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## The interrelationship of body mass index with gray matter volume and resting-state functional connectivity of the hypothalamus

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### Abstract

**Background**—The hypothalamus plays an important role in regulating body weight through its interactions with multiple brain circuits involved in distinct aspects of feeding behavior. Yet, how hypothalamic gray matter volume (GMV) and connectivity may be related to individual differences in body weight remains unclear. We tested the hypothesis that the hypothalamus shows enhanced resting-state functional connectivity (rsFC) with regions of the reward, motivation, and motor circuits in positive correlation with body mass index (BMI) and the opposite with those associated with inhibitory control. We further examined the interdependent relationships between hypothalamic GMV, connectivity, and body weight.

**Methods**—Using seed-based rsFC and voxel-based morphometry analyses, we examined the relationship between the rsFC and GMV of the hypothalamus and BMI in 105 healthy humans. Additionally, we employed mediation analyses to characterize the inter-relationships between hypothalamic connectivity, GMV, and BMI.

**Results**—A whole-brain multiple regression showed that BMI was positively correlated with hypothalamic rsFC with the insula, thalamus, globus pallidus, and cerebellum, and negatively correlated with hypothalamic rsFC with the superior parietal lobule. Thus, higher BMI was associated with enhanced hypothalamic connectivity with regions involved in motivated feeding and reduced connectivity with those in support of cognitive control of food intake. A second whole-brain multiple regression revealed a positive correlation between hypothalamic GMV and the hypothalamus-posterior insula connectivity. Finally, the relationship between hypothalamic

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GMV and BMI was significantly and bidirectionally mediated by the hypothalamus-posterior insula connectivity.

**Conclusions**—The current findings suggest that the hypothalamus differentially interacts with the motivation, motor, and control circuits to regulate BMI. We further found evidence for the interdependence of hypothalamic structure, function, and body weight, which provides potential insights into the brain mechanisms of obesity.

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## 1. Introduction

The hypothalamus plays a critical role in regulating energy balance and body weight. In early rodent studies, lesions of the lateral and ventromedial hypothalamus altered food intake, resulting in weight loss and weight gain, respectively [1]. In humans, hypothalamic dysfunctions have been implicated in eating disorders including anorexia and obesity [2]. As feeding behavior involves multiple neural circuits of motivation and behavioral control [3], it is important to examine the cortical and subcortical connectivities with the hypothalamus to understand the complex mechanisms of body weight maintenance.

Many studies have employed resting-state functional connectivity (rsFC) to examine the roles of hypothalamic circuits in the regulation of energy intake. For instance, the hypothalamus is functionally connected with the striatum and orbitofrontal cortex in healthy individuals [4] and this rsFC was shown to be elevated in those with obesity [5–7]. The hypothalamus exhibited attenuated connectivity with the posterior insula following satiety from milkshake consumption [8] but enhanced connectivity with the inferior frontal gyrus in correlation with self-reported scores of cognitive restraint [9]. After sucrose ingestion, obese relative to lean women exhibited greater hypothalamic connectivity with the putamen but weaker connectivity with the nucleus tractus solitarius in the brainstem involved in cardiovascular and gastrointestinal control [10]. Obese individuals also demonstrated elevated connectivity between the hypothalamus and the occipital and dorsal anterior cingulate cortices in response to food cues, indicating enhanced sensitivity to food-related saliency [11]. Together, these findings suggested altered hypothalamic connectivity with distributed regions implicated in motivation, cognitive control, and saliency as a result of food intake or obesity.

Individual differences in body weight have been linked with alterations in the gray matter volumes (GMV) of the hypothalamus. For instance, hypothalamic GMV was positively correlated with body mass index (BMI) and leptin levels in healthy individuals [12] as well as hunger scores in a sample of both normal-weight and overweight subjects [13]. In contrast, patients with anorexia nervosa exhibited hypothalamic atrophy [14], the extent of which was negatively correlated with BMI [15]. Work in rodents demonstrated that food restrictions shortened dendrite length of neurons and reduced the number of orexin-immunoreactive cells in the ventromedial hypothalamus [16]. Diets rich in saturated fat were associated with accumulation of astrocytes and activated microglia as well as saturated fatty acids in the hypothalamus [17]. Thus, altered food intake can modify the neuronal morphology in the hypothalamus and axonal projections to extranuclear targets, potentially impacting hypothalamic volume and connectivity.

Here, we sought to understand whether or how individual differences in hypothalamic GMV and rsFC may be related to BMI in healthy humans. We tested the hypothesis that BMI exhibits a positive relationship with hypothalamic connectivity with reward, motivation, and motor circuits to support habitual approach to food but a negative relationship with hypothalamic connectivity with executive control regions involved in the regulation of food intake. Additionally, we examined whether hypothalamic GMV varies in relation to BMI and how hypothalamic GMV and connectivity may inter-relate to impact individual differences in BMI in a mediation analysis.

## 2. Methods

### 2.1 Participants

One hundred and five healthy adults (58 women; age =  $31.4 \pm 12.6$  years; BMI in  $\text{kg/m}^2 = 25.8 \pm 4.7$ , mean  $\pm$  S.D., range: 18.2 – 40.4) participated in the study. All subjects were screened to be free from major medical, including neurological, illnesses and Axis I psychiatric disorders according to DSM-IV. No participants were currently on psychotropic medications and all tested negative for illicit substances on the study day. Subjects provided written informed consent after details of the study were explained, in accordance to institute guidelines and procedures approved by the Yale Human Investigation Committee.

