ARTICLE OPEN

Check for updates

Deciphering the association between morphological differences in hypothalamic subregions and circulating ghrelin and leptin concentrations: exploratory evidence in anorexia nervosa and obesity

Enrico Collantoni[1,2,3,15], Romina Miranda-Olivos[4,15], Sanberk Uğur[1], Isabel Baenas[5,6,7], Sulay Tovar[7,8], Carlos Dieguez[7,8], Nuria Vilarrasa[9,10], Rafael López-Urdiales[9], Fernando Guerrero-Pérez[9], Susana Jiménez-Murcia[5,6,7,11], Carles Soriano-Mas[12,13,14] and Fernando Fernández-Aranda[5,6,7,11] ✉

© The Author(s) 2025

The hypothalamus, a central regulator of hunger and metabolism, contains subnuclei responsive to peripheral signals such as leptin and ghrelin, which may be altered in anorexia nervosa (AN) and obesity (OB). This exploratory study employed an advanced neuroimaging tool to segment specific hypothalamic subregions in 127 adult women: 24 with AN, 26 with obesity without eating disorders (OB-ED), 26 with obesity and eating disorders (OB + ED), and 51 healthy controls (HC). Participants underwent clinical assessments, fasting blood samples, and T1-weighted 3-Tesla MRI scans. The AN group showed reduced volumes in the total hypothalamus, as well as in the posterior and inferior tuberal subregions, compared to HC, which remained significant after adjusting for total brain volume (TBV). The OB + ED displayed increased volumes in the inferior tuberal and anterior-inferior subregions compared to the HC and OB-ED groups, but differences did not persist after TBV adjustment. In AN, anterior hypothalamic subregions were negatively correlated with leptin concentrations. In contrast, in OB-ED, the same subregions, along with the superior tuberal hypothalamus, showed a positive association with body mass index (BMI). Additionally, an earlier onset of AN correlated with decreased volumes of several hypothalamic subregions, whereas in OB + ED, disorder duration was positively associated with the anterior-superior subregion. Alterations in the volumes of specific hypothalamic subnuclei may serve as clinical indicators of both the severity of obesity (i.e., BMI) and the onset and duration of eating disorders. Although preliminary, these findings contribute to our understanding of the neurobiological mechanisms involved in extreme eating and weight conditions.

Translational Psychiatry (2025)15:483 ; https://doi.org/10.1038/s41398-025-03708-6

INTRODUCTION

The hypothalamus is a small but functionally essential brain region consisting of anatomically distinct subnuclei, which are highly specialized in vital functions, including body temperature control and regulating thirst, hunger, and satiety, among others [1]. Specifically, the hypothalamic nuclei involved in regulating hunger, satiety, and metabolism include the arcuate (ARC), ventromedial, dorsomedial, paraventricular (PVN), and lateral hypothalamic (LH) nuclei. These nuclei have garnered scientific interest as a potential neurobiological factor underlying persistent maladaptive eating behaviors, from anorexia nervosa (AN) to obesity (OB) [2]. For instance, studies in animal models have demonstrated that lesions in neuropeptide Y (NPY)-expressing neurons (NPY) in the ARC nucleus can induce hyperphagia [1]. In humans, studies have reported that lesions affecting the LH can cause food restriction in individuals without an eating disorder (ED) diagnosis [3].

In line with these initial findings, some studies have examined whether maladaptive eating patterns may both result from and contribute to structural alterations in specific hypothalamic nuclei involved in regulating food intake in AN and OB, including those with ED, such as bulimia nervosa (BN) and binge eating disorder

[1]Department of Neuroscience, University of Padua, Padova, Italy. [2]Padova Neuroscience Center, University of Padua, Padova, Italy. [3]Department of Medicine, University of Padua, Padova, Italy. [4]Sant Pau Mental Health Research Group, Sant Pau Research Institute, Barcelona, Spain. [5]Clinical Psychology Department, Bellvitge University Hospital, Barcelona, Spain. [6]Psychoneurobiology of Eating and Addictive Behaviors Research Group, Neurosciences Program, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain. [7]CIBER Physiopathology of Obesity and Nutrition (CIBERobn), Carlos III Health Institute (ISCIII), Barcelona, Spain. [8]Department of Physiology, Centre for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela, Santiago de Compostela, Spain. [9]Department of Endocrinology and Nutrition, Bellvitge University Hospital-IDIBELL, Barcelona, Spain. [10]CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM), Carlos III Health Institute (ISCIII), Madrid, Spain. [11]Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain. [12]CIBER of Mental Health (CIBERSAM), Carlos III Health Institute (ISCIII), Barcelona, Spain. [13]Department of Psychiatry, Bellvitge University Hospital-IDIBELL, Barcelona, Spain. [14]Department of Social Psychology and Quantitative Psychology, School of Psychology, University of Barcelona, Barcelona, Spain. [15]These authors contributed equally: Enrico Collantoni, Romina Miranda-Olivos. ✉email: ffernandez@bellvitgehospital.cat

Received: 18 December 2024 Revised: 16 September 2025 Accepted: 10 October 2025
Published online: 18 November 2025

(BED) [4–7]. BN and BED are notably prevalent in individuals with OB due to frequent episodes of excessive food intake, independent of hunger and satiety cues.

A plausible explanation is the existence of potential structural alterations in specific hypothalamic nuclei involved in regulating eating behavior [8–10]. These studies suggest this may be due to inflammatory or atrophic processes resulting from overeating [10] or starvation [11], respectively. Peripheral inflammatory factors and the central nervous system processes may lead to microstructural changes in the hypothalamus, further disrupting metabolic balance and mechanisms involved in hunger regulation and calorie consumption [12]. For instance, animal studies have described neuroinflammatory responses in hypothalamic subregions, including the PVN, associated with binge-like eating behavior [12, 13]. A strong association exists between high-fat diets and hypothalamic inflammation, with microglial and astrocytic cell populations primarily responsible for mediating this inflammatory response [12]. Consistent with this notion, subsequent weight loss may attenuate hypothalamic inflammation, thereby restoring sensitivity to hormones and improving the regulation of body energy homeostasis [6, 14]. Similarly, peripheral inflammatory activation mechanisms have also been described in AN [15], which could potentially contribute to neurodevelopmental dysregulation and cortical atrophy involving hypothalamic subnuclei, such as the ARC, as a result of prolonged starvation and metabolic stress in AN [16].

