be short to fully represent the characteristics of HO. Second, I was unable to collect detailed information regarding eating behaviors or energy expenditure status of the study subjects owing to the retrospective nature of the study. Third, HT volume measurements were only performed using postoperative MR images. Therefore, I was unable to evaluate differences in pre and postoperative HT volume or distinguish relative contributions of the tumor itself and surgical resection on hypothalamic damage. Fourth, I measured the total volume of HT to evaluate the degree of hypothalamic damage, but not the volume according to the detailed hypothalamic region. Considering the importance of affected hypothalamic nuclei for the occurrence of HO, a meticulous approach for the regional measurement of the HT volume seems to be ideal. However, I could not confirm the association between the HT volume and postoperative weight change and region-specific assessment of damaged HT. Fifth, the present study could not compare the present

method to 1mm slice thickness MRI images. Future studies with 1 mm slice thickness MRI images would provide direct comparisons regarding the performance of HT volume measurement using 1 mm or 3 mm slice thickness. Moreover, although the T2-weighted MR images showed superior results in HT volume measurement compared with the T1-weighted MR images, it did not show robust associations with clinical parameters. Although the *P* value showed significant results in some parameters, the correlation coefficient was not as high as 0.3. There also may be false discoveries from the analysis due to multiple testing. Therefore, further validation studies are needed to better understand the clinical relevance of HT volume measurements assessing hypothalamic damage in CP patients. Finally, only patients with adult-onset CP were included in the present study, hence, it is unclear whether this approach is beneficial for childhood-onset CP as well.

Study 2

Summary of the finding

To elucidate the multifaceted mechanisms of hypothalamic obesity, I comprehensively performed multiple-dimensional analyses of hypothalamic structural damage, whole-brain response to food images, food-related cognition, food-related psychological characteristics, eating behaviors, and weight gain. Compared with controls, CP patients showed greater postoperative weight gain, lower neural activation in the left caudate nucleus in response to food images, higher food inattention, lower satiety, and higher restrained eating behavior. Within the CP group, a higher restrained eating behavior was significantly associated with lower activation in the bilateral fusiform gyrus.

Group difference: weight change and brain response

CP patients showed reduced activation in the left caudate nucleus and increased activation in the occipital gyrus and inferior frontal gyrus in response to food images. This reduced activation in the caudate nucleus, which plays a key role in controlling visual

attention and has been linked to attention-deficit hyperactivity disorder[61-63], may explain the lower attention to food observed in the Go/NoGo task. Similarly, the CP group had a lower activation compared to control group in the right caudate, which was not significant.

In Roth's study, CP patients showed reduced activation of the nucleus accumbens which is regarded as a reward center, when viewing pictures of food compared to controls [41]. Although the nucleus accumbens of the previous study and the caudate nucleus of the present study is not identical brain regions, I believe these two results are related with regard to striatal structures and reward processing. Thus, this result could add to the finding that CP patients show reduced activation in reward-related brain regions.

Moreover, since satiety is closely related to food reward, the present results of lower satiety could be explained by impaired activation of the caudate nucleus, which has a major role in food reward processing [61]. The occipital gyrus is well known to be the visual processing center of the brain [62], and the inferior frontal gyrus has been reported to have an important role in visual attention [63]. Therefore, it could be concluded that the brain regions with increased activation were associated with processing visual stimuli. In short, these between-group differences suggest that

hypothalamic damage could have altered brain function (attention to food images), which could be related to abnormal cognitive and behavioral responses to food and eating.

These results were not influenced by visual dysfunction since all participants did not have visual disturbance.

Group difference: psychologies and cognition

Patients with hypothalamic damage demonstrated impaired attention to food images and lower satiety. Our results are partly in concordance with previous studies that reported an altered perception of food images [41], increased eating disorder symptoms [7, 9], and less efficient use of executive control processes [17]. The lower attention to food could be the major driver of lower satiety (higher hunger) and abnormal eating behavior. Lower attention to eating (i.e., mindless eating) is suggested as one of the major causes of obesity [64, 65]. Furthermore, paying attention to food has been proposed to be a better solution for maladaptive eating behaviors [66]. These findings suggest that a frequent mindless eating pattern could be a unique pathogenic mechanism of hypothalamic obesity, due to low satiety and low attention to food.

Higher restrained eating behavior was observed in patients

with hypothalamic damage. According to previous studies, restrained eating behavior results in binge eating and overeating once food is available [67, 68], which leads to weight gain. A higher restrained eating score has been reported in patients with childhood-onset craniopharyngioma [7, 15, 69]. The present study validates these findings and further expands the findings in patients with adult-onset craniopharyngioma.