### 2.2 Imaging protocol and data preprocessing

Conventional T1-weighted spin echo sagittal anatomical images were acquired for slice localization using a 3T scanner (Siemens Trio). Anatomical images of the functional slice locations were next obtained with spin echo imaging in the axial plane parallel to the AC–PC line with TR = 300ms, TE = 2.5ms, bandwidth = 300 Hz/pixel, flip angle =  $60^\circ$ , FOV =  $220 \times 220\text{mm}$ , matrix =  $256 \times 256$ , 32 slices with slice thickness = 4mm and no gap. Functional, blood oxygen level-dependent (BOLD) signals were acquired with a single-shot gradient echo echoplanar imaging (EPI) sequence. 32 axial slices parallel to the AC–PC line covering the whole brain were acquired with TR = 2,000ms, TE = 25ms, bandwidth = 2,004 Hz/pixel, flip angle =  $85^\circ$ , field of view =  $220 \times 220\text{mm}$ , matrix =  $64 \times 64$ , 32 slices with slice thickness = 2.5mm and no gap. One 10-min resting state BOLD scan was obtained for each participant with eyes closed.

Data were analyzed with SPM12 (Wellcome Trust Centre for Neuroimaging). Images from the first five TRs were discarded to enable the signal to achieve steady-state equilibrium between RF pulsing and relaxation. Standard image preprocessing was performed. Images were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject per run from the realigned image volumes. These mean images were co-registered with the high-resolution structural image and then segmented for normalization with affine registration followed by nonlinear transformation with a voxel size of 2-mm isotropic. The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. Finally, the images were smoothed with a Gaussian kernel of 4-mm FWHM.

To reduce spurious BOLD variances that were unlikely to reflect neuronal activity, additional preprocessing was applied to the data. Signals from the ventricular system, white matter, and whole brain were removed through a linear regression in addition to the six parameters obtained by rigid body head-motion correction. As BOLD fluctuations below a frequency of 0.1Hz may contribute to regionally specific BOLD correlations, we applied a temporal band-pass filter ( $0.009\text{Hz} < f < 0.08\text{Hz}$ ) to the time course to obtain low-frequency fluctuations.

To minimize the effects of micro head motion ( $>0.1\text{mm}$ ) which represents a significant source of spurious correlations in rsFC analysis, we implemented the “scrubbing” method [18] to remove time points affected by head motions. Briefly, for every time point  $t$ , we computed the frame-wise displacement given by  $FD(t) = |d_x(t)| + |d_y(t)| + |d_z(t)| + |\alpha(t)| + |\beta(t)| + |\gamma(t)|$  where  $(d_x, d_y, d_z)$  and  $(\alpha, \beta, \gamma)$  are the translational and rotational movements, respectively. The second head movement metric was the root mean square variance (DVARs) of the differences in % BOLD intensity  $I(t)$  between consecutive time points across voxels, computed as follows:  $DVARs(t) = \sqrt{\langle |I(t) - I(t-1)|^2 \rangle}$ , where the brackets indicate the mean across voxels. Finally, to compute each subject’s correlation map, we removed time points that exceeded the head motion limit  $FD(t) > 0.5\text{mm}$  or  $DVARs(t) > 0.5\%$  [18]. On average, 1% of the time points were removed across subjects.

### 2.3 Seed Based Correlation and Regression Analyses

For seed-based functional connectivity, we obtained the hypothalamus mask from the WFU PickAtlas [19] (Fig. 1, inset). For each subject, the correlation coefficient between the averaged time course of the seed region and the time courses of every other voxel was computed. Correlation maps were then converted to z score maps by Fisher’s z transform:  $z = 0.5 \log_e \left[ \frac{1+r}{1-r} \right]$ . The Z maps were used in group, random effect analyses, in which we conducted whole-brain multiple regressions against the normalized BMI score (see below) with age and sex as covariates in one model as well as against hypothalamic GMV (see below), again controlling for age and sex, in another model. All activations were reported in MNI coordinates. Unless otherwise noted, the results of the multiple regressions were examined with  $p_{\text{voxel}} < 0.001$  in combination with  $p_{\text{cluster}} < 0.05$  with cluster size of 89 voxels as determined by AFNI’s 3dClustSim with 10,000 Monte Carlo simulations and inherent smoothness estimated from the data.

### 2.4 Voxel-Based Morphometry

We implemented voxel-based morphometry (VBM) to quantify the gray matter volume (GMV) of the same hypothalamus mask as used for rsFC with the CAT12 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>). VBM analysis identifies differences in the local composition of brain tissue, accounting for large-scale variation in gross anatomy and location. The analysis includes spatially normalizing individuals’ structural images to the same stereotactic space, segmenting the normalized images into distinct brain tissues, and smoothing the gray matter (GM) images. T1-images were first co-registered to the MNI template space ( $1.5\text{-mm}^3$  isotropic voxels) using a multiple-stage affine transformation. Co-registration was performed with a coarse affine registration using mean square differences,

followed by a fine affine registration using mutual information. Coefficients of the basis functions that minimize the residual square difference (between individual image and the template) were estimated. T1 images were then corrected for intensity bias field and a local means denoising filter and segmented into cerebrospinal fluid, gray, and white matter. The segmented and initially registered tissue class maps were normalized using DARTEL. We used the standard DARTEL template in MNI space for the DARTEL normalization. Normalized GM maps were modulated to obtain the absolute volume of GM tissue corrected for individual brain sizes. Finally, the GM maps were smoothed by convolving with an isotropic Gaussian kernel (FWHM = 6mm).