In addition to functional disruptions in the hypothalamus, some studies have examined how hypothalamic circuits interact with key circulating hormones, such as ghrelin and leptin in AN [17] and OB [18], key hormones in energy homeostasis that exert their effects primarily through the ARC. In AN, persistently low leptin and elevated ghrelin levels have been consistently reported [19–21]. Ghrelin often remains high even after weight restoration [22], whereas leptin tends to normalize with weight regain [19]. Conversely, higher leptin concentrations and leptin resistance [23], but mixed results regarding ghrelin concentrations are commonly observed in individuals with OB [14, 24, 25].

One of the main challenges in neuroimaging is enhancing resolution to assess small structures such as hypothalamic nuclei. Recent advances in high-resolution magnetic resonance imaging (MRI) and automated segmentation techniques have enabled more accurate and reliable volumetric analyses of hypothalamic subregions [26]. Some studies have implemented this volumetric segmentation of the hypothalamic subregions to explore distinct associations with body mass index (BMI) ranges [27, 28]. Results revealed that individuals with overweight and OB exhibit a larger overall hypothalamus [27, 28] and also in several subregions, such as the inferior tuberal (i.e., ARC) [27], anterior superior (i.e., PVN) [27], and superior tuberal and the posterior hypothalamus (i.e., LH) [28], compared to HC. In contrast, findings in AN are less consistent. While some studies have found hypothalamic volume reductions (e.g., inferior tuberal hypothalamus) [27], in line with the widespread brain atrophy described in AN [29], other studies have reported no significant differences [28]. One possible explanation for the mixed findings may reside in methodological differences. For instance, Brown et al. [28] found no significant hypothalamic alterations after adjusting for total intracranial volume (TIV) and correcting for multiple comparisons. In contrast, Al-Zaid et al. [27] reported reduced volume in the inferior tuberal hypothalamus in AN, additionally adjusting for total brain volume (TBV). In AN, this adjustment may highlight relative regional differences while potentially masking absolute reductions, especially in the presence of global brain atrophy.

Based on this evidence, the present exploratory study aimed to examine hypothalamic subregion volumes and their associations with peripheral hormonal and clinical measures in individuals with AN, OB + ED, and OB-ED. Considering the potential role of neuroinflammation in OB, we hypothesized that both OB + ED and OB-ED groups would exhibit increased volumes in the whole hypothalamus as well as in the inferior tuberal, superior tuberal, anterior superior, and posterior hypothalamic subregions. In AN, due to the heterogeneity of previous findings, we initially expected reduced volumes in these same hypothalamic subregions compared to healthy controls. However, we also sought to determine whether these volume differences reflect absolute brain volume loss or represent relative reductions beyond the global brain atrophy commonly reported in this population [29]. Furthermore, given the critical influence of leptin and ghrelin signaling on eating behavior, we hypothesized that volumes of the inferior and superior tuberal, anterior superior, and posterior hypothalamic subregions would be differentially associated with these appetite-related hormones in the AN and OB groups, as well as with clinical measures including BMI, severity of eating disorder symptomatology, and general psychopathology.

METHODS

Participants

A total of 127 adult women participated in this preliminary cross-sectional study. The clinical sample included 24 individuals with AN, of whom one participant met criteria for AN-OSFED (BMI = 18.01), 26 individuals with OB-ED, and 26 individuals with OB + ED [namely BN (n = 5) and BED (n = 21)]. Considering individuals with AN are typically younger compared to those with OB, two age-matched HC groups were enrolled: one age-matched to the AN group (HC-AN; n = 25) and another age-matched to the OB-ED and OB + ED groups (HC-OB; n = 26). This approach aims to control and mitigate the potential confounding effects of age on the variables of interest in our study.

ED diagnoses were established using DSM-5 criteria based on the Structured Clinical Interview (SCID-5) [30] conducted by experienced clinical psychologists and psychiatrists. All participants underwent the Mini-International Neuropsychiatric Interview (M.I.N.I.) [31] to assess psychiatric disorders. Participants in HC groups were excluded if they had a lifetime history of ED or obesity. At the same time, any current psychiatric diagnosis led to exclusion from both the HC and OB groups. Exclusion criteria for all participants included male sex, presence of organic mental disorders, intellectual disability, neurological conditions (e.g., epilepsy, multiple sclerosis), history of significant brain injury, and any contraindications for MRI (e.g., metallic implants, claustrophobia).

Participants from the ED and OB groups were recruited from the Eating Disorders Unit at the Department of Clinical Psychology and Endocrinology and Nutrition Unit at Bellvitge University Hospital in Barcelona, Spain. The age-matched HC groups were recruited through advertisements from the same catchment area.

Final sample selection and exclusions. In the anorexia nervosa (AN) group, of the initial 25 participants, one was excluded for not meeting MRI quality control criteria (n = 1). The OB + ED group initially consisted of 30 participants, of whom four were excluded due to missing T1-weighted MRI data (n = 4). The OB–ED group was drawn from a larger cohort of 60 women who were candidates for bariatric surgery and recruited for a longitudinal study. From this cohort, only a subset had available MRI data. Thus, 26 participants were selected who had complete datasets (T1-weighted MRI and hormonal measurements), passed MRI quality control, and had no psychiatric comorbidities. Finally, healthy control participants were selected based on the availability of complete data, MRI quality control compliance, and age-matching with the clinical groups.

Procedures

Participants completed assessments across two separate sessions. The first session included a clinical interview, self-reported questionnaires, measurement of height and weight for BMI calculation, and fasting blood sampling (08:00–09:00 a.m., after an ≥8-h fast) to quantify total ghrelin and leptin concentrations. The second session involved undergoing a magnetic resonance imaging (MRI) scan. To minimize variability due to daily hormonal fluctuations, all assessments were scheduled at the same time of day. Although the interval between blood sampling and MRI scan varied among participants, it was restricted to within the same week for all cases. For individuals with ED, these assessments were conducted during the first week of admission to treatment.

Ethics

The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Bellvitge University Hospital (PR146/14). All participants were thoroughly informed of the procedures and provided written informed consent.

Assessments

Clinical measures. The Eating Disorders Inventory-2 (EDI-2) [32], Spanish validation [33], it is a 91-item self-report questionnaire answered on a 6-point Likert scale. The EDI-2 assesses 11 ED-related symptoms, such as drive for thinness, body dissatisfaction, and impulse regulation, among others. For this study, we used the EDI-2 total score, which effectively measures the overall severity of ED symptoms.