In patients with hypothalamic damage, brain responses in the fusiform gyrus, OFC, hippocampus, and amygdala correlated with restrained eating, hypothalamic damage, disordered eating attitude, inhibitory control, attention bias, attention orienting, or weight percent change. Higher brain response in the fusiform gyrus was associated with lower restrained eating. This result is consistent with recent reports showing an association between the fusiform gyrus and distorted body image perception among patients with eating disorders [39, 70, 71]. The brain response in the OFC was associated with a disordered eating attitude and inhibitory control. The OFC is a well-known brain region related to behavior control [40, 72]. The brain response in the hippocampus was associated with weight gain and attention. The hippocampus is well-known to regulate selective attention and energy balance [73, 74]. Hippocampal damage may interfere with the inhibition of appetitive and eating behaviors [75].

The amygdala is recognized to have an important role in attention and is related to food reward processing [40, 76]. These findings provide mechanistic links through which hypothalamic damage could lead to brain network dysfunctions and psychological problems.

Cognitive dysfunctions in CP patients

The major strength of our study is that it is the first to provide direct evidence to elucidate the mechanism of the link between hypothalamic damage and neural/psychological/behavioral dimensions and health outcomes. Particularly, this study investigated cognitive dysfunctions in patients with craniopharyngioma and endeavored to establish their correlation with psychological and brain dysfunctions. In addition, to the best of our knowledge, this is the only adult-onset craniopharyngioma fMRI study with an adequate control group and a sufficient number of hypothalamic damage patients (compared to a similar previous study with four patients) [41].

Benefits of HT volume assessment methods

Unlike Muller or Puget grading method, the hypothalamic volume assessment method is expressed as a continuous variable. The ANOVA by muller grading in the CP group did not reveal any significant results. I only found a difference in body weight gain between the grade 0+1 group and the grade 2 group. However, the hypothalamic volume index was used to analyze the correlation with various brain regions, questionnaires, and cognitive variables. Therefore, I propose that the hypothalamic volume index is a superior HD assessment method for identifying predictors of hypothalamic obesity and understanding hypothalamic obesity.

Prospection for treatment

Based on these results. There is a need for cognitive interventions to improve food cognition in patients with severe hypothalamic damage. Examples of such interventions include keeping a food diary and food attention training. Pharmacologically, GLP-1 can be an effective treatment. Overall, appropriate psychological, cognitive, and pharmacologic treatments are all needed to prevent hypothalamic obesity.

Limitation

Regarding limitations, first, I have used a neuroimaging statistical threshold level (uncorrected $P< 0.005$) that has been recommended by previous studies [77, 78]. This may lead to a probability of false positivity. Second, the present study did not have measurements available of resting energy expenditure or circadian rhythm. Third, I only conducted fMRI scans at the baseline level. I did not assess brain responses related to satiety due to difficulties in controlling the internal state in our outpatient setting. Since the hypothalamus is associated with the internal state, further research is suggested to investigate the association between various eating-related phenotypes and brain responses regarding the internal state. Fourth, since hypothalamic obesity occurs in only around half of the patients who have undergone surgical removal of craniopharyngioma, a considerable proportion of CP patients shared similar clinical features with the control group. A future study focused on more severe CP patients would provide more severe phenotype results. Fifth, there is a significant difference in follow-up duration between the groups. Due to difficulties in recruiting CP patients, it was not possible to match the follow-up duration with the control group. this could confound the results. Sixth, the data analysis was not blinded

regarding CP or control. This lack of blinding may have confounded the analysis. Seventh, some of the fMRI results have discrepancy between the left and right results. These discrepancies indicate that there could be high chance of false positivity. Finally, the present study was an explorative study to discover hypothalamic obesity-related cognitive and neurofunctional mechanisms using various phenotypes. Therefore, due to multiple comparisons, there is a substantial risk of reporting false-positive results.