In group analyses, we used BMI as the predictor and age and sex as the covariates to examine volumetric correlates of the BMI in a whole-brain regression. As BMI did not exhibit a normal distribution ( $p = .001$ , Shapiro Shapiro-Wilk test), we applied log transformation to the data, which normalized the distribution ( $p = .11$ ). The log transformed BMI was used in subsequent analyses. We conducted a separate set of analyses with the non-transformed BMI and found almost identical results. In addition to the whole brain analyses, we also used the hypothalamus (same mask used in rsFC) in a region-of-interest analysis to determine the relationship between hypothalamic GMV and BMI.

## 2.5 Mediation analysis

To examine the potential inter-relationships of hypothalamic connectivity, GMV, and BMI, we conducted mediation analyses using a single-mediator model [20,21]. Specifically, in a mediation analysis, the relation between the independent variable  $X$  and dependent variable  $Y$  (i.e.,  $X \rightarrow Y$ ) is tested to determine whether it is significantly mediated by a variable  $M$ . The mediation test is performed using the following three regression equations:

$$Y = i1 + cX + e1$$

$$Y = i2 + c'X + bM + e2$$

$$M = i3 + aX + e3$$

where  $a$  represents  $X \rightarrow M$ ,  $b$  represents  $M \rightarrow Y$  (controlling for  $X$ ),  $c'$  represents  $X \rightarrow Y$  (controlling for  $M$ ), and  $c$  represents  $X \rightarrow Y$ .  $a$ ,  $b$ ,  $c$ , and  $c'$  are commonly referred to as “path coefficients” or simply “paths”. Variable  $M$  is said to be a mediator of connection  $X \rightarrow Y$ , if  $(c - c')$ , which is mathematically equivalent to the product of the paths  $a \times b$ , is significantly different from zero [20]. If  $(c - c')$  is different from zero and the paths  $a$  and  $b$  are significant, then one concludes that  $X \rightarrow Y$  is mediated by  $M$ . In addition, if path  $c'$  is not significant, it indicates that there is no direct connection from  $X$  to  $Y$  and that  $X \rightarrow Y$  is completely mediated by  $M$ . Significant correlations between  $X$  and  $Y$  and between  $X$  and  $M$  are required to perform the mediation test. The analysis was performed with package Lavaan [22] in R (<https://www.r-project.org>). To test the significance of the mediation effect,

we used the bootstrapping method as it is generally considered advantageous to the Sobel test [20].

Specifically, we evaluated the inter-relationships between hypothalamic GMV, hypothalamus-insula connectivity strength (see Results), and BMI. We considered all six models (see Results). In Model 1, hypothalamic GMV served as the independent variable (X), hypothalamus-insula connectivity as the dependent variable (Y), and BMI as the mediator (M):  $GMV \rightarrow BMI \rightarrow \text{connectivity}$ . In Model 2, GMV, BMI, and connectivity served as X, Y, and M, respectively. In Model 3, GMV, BMI, and connectivity served as X, Y, and M, respectively. In Model 4, BMI, connectivity, and GMV served as X, Y, and M, respectively. In Model 5 connectivity, BMI, and GMV served as X, Y, and M, respectively. Finally, in Model 6 connectivity, GMV, and BMI served as X, Y, and M, respectively.

### 3. Results

#### 3.1. BMI and hypothalamic connectivity

A whole-brain multiple regression of hypothalamic connectivity with BMI as the predictor and age and sex as the covariates showed that BMI was positively correlated with hypothalamic connectivity with the left insula, cerebellum, and a cluster containing both the bilateral thalamus and right globus pallidus. BMI also exhibited a negative correlation with hypothalamic connectivity with a cluster containing the left superior parietal lobule (SPL) and dorsal precuneus (Fig. 1, Table 1).

#### 3.2. BMI and hypothalamic GMV

A whole-brain regression of GMV with BMI as the predictor revealed no significant results. In a region-of-interest analysis, the hypothalamic GMV was significantly and positively correlated with BMI after controlling for age ( $r = .2, p = .04$ ).

#### 3.3. Hypothalamic GMV and functional connectivity

We examined hypothalamic connectivity in a whole-brain analysis with the GMV as a predictor and age and sex as covariates. The GMV of the hypothalamus showed a significant negative relationship with the hypothalamic connectivity with the gray matter along bilateral parieto-occipital fissure and anterior calcarine sulcus (Fig. 2). At a slightly more liberal threshold (cluster size = 84), hypothalamic GMV was also positively correlated with hypothalamic connectivity with the left posterior insula.

Hypothalamic connectivity with the posterior insula was positively correlated with both BMI and hypothalamic GMV. Indeed, the results of the two regressions (i.e., with BMI as well as with hypothalamic GMV as the predictor, as shown in Fig. 1 and Fig. 2) overlapped in the left posterior insula (Fig. 3A). We extracted the connectivity Z values for the overlapping voxels in the posterior insula for each subject and verified that the connectivity Z values were significantly and positively correlated both with BMI and hypothalamic GMV across subjects (Fig. 3B, C).