The Symptom Checklist-90 Items-Revised (SCL-90-R) [34], validated in Spanish [35], assesses general psychopathology across nine scales such as somatization, depression, anxiety, and psychoticism, among others. In this study, we focused on the Global Severity Index (GSI) to measure general psychopathology.

Biological measures. Blood samples were collected in the morning following an overnight fast of at least 8 h. Samples were centrifuged at 1700 g for 20 min at 4 °C in a refrigerated centrifuge. Total ghrelin and leptin concentrations were quantified from peripheral blood drawn via venous aspiration with ethylenediamine tetraacetic acid (EDTA) at a final concentration of 25 mM. Plasma was immediately separated from serum and stored at -80 °C until analysis.

Total ghrelin (pg/ml) was measured using an ELISA kit (Invitrogen-Thermofisher Scientific) with a specificity of 100%. The intra-assay coefficient of variation was <6% and the inter-assay coefficient was <8.5%. The assay sensitivity limit was 11.8 pg/ml.

Leptin (ng/ml) was measured using a solid-phase sandwich ELISA kit (Invitrogen-Thermofisher Scientific) with a specificity of 100%. The intra-assay and inter-assay coefficients of variation were <4 and <5%, respectively, and the assay sensitivity limit was 3.5 pg/ml for leptin. Absorbance for each sample was measured in duplicate using a spectrophotometric microplate reader at a wavelength of 450 nm (Epoch 2 microplate reader, Biotek Instruments, Inc.).

Body mass index. Height was measured with a stadiometer and entered into a Tanita Multi-Frequency Body Composition Analyzer BC-420MA (Tanita Corp., Tokyo, Japan) to calculate BMI.

Magnetic resonance imaging measures

Imaging data acquisition. Whole-brain MRI data were obtained using a 3.0 Tesla clinical MRI scanner with an 8-channel phased-array head coil (Intera Achieva Philips Medical Systems, Eindhoven, Netherlands). A high-resolution three-dimensional T1-weighted turbo-gradient-echo sequence was acquired in the axial plane, lasting 6 min and 6 s. This sequence consisted of 233 contiguous slices with the following parameters: TR = 10.5 ms, TE = 4.8 ms, flip angle = 8°, FOV = 24 cm, a 320×320-pixel matrix, and 0.75 × 0.75 × 0.75 mm isotropic voxels.

Imaging processing. Structural T1 MRI data were processed using FreeSurfer software (version 7.4, Boston, MA). The preprocessing procedures followed the standard protocol encompassing automated corrections to address intensity non-uniformity and motion artifacts. Subsequently, cortical surface extraction employed statistical and geometric modeling techniques to create detailed three-dimensional models of the cortical surface, delineating boundaries between gray matter, white matter, and cerebrospinal fluid. Automated segmentation using FreeSurfer then classified brain structures into gray matter, white matter, and cerebrospinal fluid compartments, enabling volumetric measurements of standard regions of interest (ROIs) and cortical thickness assessments across the entire cortical surface.

Hypothalamic segmentation. The T1-weighted images underwent preprocessing before being analyzed with the automated tool for hypothalamic extraction (SynthSeg) [26, 36]. This tool uses a deep convolutional neural network trained on manually labeled T1-weighted images to accurately segment the hypothalamus into five anatomically defined subregions (see Fig. 1), as directly provided by SynthSeg, without requiring any manual editing or post hoc aggregation of smaller nuclei. These subregions include the anterior–inferior, anterior–superior, tubular–inferior, tubular–superior, and posterior regions, as defined in the SynthSeg segmentation protocol. SynthSeg has demonstrated high accuracy and reproducibility, with inter-rater and intra-rater performance

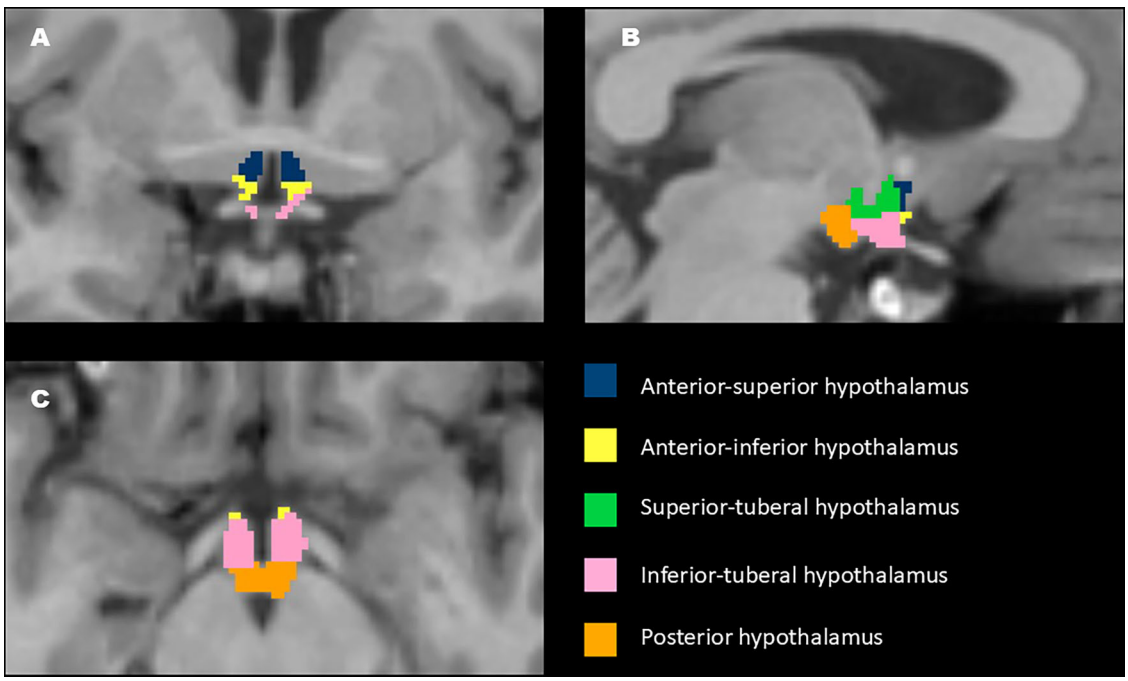


Fig. 1 Segmentation of the hypothalamus and its nuclei using an automated tool based on a deep convolutional neural network (Billot et al. [26]), integrated into FreeSurfer development version 7. Coronal (**A**), sagittal (**B**), and axial (**C**) brain slices showing segmented hypothalamic nuclei. The hypothalamic nuclei are shown in different colors: blue (anterior-inferior hypothalamus); yellow (anterior-superior hypothalamus); orange (posterior hypothalamus); green (inferior tuberal portion of the hypothalamus), and pink (superior tuberal portion of the hypothalamus).

comparable to manual delineations and low error rates across various image contrasts and resolutions [36, 37].