Conclusion

In conclusion, our study demonstrated a new method of HT volume measurement using T2-weighted MR images obtained from a conventional clinical setting using a 3 mm slice thickness for the MR images. In CP patients, significant negative associations of postoperative HT volume with preoperative/ postoperative body weight and tumor volume were observed, suggesting a relatively greater effect of tumor-induced hypothalamic injury than of surgically induced hypothalamic injury on body weight. Unlike previous HT volume measurement methods based on MR images with 1 mm slice thickness, the novel HT volume measurement method can be used in conventional MRI to provide a new, broader practical opportunity for the analysis of HO in the clinical setting. Moreover. Multi phenotyping analysis study elucidated that hypothalamic damage could lead to dysfunction in brain regions related to attention and food reward processing and result in food inattention, restrained eating behavior, and weight gain. This understanding of the pathological mechanisms could break new grounds on psycho-behavioral therapeutics targeted for hypothalamic obesity patients.

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국문 초록

이미우
의과학 전공
서울대학교 의과대학원

목적: 에너지 항상성을 조절하는 중추로 알려진 시상하부의 손상은 때때로 심각한 비만을 야기할 수 있다. 본 논문은 두개인두종 환자 코호트 대상으로 시상하부의 손상 정도를 MR 이미지 기반으로 평가하는 방법을 개발하고, 다차원 표현형 분석을 통해 시상하부 비만의 특성을 알아본 두 가지 연구로 진행되었다.

방법: 첫번째 연구는 78 명의 종양 제거 수술을 받은 성인 발병 두개인두종 환자를 대상으로 진행되었다. T1 강조 MR(Magnetic resonance; 자기 공명) 이미지와 T2 강조 MR 이미지를 사용하여 각각 시상하부의 부피를 측정하였고, 뇌의 크기를 보정하기 위하여 측두엽의 부피를 측정하였다. 두번째 연구에서는 29 명의 수술 후 두개인두종 환자와 31 명의 비기능성 뇌하수체 종양 환자를 대상으로 뇌의 구조와 기능. 그리고 심리, 인지, 행동 표현형의 다차원 분석을 하였다. 연구 대상자들은 구조 MR 영상과 기능 MR 영상을 촬영한 후 다양한 심리 설문지와 인지과제를 진행하였다.

결과: 첫번째 연구에서 뇌의 크기를 고려해 보정된 수술 후 시상하부의 볼륨은 T1 강조 MR 이미지를 사용한 값과 T2 강조 MR 이미지를

사용한 값이 유의한 상관을 나타냈다. 하지만 T1 강조 MR 이미지를 사용하였을 때에는 MR 신호의 문제 때문에 시상이 보이지 않아 심각한 시상하부의 손상이 있는 환자에서는 시상하부의 부피 측정이 과대 측정되는 것을 발견하였다. 따라서 의료데이터를 가진 72 명의 환자를 대상으로 T2 강조 MR 이미지를 통해 측정된 시상하부 부피를 사용하여 그 임상적 의의를 평가하였다. 수술 후의 시상하부 볼륨은 수술 전 체중, 그리고 종양의 부피와 부적 상관을 보였다. 일차 수술을 받은 두개인두종 환자들의 하위 집단 분석(n=56)에서는 수술 전과 수술 후 체중 모두 시상하부의 부피와 부적인 상관이 있었다.

두번째 연구에서 두개인두종 환자군은 대조군에 비해 유의하게 높은 수술 후 체중 증가를 보였다. 시상하부 손상 환자군은 또한 대조군에 비해 더 많은 시상하부 손상이 있었으며, 음식 사진을 보았을 때 왼쪽 미상핵의 낮은 활성 반응이 관찰되었다. 두개인두종 환자군은 대조군에 비해 더 낮은 포만감과 더 많은 제한 섭식 행동을 보고하였으며, 인지과제에서 음식에 대해 더 부주의함을 관찰하였다. 두개인두종 그룹 내 분석에서는 식이 행동 점수와 주의력 관련 지표들은 방추상회, 안와전두피질, 편두체와 같은 음식 인지 및 보상 영역의 활성화와 연관이 있었다.

결론: 첫번째 연구를 통해 T2 강조 MR 이미지를 사용하는 새로운 시상하부 부피 측정 방법을 통해 성인 발병 두개인두종 환자에서 수술 후 시상하부의 볼륨이 수술 전후 체중과 연관이 있음을 밝혔고, 두번째

연구를 통해 섭식과 관련된 다양한 표현형의 결과는 시상하부의 손상이 뇌 반응, 주의, 포만감, 섭식 행동의 변화를 일으키고, 그 결과로 체중 증가를 야기할 수 있음을 시사한다. 본 연구들은 시상하부 비만의 새로운 신경-심리-행동 메커니즘을 제안한다.

Keyword: 비만, 기능 자기 공명 영상, 주의, 두개인두종, 시상하부 비만

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