### 3.4. Mediation analysis

As the left posterior insula connectivity with hypothalamus was significantly correlated with both BMI and hypothalamic GMV, we examined their inter-relationships in a mediation analysis (Fig. 4; Table 2). In Model 1, BMI contributed to hypothalamic GMV, which in turn contributed to hypothalamic-insula connectivity: BMI  $\rightarrow$  GMV  $\rightarrow$  connectivity. That is, BMI and hypothalamus-insula connectivity served as the independent and dependent variable, respectively, whereas hypothalamic GMV served as the mediator. The model was not significant (mediation effect  $p = .076$ ). In Model 2, GMV  $\rightarrow$  BMI  $\rightarrow$  connectivity, there was no significant mediation effect ( $p = .068$ ). Model 3, GMV  $\rightarrow$  connectivity  $\rightarrow$  BMI, showed a significant mediation effect ( $c - c' = 13.79$ ,  $p = .009$ , 95% confidence interval = [5.20 25.87]). Specifically, the path coefficient  $c$  (i.e., GMV  $\rightarrow$  BMI before accounting for the mediating effect of hypothalamus-insula connectivity) was significant ( $p = .02$ ) and the path coefficient  $c'$  (i.e., after accounting for the mediating effect) was not significant ( $p = .35$ ). Thus, the hypothalamus-insula connectivity fully mediated the relationship between hypothalamic GMV and BMI. Model 4, BMI  $\rightarrow$  connectivity  $\rightarrow$  GMV, also showed a significant mediation effect ( $c - c' = .001$ ,  $p = .014$ , 95% confidence interval = [.001 .002]). The path coefficient  $c$  (i.e., BMI  $\rightarrow$  GMV before accounting for the mediating effect of hypothalamus-insula connectivity) was significant ( $p = .016$ ) and the path coefficient  $c'$  (i.e., after accounting for the mediating effect) was not significant ( $p = .32$ ), indicating a full mediation. In Model 5, connectivity  $\rightarrow$  BMI  $\rightarrow$  GMV, and Model 6, connectivity  $\rightarrow$  GMV  $\rightarrow$  BMI, the mediation effect was not significant ( $p$ 's  $> .38$ ). Both Model 3 and 4 remained significant after correction for false discovery rate.

## 4. Discussion

We found that the hypothalamus exhibited contrasting connectivity patterns with distinct brain regions in relation to BMI. Specifically, higher BMI was associated with greater hypothalamic rsFC with brain regions involved in interoception and motivation, including the insula and thalamus, as well as regions in the motor circuit, including the globus pallidus and cerebellum. In contrast, BMI was negatively associated with hypothalamic rsFC with the superior parietal lobule, a region implicated in executive control. BMI was also positively correlated with hypothalamic GMV, both of which were positively predictive of the strength of hypothalamic connectivity with the left posterior insula. Mediation models revealed that hypothalamic connectivity with the left posterior insula mediated the bidirectional influence between the hypothalamic GMV and BMI. Together, the findings characterized the relationships between BMI and hypothalamic morphology as well as functional connectivity.

### 4.1 Hypothalamus circuits in regulation of body weight

Food intake is regulated by interconnected brain circuits in which the hypothalamus interacts with various cortical and subcortical regions implicated in reward, cognitive, and motor functions [3]. Within this system, regions associated with reward processing including the orbitofrontal cortex and ventral striatum and with interoception including the posterior insula have been shown to respond to the appetitive characteristics of food, potentially promoting feeding behavior. Indeed, studies reported increased hypothalamic rsFC with the insula, medial orbitofrontal cortex, and ventral striatum in obese individuals [5–7] and

decreased connectivity with the posterior insula during satiety [8]. In contrast, activity and connectivity in the frontal and parietal cortices have been associated with inhibitory control of eating behavior [23]. Yet, the evidence that supports hypothalamic connectivity with these regions in the regulation of energy balance and body weight remains sparse.

The finding of hypothalamic connectivity with the insula in correlation with BMI is supported by a recent study showing that hypothalamic connectivity with the insula was positively correlated with BMI as well as diminished quality of life related to body weight in both lean and obese subjects [24]. Importantly, the same study additionally used positron emission tomography to demonstrate that this connectivity was related to attenuated hypothalamic norepinephrine transporter availability which is implicated in emotional processing, suggesting the close relationship between body weight, neurobiological alterations, and mental well-being [24]. The current work is also in keeping with previous reports of increases in the right insular activation to hunger and food cues [25] but decreases in the right posterior insular activity after eating [26]. Meta-analyses have also implicated both the anterior and posterior insula in response to food reward [27]. Greater hypothalamic and bilateral (anterior and posterior) insular activations were demonstrated in response to high- than low-calorie food images in overweight and healthy individuals [28]. In contrast, glucose ingestion decreased activity in the left anterior and posterior insula [29] and hypothalamus [30] with the hypothalamus showing less reduction in obese compared to lean subjects [31]. Thus, the hypothalamus and posterior insula are involved in motivating food intake both in healthy and overweight individuals.

While the insula is commonly associated with interoception, recent research has demonstrated the heterogeneity of insular functions which may encompass energy balance and reward. For instance, the posterior insula is involved in the emotional and motivational aspects of food intake [32] and functionally connected with sensorimotor regions [33]. As such, the insula may contribute to the processing of interoceptive information about bodily states important for homeostatic regulation. Additionally, studies have implicated the insula in drug addiction. Individuals with cocaine and heroin dependence showed reduced GMV in the right posterior insula [34]. Smokers who suffered damage to the insula, as compared to other brain regions, were more successful in smoking cessation, likely as a result of reduced craving [35]. Finally, as demonstrated in humans [36], the anatomical connections between hypothalamus and insula may directly facilitate the integration of taste/gustatory, interoceptive, and hedonic signals to motivate drug/food seeking and consumption.