All FreeSurfer-based preprocessing steps underwent a structured quality control pipeline. First, cortical reconstructions were evaluated using Freeview following FreeSurfer's official QC guidelines. Two independent raters (EC, SU) inspected each subject's pial and white matter surfaces, *aseg* segmentations, and *brainmask* volumes to verify anatomical fidelity and rule out motion artifacts or topological errors. No significant errors were detected in this stage. A quality control procedure was also conducted for hypothalamic segmentation using SynthSeg. Specifically, hypothalamic masks were visually inspected in native space for spatial misalignment, under- or over-segmentation, or inclusion of non-hypothalamic tissue. Based on these criteria, one participant from the AN group was excluded due to poor segmentation quality. Additionally, the distribution of hypothalamic subregion volumes was visually inspected and checked for outliers (> 3 SD), none of which were detected. To account for individual differences in brain size and age, group-comparison GLMs were run on raw hypothalamic volumes (mm^3) with age, total intracranial volume (TIV), and total brain volume (TBV) entered as covariates. Correlational analyses only used covariate-adjusted (residualized) volumes, obtained by regressing raw volumes on age, TIV, and (where specified) TBV.

Based on this hypothalamic segmentation, five subregions were identified (see Fig. 1): (1) the anterior-superior subregion (ASS), including the preoptic area and the PVN; (2) the anterior-inferior subregion (AIS), encompassing the suprachiasmatic nucleus and the supraoptic nucleus (SON); (3) the superior tuberal nucleus (STS), comprising the dorsomedial nucleus, the PVN, and the LH; (4) the inferior tuberal nucleus (ITS), comprising the ARC, ventromedial, lateral tuberal, and tuberomammillary nuclei (TMN); (5) the posterior subregion (PS), including the mammillary body, the LH, and the TMN.

Data analysis

Statistical analyses of non-imaging data. Statistical analyses of demographics, clinical variables, leptin and ghrelin concentrations, and brain-derived measures were performed using SPSS (version 27). Independent samples t-tests were used to compare the AN group with the HC-AN group. A one-way analysis of variance (ANOVA) was conducted to compare the HC-OB, OB-ED, and OB + ED groups, followed by uncorrected post hoc pairwise comparisons. Onset and duration in the ED groups (i.e., AN and OB + ED) were also analyzed using independent samples t-tests.

Statistical analysis of neuroimaging data. Between-group differences in hypothalamic subregion volumes were examined using general linear models (GLMs). Separate multivariate GLMs were conducted to compare the AN and the HC-AN group, and between the OB + ED, OB-ED, and HC-OB. To evaluate whether differences in hypothalamic volumes could be attributed to global brain volume reductions or region-specific effects beyond overall potential atrophy or inflammation, two models were applied: one adjusted for age and TIV, and total TBV, and a second model only adjusted for age and TIV as covariates. This two-step approach allowed us to examine both global and region-specific effects. Bonferroni correction was applied in the obesity models to control for multiple comparisons.

Spearman's partial correlations were conducted within each clinical group (i.e., AN, OB + ED, OB-ED) to assess the associations between hypothalamic subregion volumes, circulating ghrelin and leptin concentrations, and clinical variables. Normality tests were performed, and non-parametric correlations were analyzed using Spearman's method due to the non-normal distribution of the data. For these correlational analyses only, unstandardized residuals of hypothalamic volumes were calculated by regressing out the effects of age and TIV in the first model, and the effects of age, TIV, and TBV in the second model. Statistical significance was set at $p < 0.05$, and corrections for multiple comparisons were made using the false discovery rate (FDR) method.

RESULTS

Table 1 summarizes the demographic data, clinical characteristics, and appetite-related hormone concentrations of the study participants. No significant differences in age were observed between the AN group and the HC-AN group ($p = 0.072$), nor between the HC-OB group and the OB + ED ($p = 0.578$) or OB-ED ($p = 0.613$) groups. As expected, significant differences in BMI were observed between the AN and HC-AN groups ($p < 0.001$), as well as between the HC-OB group and OB + ED ($p < 0.001$) and the OB-ED ($p < 0.001$) groups. Detailed ranges for each variable within groups, as well as the composition of the OB + ED group, including individuals with BED and BN, are provided in Supplementary Material (Table S1).

In terms of clinical characteristics, groups with ED displayed higher levels of general psychopathology and severity of ED symptomatology in comparison to their respective age-matched HC group. As expected, the OB + ED group showed significantly higher levels of ED symptomatology (EDI-2) compared to the OB-ED group ($p < 0.001$) and the HC-OB group ($p < 0.001$). Likewise, the AN group showed higher total EDI-2 scores compared to the HC-AN group ($p < 0.001$). Similarly, higher scores in the general psychopathology index (SCL-90R-GSI) were observed in the OB + ED group compared to the OB-ED ($p < 0.001$) and the HC-OB ($p < 0.001$) groups. The AN group displayed significantly higher SCL-90R-GSI scores compared to HC-AN ($p < 0.001$) (Table 1).

Regarding circulating total ghrelin and leptin concentrations, the AN group exhibited significantly decreased concentrations of leptin compared to the HC-AN ($p < 0.001$). Still, no significant differences in total ghrelin concentrations were found ($p = 0.288$) (Table 1). Regarding the rest of the groups, the HC-OB group had significantly lower concentrations of circulating ghrelin compared to both the OB + ED ($p < 0.001$) and OB-ED ($p < 0.001$) groups. No significant differences were observed between the OB + ED and the OB-ED group in ghrelin ($p = 0.401$) and leptin ($p = 0.807$) concentrations. Finally, TBV was significantly lower in the AN than in the HC-AN group ($p = 0.004$) (Table 1).

Differences between groups in hypothalamic volumes

GLM adjusting for age TIV and TBV revealed decreased volume of the whole hypothalamus ($F = 5.54$, $p < 0.001$), the PS ($p = 0.004$), and the ITS ($F = 7.912$, $p < 0.001$), in the AN compared to the HC-AN group (Table 2). In the second model, excluding TBV as a covariate, these group differences remained statistically significant, indicating that the findings are robust to the inclusion of TBV see Supplementary Material Table S2). All results were Bonferroni-corrected at $p < 0.05$. (see Supplementary Material Table S4).