BMI was positively correlated with hypothalamic connectivity with the thalamus, consistent with a role of the hypothalamic-thalamic-striatal circuit in motivating feeding behaviors. In rodents, lesions of the thalamus impaired locomotor activity to acquire food [37], food preference learning, and instrumental conditioning for food reward [38]. Food expectation as well as learning of cue-sucrose association activated the thalamus, as assessed by c-Fos expression, a marker of neuronal excitation [39]. In non-human primates, neurons in the centromedian thalamus responded differentially to distinct contingencies to obtain food rewards [40]. In human imaging, the thalamus responded not only to action selection vs. rest [41] but also to food vs. non-food imagery [42] as well as intake of caloric vs. non-caloric sweetener [43]. The thalamus receives extensive inputs from the hypothalamus, including



serotonergic and peptidergic projections, both of which have been associated with the control of food intake [44]. Thus, the current findings add to the literature by shedding light on the influence of thalamus-hypothalamus connectivity on body weight.

Food intake requires the integration of motivational and motor processes [45]. Here, we found that hypothalamic connectivity with the globus pallidus and cerebellum, both central to the cerebellar-thalamic-striatal-cortical circuit of action control, was positively correlated with the BMI. Neurons in the globus pallidus increased firings when monkeys reached for food or initiated motor response to receive food reward but not to avoid electric shock [46]. Neuronal activity in the cerebellum also reflected food anticipation and cerebellar stimulation induced feeding behavior in rodents [47]. In humans, the globus pallidus showed higher activation to high-calorie food vs. neutral stimuli in positive correlation with BMI in obese individuals [48] and reduced activation after leptin treatment in leptin-deficient patients [49]. The cerebellum showed increased regional cerebral blood flow [50] as well as connectivity with the left posterior insula [9] during fasting vs. satiation and enhanced activation to images depicting high vs. low calorie-food [51]. Further, lower cerebellum-hypothalamus resting state connectivity predicted weight loss in a 3-month diet follow-up in overweight individuals [5]. Thus, the current findings extend the literature in implicating the globus pallidus and cerebellum in feeding behavior.

The negative correlation between BMI and hypothalamic connectivity with the SPL likely reflects diminished behavioral control in individuals with higher BMI. In support, the SPL showed higher activation when participants inhibited their urge to eat as compared to when they imagined eating during the presentation of visual food stimuli [52]. Further, the SPL responded to incongruent vs. congruent trials in the Stroop task in positive correlation with the restraint scores of the Eating Disorder Examination Questionnaire [53]. When instructed to “crave” rather than “resist” during exposure to food cues, patients who underwent gastric-bypass surgery showed attenuated SPL activation [54]. Taken together, the current study found a contrasting pattern of hypothalamic connectivities with regions involved in reward, saliency, interoception and motor processing and those involved in executive control, in relation to BMI.

#### **4.2 BMI, hypothalamic GMV, and hypothalamic connectivity with posterior insula**

The finding of hypothalamic GMV in positive correlation with BMI is in line with a previous report of a positive relationship between hypothalamic GMV and BMI as well as plasma leptin levels in healthy individuals [12]. Patients with anorexia nervosa also demonstrated atrophy in the hypothalamus [14] and the extent of this atrophy was negatively related to BMI [15]. It is worth noting that another study reported a negative correlation between BMI as well as waist circumference and hypothalamic GMV [55]. Other investigations including one of over 2,300 individuals showed no relationship between waist circumference and hypothalamic GMV [56,57]. Sample size and heterogeneity in sample characteristics (e.g., range of BMI; comorbidity; dietary restrictions) may have contributed to the inconsistencies in findings.

We showed that hypothalamic GMV was positively correlated with the strength of hypothalamus-posterior insula connectivity. Further, hypothalamus-insula connectivity

mediated the bidirectional relationship between BMI and hypothalamic GMV. Although no previous work has examined the relationship between hypothalamic morphology and connectivity in the context of body weight, the broad relationship between regional GMV and functional connectivity has been observed for other brain regions [58]. Furthermore, recent investigations have demonstrated that hypothalamic connectivity with regions including the insula and orbitofrontal cortex may be related to norepinephrine [24] and serotonin [59] transporter availability, both of which have been implicated in negative emotionality. It is plausible that psychological distress from weight gains enhances hypothalamic connectivity via the noradrenergic and serotonergic systems and in turn leads to overeating and worsening of mood [24]. As shown in animal studies, diet-induced body weight gains or losses altered the cytoarchitecture of the hypothalamus, including changes in dendrite length, dendrite number, and soma size [60]. Such changes in morphology may impact synaptic activity and potentially connectivity and molecular functions of the hypothalamus. Thus, consistent with the mediation analysis, body weight, hypothalamic connectivity strength, and GMV may be intricately interrelated. Nonetheless, the mechanistic relationship between GMV, connectivities and molecular profiles of the hypothalamus in relation to food intake require additional research.

## 5. Conclusions

Higher BMI was positively correlated with greater hypothalamic GMV and connectivity with the insula, thalamus, globus pallidus, and cerebellum but negatively correlated with hypothalamic connectivity with the superior parietal lobule. Morphometric and connectivity analyses together pointed to a potentially specific role of the hypothalamic-posterior insula connectivity in the regulation of food intake. The current report adds to the growing literature of hypothalamic dysfunctions in obesity and disordered eating. Longitudinal research is needed to understand whether these neural features reflect the consequences of chronic increases in food intake or represent a biomarker that may dispose individuals to excessive food consumption.

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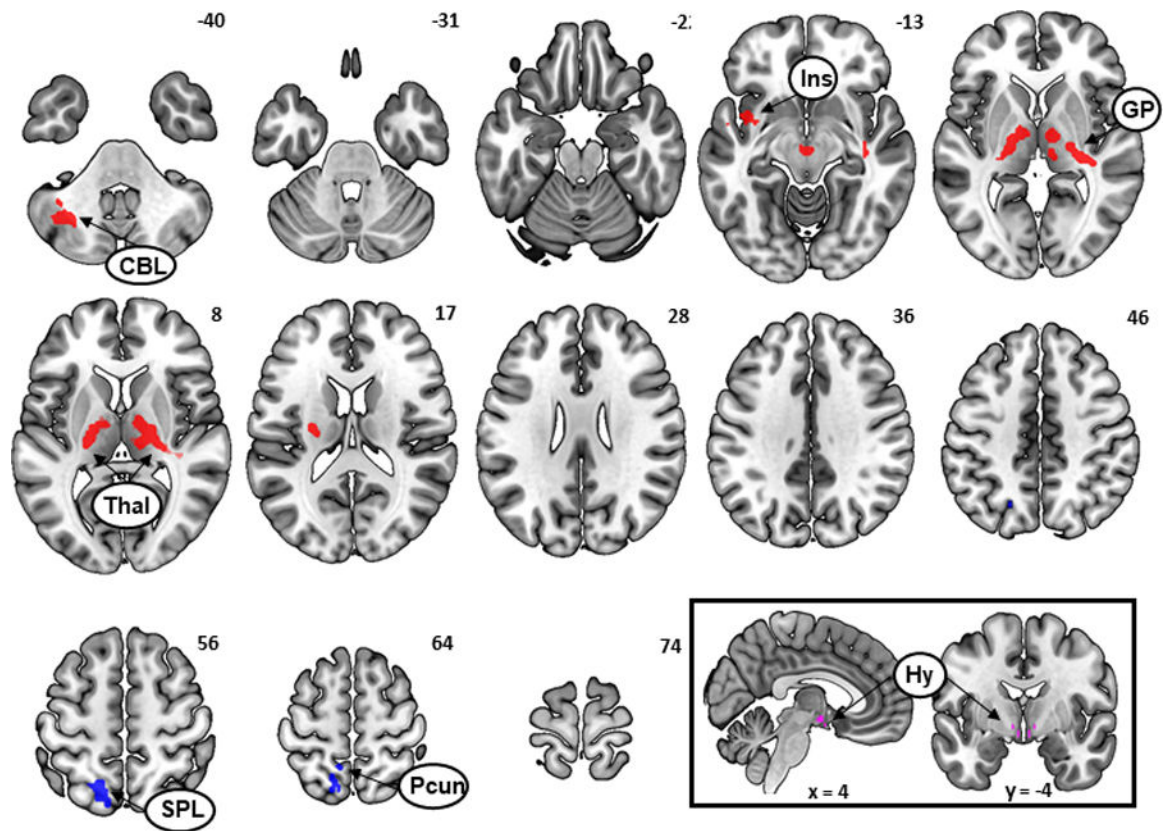
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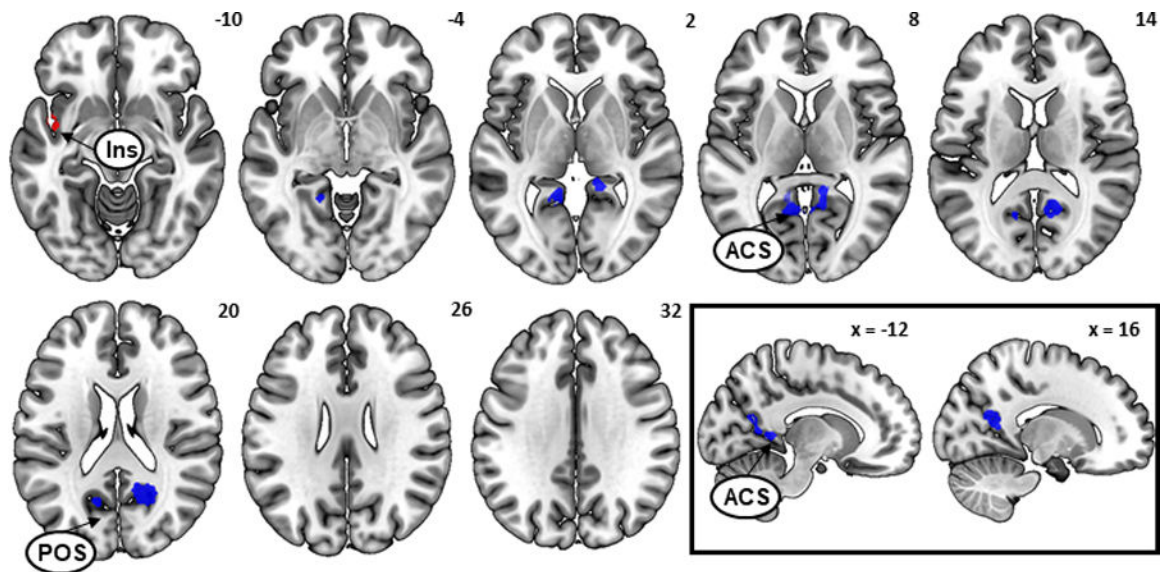
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**Figure 1:**