In the OB groups, GLM adjusting for age TIV, and TBV showed increased volumes of the ITS in the OB + ED group compared to the HC-OB group ($p = 0.038$). Likewise, an increased volume of the AIS was observed in the OB + ED group compared to the OB-ED group ($p = 0.022$). No significant differences in hypothalamic subregion volumes were observed between the OB-ED and HC-OB groups (Table 3). In the second model, excluding TBV as a covariate, only the increased volume of the AIS in the OB + ED group relative to the OB-ED group remained statistically significant. ($p = 0.021$) (see Supplementary Material Table S3). All results were Bonferroni-corrected at $p < 0.05$.

Associations between hypothalamic subregions, circulating total ghrelin, leptin concentrations, and clinical variables

Adjusting for age TIV and TBV, in the AN group, leptin concentrations were negatively associated with the AIS (rho = -0.444; $p_{uncorr} = 0.030$) and ASS (rho = -0.423; $p_{uncorr} = 0.039$) of the hypothalamus. Likewise, a significant positive association was observed between the onset of the disorder and the whole hypothalamic volume (rho=0.578; $p_{uncorr} = 0.005$), the AIS (rho=0.623; $p_{uncorr} = 0.002$), the ASS (rho=0.670; $p_{uncorr} = 0.001$), the PS (rho=0.524; $p_{uncorr} = 0.012$), and the ITS (rho=0.569; $p_{uncorr} = 0.006$) (Table 4). Excluding TBV as a confounding variable, the significant correlations observed in the initial model remained. Additionally, new significant negative correlations emerged between leptin levels and the ITS (rho = -0.411; $p_{uncorr} = 0.046$) and whole hypothalamus (rho = -0.427; $p_{uncorr} = 0.037$) (see Supplementary Material Table S4). After FDR correction, only the

Table 1. Demographic and clinical characteristics of study participants (AN, HC-AN, HC-OB, OB-ED, and OB + ED).

	AN		HC-AN		HC-OB		OB + ED		OB-ED	
	n = 24		n = 25		n = 26		n = 26		n = 26	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age	21.71	4.52	23.80	3.39	41.88	7.90	40.73	7.80	40.62	8.80
BMI	16.23	1.51	21.34	2.02	22.44	2.04	39.88	6.61	43.24	6.81
EDItotal	83.46	42.04	30.36	17.83	25.81	25.91	109.64	30.74	61.12	28.61
SCLgsi	1.68	0.72	0.45	0.32	0.59	0.52	1.85	0.68	0.99	0.52
Onset	17.14	3.75	–	–	–	–	22.38	9.37	–	–
Duration	4.86	4.20	–	–	–	–	19.00	12.06	–	–
TIV	1279.75	153.50	1344.73	142.10	1387.66	194.56	1435.62	156.57	1375.33	170.63
TBV	1018.42	81.56	1079.40	55.68	1064.19	117.14	1063.83	78.60	1041.17	78.96
Ghrelin	1772.58	451.33	1615.73	562.55	1931.57	496.01	1128.83	533.54	1013.70	438.97
Leptin	0.13	0.13	0.49	0.26	0.61	0.70	1.96	0.82	2.01	1.04
	Two-group comparisons				*Pairwise comparison*					
	HC-AN vs AN		HC-AN vs HC-OB		HC-OB vs OB + ED		HC-OB vs OB-ED		OB + ED vs OB-ED	
	p	*|d|*	*p*	*|d|*	*p*	*|d|*	*p*	*|d|*	*p*	*|d|*
Age	0.072	0.52	**<0.001**	**2.96**	0.578	0.15	0.613	0.15	0.960	0.01
BMI	**<0.001**	**2.86**	0.056	0.54	**<0.001**	**3.57**	**<0.001**	**4.14**	**0.034**	**0.50**
EDItotal	**<0.001**	**1.66**	0.470	0.20	**<0.001**	**2.95**	**<0.001**	**1.29**	**<0.001**	**1.63**
SCLgsi	**<0.001**	**2.22**	0.242	0.33	**<0.001**	**2.08**	**0.018**	**0.77**	**<0.001**	**1.42**
TIV	0.131	0.44	0.374	0.25	0.325	0.27	0.800	0.07	0.217	0.37
BTV	**0.004**	**0.88**	0.559	0.16	0.989	0.00	0.377	0.23	0.384	0.29
Ghrelin	0.288	0.31	**0.038**	**0.60**	**<0.001**	**1.56**	**<0.001**	**1.96**	0.401	0.24
Leptin	**<0.001**	**1.74**	0.438	0.23	**<0.001**	**1.77**	**<0.001**	**1.58**	0.807	0.05

Bold: significant at p < 0.05. Cohen's d: small ≥ 0.2, moderate ≥ 0.5, large ≥ 0.8.
AN, anorexia nervosa; *HC-AN*, the age-matched control group for AN; *HC-OB*, the age-matched control group for OB; *OB+ED*, obesity with eating disorder; *OB-ED*, obesity without eating disorder; *BMI*, body mass index; *EDI-2*, eating disorder inventory total score; *SCL-90*, general psychopathological distress score; *TBV*, total brain volume; *TIV*, total intracranial volume.

Table 2. Comparison of hypothalamic subregion volumes between AN and the age-matched healthy control group (HC-AN) using general linear models adjusted for age, total intracranial volume (TIV), and total brain volume (TBV).

Hypothalamic volumes measures	AN		HC-AN				
	n = 24		n = 25		*F*	*p*	*d*
	Mean	*SD*	*Mean*	*SD*			
Anterior-inferior	17.74	7.57	20.78	8.63	1.43	0.239	0.12
Anterior-superior	31.59	7.57	34.52	11.17	2.56	0.517	0.19
Posterior hypothalamus	203.90	21.05	221.44	22.59	**4.42**	**0.004**	**0.29**
Inferior tuberal	212.61	18.63	243.01	20.68	**7.91**	**<0.001**	**0.42**
Superior tuberal	186.17	21.92	195.26	19.66	1.70	0.168	0.13
Whole hypothalamus	652.00	48.49	715.01	56.91	**5.54**	**0.001**	**0.33**

Bold: significant comparison (p < 0.05), Bonferroni corrected.
AN, anorexia nervosa; *HC-AN*, the age-matched control group for AN.

association between the onset of the disorder and the ASS remained statistically significant ($p_{FDR} = 0.001$).

In the OB + ED group, adjusting for age TIV and TBV, a positive association between the volume of the ASS and the ED duration was also observed (rho=0.435; $p_{uncorr} = 0.049$). When TBV was excluded from the model, this association remained, and an additional positive correlation emerged between ED duration and the AIS (rho=0.435, $p_{uncorr} = 0.049$), as well as BMI showed a positive association with the volume of the ITS (rho=0.391; $p_{uncorr} = 0.048$) and the whole hypothalamus (rho = 0.390; p_{uncorr}=0.049). None of these associations remained significant after FDR correction (see Supplementary Material Table S4).

Finally, in the OB-ED group, adjusting for age TIV and TBV, a positive correlation between BMI and the volumes of the ASS (rho= 0.416; p = 0.034), the AIS (rho= 0.480; $p_{uncorr} = 0.013$), and STS (rho= 0.405; $p_{uncorr} = 0.040$) was observed (Table 4). When

Table 3. Comparison of hypothalamic subregion volumes between obesity groups (OB-ED, OB + ED) and the age-matched healthy control group (HC-OB) using general linear models adjusted for age, total intracranial volume (TIV), and total brain volume (TBV).

Hypothalamic volumes measures	**HC-OB**		**OB + ED**		**OB-ED**				***Pairwise comparison***					
									HC-OB vs		**HC-OB vs**		**OB + ED vs**	
	n = 26		**n = 26**		**n = 26**				**OB + ED**		**OB-ED**		**OB-ED**	
	Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***	***F***	***Sig.***	***p***	***|d|***	***p***	***|d|***	***p***	***|d|***
Anterior-inferior	23.90	9.00	29.62	7.41	22.52	9.04	2.50	0.038	0.104	0.19	1.000	0.05	**0.022**	**0.17**
Anterior-superior	40.54	8.16	42.21	7.94	36.55	7.53	2.04	0.083	1.000	0.06	0.270	0.12	0.061	0.15
Posterior hypoth.	213.98	23.20	223.57	25.62	220.58	23.42	1.74	0.136	0.353	0.16	0.582	0.16	1.000	0.04
Inferior tuberal	226.91	30.39	241.83	22.40	235.51	16.01	5.81	0.000	**0.038**	**0.37**	0.135	0.33	1.000	0.11
Superior tuberal	197.91	26.27	204.18	19.99	189.73	27.23	2.41	0.044	1.000	0.22	0.592	0.11	0.180	0.18
Whole hypoth.	703.24	79.40	741.41	57.15	704.89	53.02	3.70	0.005	0.110	0.32	1.000	0.16	0.254	0.13

Bold indicates a significant comparison ($p < 0.05$), Bonferroni corrected.
HC-OB, the age-matched control group for OB; *OB+ED*, obesity with eating disorder; *OB-ED*, obesity without eating disorder.

TBV was excluded from the correlation model, the positive associations between BMI and both ASS and AIS volumes remained, and additional correlations emerged with the ITS (rho= 0.493, $p_{uncorr} = 0.011$), PS ($\rho = 0.495$, $p_{uncorr} = 0.010$), and total hypothalamic volume ($\rho = 0.525$, $p_{uncorr} = 0.006$). However, the association between BMI and STS volume was no longer statistically significant ($\rho = 0.373$, $p_{uncorr} = 0.059$). None of these associations remained significant after FDR correction (see Supplementary Material Table S4).

DISCUSSION

This exploratory study investigated structural alterations in hypothalamic subregions in individuals with AN, OB + ED, and OB-ED, in comparison to HC, as well as their associations with clinical and neuroendocrine variables such as leptin and ghrelin concentrations. Although these results are preliminary, in line with the hypothesis that inflammation and neurodegenerative mechanisms may underlie hypothalamic vulnerability in AN and OB, we observed distinct region-specific alterations across clinical groups. Individuals with AN showed an overall reduction in hypothalamic volumes, particularly pronounced in posterior and inferior subregions. Notably, these reductions remained after adjusting for TBV, particularly in the PS, ITS, and whole hypothalamus, suggesting structural alterations in AN may extend beyond the global brain atrophy. Reduced ITS volume has been associated with this structural alteration, with prolonged starvation and metabolic stress in AN [16, 27].

In contrast, individuals with OB + ED initially exhibited increased volume in the AIS compared to HC. However, this increased volume in the AIS in the OB + ED did not persist after adjusting for TBV, indicating that these differences may be more dependent on overall brain size and may not represent region-specific neurobiological alterations. However, the AIS enlargement in OB + ED relative to OB-ED remained significant after TBV adjustment. This pattern could reflect a distinct pathophysiological profile in OB + ED compared to OB-ED, which describes a more pronounced neuroinflammatory process associated with binge-like eating behavior [12, 13]. Although our findings do not establish a direct link between hypothalamic volume and the frequency of binge episodes, it seems reasonable to suggest that hypothalamic morphological alterations are more closely associated with the presence of an ED within the context of OB than the OB per se. Further studies, including neuroimaging research, are needed to clarify the pathophysiological pathways that may differentiate these two OB conditions.

Although no significant group-level differences emerged in some hypothalamic subregions, these regions exhibited significant within-group associations with specific clinical and hormonal variables, suggesting a differentiated and condition-specific pattern of hypothalamic involvement. In individuals with AN, an earlier onset was initially associated with reduced volume in the whole hypothalamus, as well as in the AIS, ASS, PS, and ITS. However, after correction for multiple comparisons, only the reduced volume in the ASS subregion remained significantly associated with earlier age of onset, suggesting a particularly sensitive involvement of this region during the early stages of the disorder. The ASS includes the PVN, which plays a critical role in regulating the stress response by controlling the hypothalamic-pituitary-adrenal (HPA) axis. While our results do not specifically isolate the PVN, it is plausible that this subnucleus may contribute to the exacerbation of psychopathology (i.e., anxiety and depression), metabolism, and appetite regulation. [38], in the context of stress in ED. The early psychopathological context of patients with ED may interfere with neurodevelopmental processes or have a more substantial impact on brain morphology [39]. or critical brain regions, such as the hypothalamus [17, 38].

Our results may support the hypothesis that AN is a metabo-psychiatric disorder (40,41), characterized by a disruption in

Table 4. Spearman partial correlations adjusted for age, TIV, TBV, between hypothalamic volumes and appetite-regulating hormone concentrations, and clinical variables within each clinical group (AN, OB + ED, OB-ED).