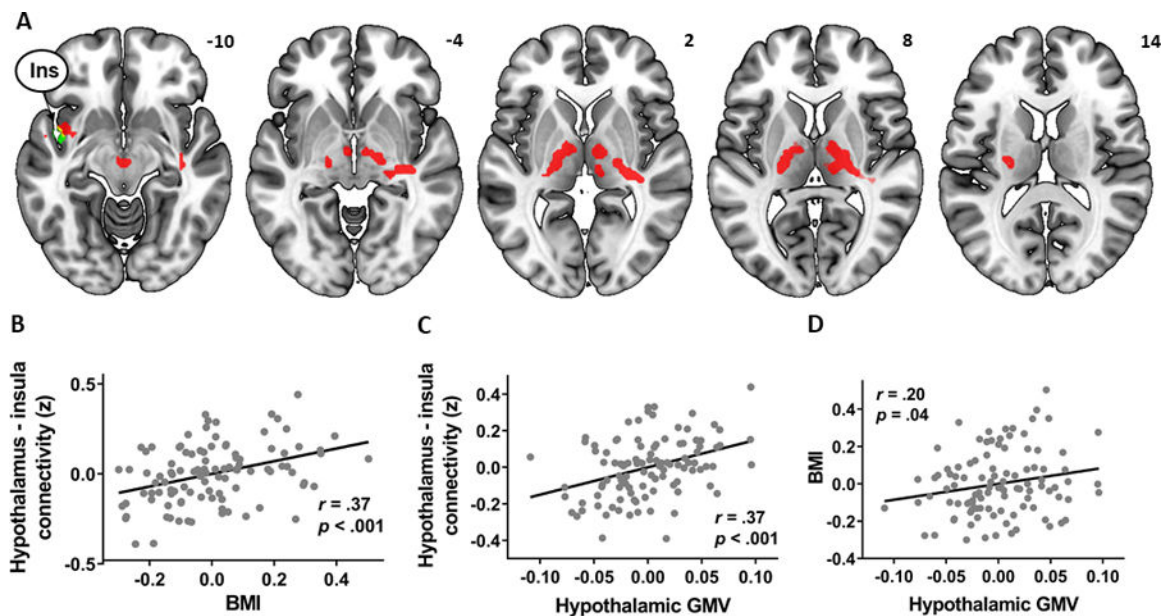
BMI was positively correlated with hypothalamic (Hy) (seed shown in violet - inset) connectivity with the right globus pallidus (GP), left insula (Ins), bilateral thalamus (Thal), and left cerebellum (CBL) (red). BMI was negatively correlated with hypothalamic connectivity with the left superior parietal lobule (SPL) and dorsal precuneus (Pcun) (blue).



**Figure 2:**

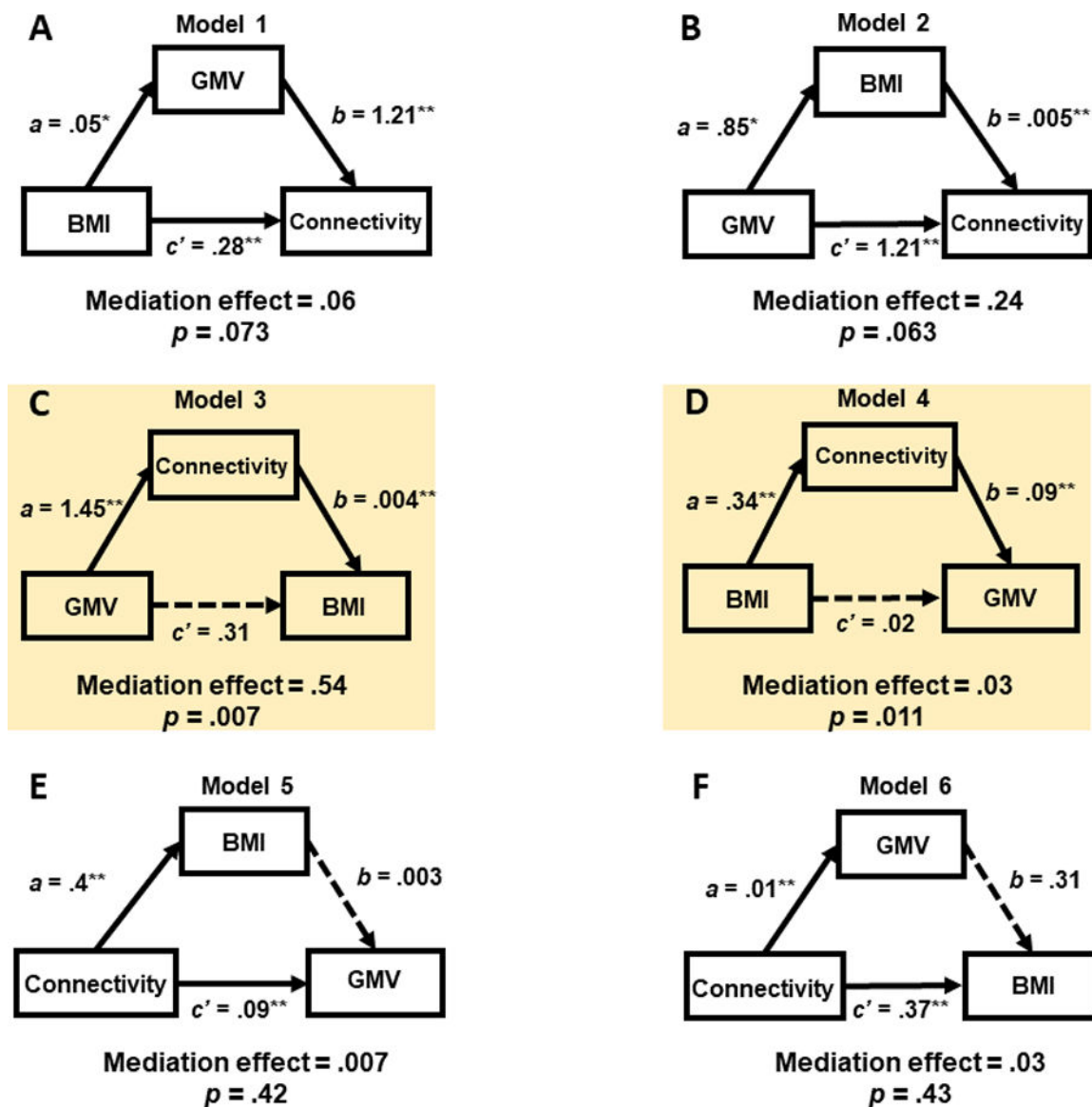
Hypothalamic GMV was negatively correlated with the strength of hypothalamic connectivity with a cluster in parieto-occipital fissure/sulcus (POS) and anterior calcarine sulcus (ACS) (blue). At a slightly more liberal threshold (cluster size = 84), hypothalamic GMV was positively correlated with the connectivity with the left posterior insula (Ins) (red).





**Figure 3:**

(A) Hypothalamic connectivity in correlation with BMI (red) and with hypothalamic GMV (green) overlapped in the left posterior insula (Ins, yellow). (B) BMI was positively correlated with the strength of the hypothalamus-insula connectivity. (C) Hypothalamic GMV was positively correlated with the strength of the hypothalamus-insula connectivity. (D) BMI and hypothalamic GMV were positively correlated. Note that residuals are plotted in these partial correlations with age as the covariate.



**Figure 4:** Mediation analysis of the inter-relationships between body mass index (BMI), hypothalamic gray matter volume (GMV), and hypothalamus-left posterior insula connectivity (Connectivity). All six models of mediation were tested: (A) Model 1: BMI → GMV → Connectivity; (B) Model 2: GMV → BMI → Connectivity; (C) Model 3: GMV → Connectivity → BMI; (D) Model 4: BMI → Connectivity → GMV; (E) Model 5: Connectivity → BMI → GMV; and (F) Model 6: Connectivity → GMV → BMI. Both Model 3 and 4 showed a significant and complete mediation effect. Solid and dotted arrows indicate significant and non-significant relationships, respectively.

**Table 1:**

BMI and hypothalamic GMV modulation of hypothalamic connectivity

Region	MNI coordinates (mm)			Voxel	Cluster
	x	y	z	T	k
BMI	<i>Positive correlation</i>				
Thalamus	30	-26	4	5.50	925
	-22	-20	-8	5.16	
Thalamus/Globus Pallidus	36	-22	-6	5.14	
Insula	-38	14	-14	4.04	103
	-34	-6	-16	4.03	
	-40	6	-12	4.00	
Cerebellum	-34	-62	-40	4.01	110
	-42	-62	-38	3.91	
	<i>Negative correlation</i>				
Precuneus	-12	-54	64	4.85	262
	-12	-72	52	4.22	
Superior parietal lobule	-20	-66	52	4.20	
GMV	<i>Positive correlation</i>				
Insula	-42	-2	-12	4.45	84
	<i>Negative correlation</i>				
Posterior cingulate cortex	14	-56	14	5.24	569
	20	-58	20	5.07	
	-12	-48	4	4.72	

**Table 2.**

Mediation of BMI, hypothalamic GMV, and hypothalamus-posterior insula connectivity

	<b>Path a (<math>X \rightarrow M</math>)</b>	<b>Path b (<math>M \rightarrow Y</math>)</b>	<b>Path c (<math>X \rightarrow Y</math>)</b>	<b>Path c' (<math>X \rightarrow Y</math>)</b>	<b>Mediation path (<math>c - c'</math>)</b>
Model 1: $X$ (BMI) $\rightarrow$ $Y$ (Connectivity) mediated by $M$ (GMV)					
$\beta$	0.047	1.209	0.340	0.283	0.057
p-values	0.019	0.001	0.001	0.001	0.073
Model 2: $X$ (Connectivity) $\rightarrow$ $Y$ (Connectivity) mediated by $M$ (BMI)					
$\beta$	0.851	0.283	1.449	1.209	0.241
p-values	0.03	0.001	0.001	0.001	0.063
Model 3: $X$ (GMV) $\rightarrow$ $Y$ (BMI) mediated by $M$ (Connectivity)					
$\beta$	1.449	0.373	0.851	0.311	0.541
p-values	0.001	0.001	0.030	0.41	0.007
Model 4: $X$ (BMI) $\rightarrow$ $Y$ (GMV) mediated by $M$ (Connectivity)					
$\beta$	0.340	0.088	0.047	0.017	0.030
p-values	0.001	0.001	0.019	0.39	0.011
Model 5: $X$ (Connectivity) $\rightarrow$ $Y$ (GMV) mediated by $M$ (BMI)					
$\beta$	0.403	0.017	0.095	0.088	0.007
p-values	0.001	0.39	0.001	0.001	0.417
Model 6: $X$ (Connectivity) $\rightarrow$ $Y$ (BMI) mediated by $M$ (GMV)					
$\beta$	0.095	0.311	0.403	0.373	0.030
p-values	0.001	0.41	0.001	0.001	0.431