AN	**AIS**	**ASS**	**PS**	**ITS**	**STS**	**TH**
Ghrelin	−0133	−0172	−0399	−0282	−0024	−0263
Leptin	**−0,444**[a]	**−0,423**[a]	−0042	−0192	−0315	−0246
BMI	−0.013	−0.025	0.163	0.128	0.145	0.089
EDI-2	−0.329	−0.270	−0.030	−0.170	−0.232	−0.197
SCL-90R	−0.227	−0.176	−0.036	−0.125	−0.144	−0.135
Onset	**0.623**[a]	**0.670**[a] [b]	**0.524**[a]	**0.569**[a]	0.405	**0.578**[a]
Duration	−0.095	−0.100	−0.239	−0.243	−0.253	−0.217
OB+ED	**AIS**	**ASS**	**PS**	**ITS**	**STS**	**TH**
Ghrelin	−0.113	−0.128	−0.184	−0.256	−0.174	−0.257
Leptin	−0.209	−0.186	−0.021	−0.093	−0.121	−0.105
BMI	0.320	0.289	0.251	0.325	0.346	0.324
EDI-2	0.004	0.028	−0.203	−0.130	−0.137	−0.122
SCL-90R	−0.083	−0.064	−0.130	−0.059	−0.117	−0.057
Onset	0.091	0.102	0.010	−0.006	0.025	0.004
Duration	0.403	**0.435**[a]	−0.136	−0.052	−0.069	−0.050
OB-ED	**AIS**	**ASS**	**PS**	**ITS**	**STS**	**TH**
Ghrelin	0.099	−0.022	−0.332	−0.271	0.131	−0.251
Leptin	0.314	0.326	0.058	0.264	0.275	0.292
BMI	**0.480**[a]	**0.416**[a]	0.025	0.328	**0.405**[a]	0.363
EDI-2	0.303	0.317	−0.013	0.148	−0.012	0.176
SCL-90R	0.038	−0.003	−0.310	−0.258	−0.228	−0.189

AN, anorexia nervosa; *HC-AN*, the age-matched control group for AN; *HC-OB*, the age-matched control group for OB; *OB+ED*, obesity with eating disorder; *OB-ED*, obesity without eating disorder; *BMI*, body mass index; *EDI-2*, eating disorder inventory total score; *SCL-90R*, general psychopathology score; *ASS*, anterior-superior subregion; *AIS*, anterior-inferior subregion; *STS*, superior tuberal subregion; *ITS*, inferior tuberal subregion; *PS*, posterior subregion; *TH*, total hypothalamus.
[a]Bold: significant correlation at p-uncorrected <0.05.
[b]false discovery rate (FDR) correction at p-FDR < 0.05.

communication between the brain and the neuroendocrine system [40]. The negative association between leptin concentrations and the volume of the AIS observed in patients with AN may suggest the existence of a dysregulation between leptin-sensitive pathways and the hypothalamic circuit [41, 42]. From a translational perspective, these findings may support the emerging pharmacological relevance of targeting the hypothalamic circuit as a therapeutic strategy in appetite regulation in AN with medications such as olanzapine and metreleptin [41]. Although olanzapine is an atypical antipsychotic with antihistaminergic properties, it promotes weight gain primarily through antagonism of the histamine H1 receptor within the hypothalamus. This mechanism has been replicated in both preclinical and human neuroimaging studies [42], and recent clinical guidelines underscore its utility in AN, assigning it the highest level of evidence for facilitating weight restoration [41]. Similarly, metreleptin, a recombinant analog of leptin, has been proposed as a promising therapeutic approach to re-engage leptin-sensitive pathways and promote homeostatic recovery in cases of AN [43]. Under the hypothesis of a disrupted leptin-sensitive circuit [44], our results observed that lower leptin concentration was associated with decreased volumes in the AIS. However, this correlation did not survive correction for multiple comparisons and should therefore be interpreted with caution.

Regarding neuroendocrine variables, our findings replicate prior evidence of significantly lower leptin concentrations in AN compared to age-matched HC [27, 45]. In contrast, leptin levels were higher in OB, with or without ED, relative to their respective controls, consistent with leptin's established role as an adiposity signal and supporting the notion of leptin resistance in OB [45]. On the other hand, despite mixed findings in the literature regarding ghrelin concentrations in OB [14, 24, 25], total ghrelin levels were significantly lower in both OB groups compared to HC, potentially reflecting an adaptive response to positive energy balance. In AN, no significant differences were observed between the AN group and healthy controls, which diverges from most previous reports [27, 46]. This discrepancy may be partly explained by the use of total rather than isoform-specific ghrelin measurements, which preclude distinguishing between the physiologically distinct acylated and desacylated forms [47]. Moreover, although assessments were conducted in a standardized manner, logistical constraints precluded blood sampling and MRI acquisition on the same day, which could have reduced the temporal correspondence between peripheral hormonal levels and central measures. Taken together, these aspects highlight the importance of considering both methodological and clinical context when interpreting the present findings, and suggest that future studies integrating isoform-specific assays and same-day multimodal assessments may help to clarify ghrelin dynamics across illness stages further. In individuals with OB, the hypothalamus has also emerged as a critical pharmacological target. Glucagon-like peptide-1 (GLP-1) receptor agonists, which are widely used in the management of obesity, exert their effects on appetite regulation and energy homeostasis through central pathways, primarily via hypothalamic circuits. While the association observed between the ASS volume and disorder duration in the OB + ED cohort did not withstand correction for multiple comparisons, this finding may also indicate that the chronicity of the disorder contributes to neuroinflammatory processes, potentially reflected in hypothalamic volumetric alterations, as suggested by the

existing literature. In the case of individuals with OB-ED, the observed associations primarily involved body mass index (BMI), which was positively correlated with increased volumes in anterior hypothalamic subregions, including the STS, underscoring distinct neuroanatomical patterns related to adiposity. Prior research has identified associations between elevated BMI, neuroinflammatory mechanisms, and volumetric increases in the hypothalamus [48, 49]. However, further evidence is required to validate these observations.

Limitations and strengths

Some limitations must be considered when interpreting our findings. First, the cross-sectional design prevents causal inferences. Second, as an exploratory and preliminary study, the modest sample size limited the statistical power of our analyses to capture the complexity and inherent variability in clinical populations with ED and OB. Third, we measured only total ghrelin, which limits the physiological interpretability of our findings since biologically active and inactive forms could not be distinguished. Moreover, some temporal variability between blood sampling and MRI acquisition, inherent to the clinical setting, may also have influenced the results, given the dynamic fluctuations of ghrelin. Fourth, the absence of systematic data regarding pharmacological treatments precluded controlling for medication effects, which may represent a potential confounder. Fifth, detailed information on metabolic and cardiovascular comorbidities, including diabetes and metabolic syndrome, was not collected, despite their known relevance in OB populations. Given that participants with OB without ED (OB-ED) were bariatric surgery candidates, a high prevalence of metabolic conditions in this subgroup is likely. Future research should incorporate comprehensive medical assessments to more accurately delineate the impact of metabolic factors on brain morphology and related biomarkers. Finally, the sample is not fully representative of the general population, as it includes only women who sought treatment.

Despite these limitations, our study employed a recently developed and validated segmentation method for hypothalamic volumetric analysis [36], which allows for more detailed segmentation of hypothalamic nuclei than traditional imaging techniques. Moreover, we addressed some methodological challenges in analyzing these clinical populations. Notably, the age-related disparities between the treatment-seeking groups (i.e., bariatric surgery or psychotherapy): patients with AN tend to be younger than those with OB, with or without an ED. To mitigate this potential bias, we employed age-matched HC groups, enabling between-group comparisons free from the confounding effects of age. Likewise, we implemented two complementary methodological approaches to determine whether the observed hypothalamic volume differences reflect absolute reductions or relative decreases beyond the global brain atrophy frequently reported in this population. This dual analytical strategy proved informative, as some volumetric alterations, particularly in AN, are significant even after adjusting for TBV, suggesting localized structural changes rather than global atrophy. These findings underscore the importance of considering both absolute and relative volumetric analyses when studying brain morphology in extreme weight conditions. Furthermore, this study differentiated between individuals with OB, with and without an ED. This allowed us to more precisely profile which alterations are exclusively associated with an obesogenic pattern or are specific to the pathophysiology of OB in the presence of ED-related psychopathology.

CONCLUSIONS

Overall, this study provides preliminary evidence of distinct hypothalamic structural profiles across clinical groups with extreme-weight phenotypes, shaped by a combination of metabolic, endocrine, and psychopathological factors. Additionally, the findings highlight the importance of distinguishing between absolute and relative volumetric changes when interpreting neuroimaging data in clinical populations, such as those at the extremes of the weight spectrum. The inclusion of the OB + ED group allowed us to identify specific hypothalamic alterations that are more closely associated with the presence of an ED than with OB alone. Our findings also underscore the role of the PVN in reflecting distinct aspects of ED: the age of onset in AN and the duration of the disorder in OB + ED. Specifically, an earlier age of onset in AN was linked to a significant reduction in the ASS. In contrast, a longer duration of ED with OB was associated with increased volume in the ASS, where the PVN is located. Structural alterations in HPA axis-related hypothalamic regions may reflect underlying neurobiological changes linked to both psychopathological and inflammatory processes, potentially differentiating clinical subtypes of eating disorders.

DATA AVAILABILITY

The datasets generated and analyzed during the current study are not publicly available due to legal and ethical restrictions. However, they may be made available upon request to the Principal Investigator, Prof. Dr. Fernando Fernandez-Aranda (ffernandez@bellvitgehospital.cat), in accordance with local, national, and European Union regulations.

REFERENCES

1. Williams G, Bing C, Cai XJ, Harrold JA, King PJ, Liu XH. The hypothalamus and the control of energy homeostasis: different circuits, different purposes. Physiol Behav. 2001;74:683–701.
2. Azevedo EP, Ivan VJ, Friedman JM, Stern SA. Higher-order inputs involved in appetite control. Biol Psychiatry. 2022;91:869–78.
3. Uher R, Treasure J. Brain lesions and eating disorders. J Neurol Neurosurg Psychiatry. 2005;76:852–7.
4. Simon JJ, Stopyra MA, Mönning E, Sailer S, Lavandier N, Kihm LP et al. Neuroimaging of hypothalamic mechanisms related to glucose metabolism in anorexia nervosa and obesity. J Clin Invest 2020. https://doi.org/10.1172/JCI136782.
5. Steward T, Menchón JM, Jimenez-Murcia S, Soriano-Mas C, Fernández-Aranda F, Menchon JM. Neural network alterations across eating disorders: a narrative review of fMRI studies. Curr Neuropharmacol. 2018;16:1150–63.
6. Tolle V, Ramoz N, Epelbaum J. Is there a hypothalamic basis for anorexia nervosa?. Handb Clin Neurol. 2021;181:405–24.
7. Vainik U, García-García I, Dagher A, García-García I, Dagher A. Uncontrolled eating: a unifying heritable trait linked with obesity, overeating, personality and the brain. Eur J Neurosci. 2019;50:2430–45.
8. Castro DC, Cole SL, Berridge KC. Lateral hypothalamus, nucleus accumbens, and ventral pallidum roles in eating and hunger: interactions between homeostatic and reward circuitry. Front Syst Neurosci. 2015;9:90–90.
9. Coutinho JFP, Ramos AF, Maia L, Castro L, Conceição E, Geliebter A, et al. Volumetric alterations in the nucleus accumbens and caudate nucleus in bulimia nervosa: A structural magnetic resonance imaging study. Int J Eat Disord. 2015;48:206–14.
10. Freeman CR, Zehra A, Ramirez V, Wiers CE, Volkow ND, Wang G-J. Impact of sugar on the body, brain, and behavior. Front Biosci Landmark Ed. 2018;23:2255–66.
11. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr Edinb Scotl. 2008;27:793–9.
12. Patkar OL, Mohamed AZ, Narayanan A, Mardon K, Cowin G, Bhalla R, et al. A binge high sucrose diet provokes systemic and cerebral inflammation in rats without inducing obesity. Sci Rep. 2021;11:11252.
13. Alboni S, Micioni Di Bonaventura MV, Benatti C, Giusepponi ME, Brunello N, Cifani C Hypothalamic expression of inflammatory mediators in an animal model of binge eating. Behav Brain Res 2017. https://doi.org/10.1016/j.bbr.2016.10.044.
14. Castañeda TR, Tong J, Datta R, Culler M, Tschöp MH. Ghrelin in the regulation of body weight and metabolism. Front Neuroendocrinol. 2010;31:44–60.
15. Brooks SJ, Dahl K, Dudley-Jones R, Schiöth HB. A neuroinflammatory compulsivity model of anorexia nervosa (NICAN). Neurosci Biobehav Rev. 2024;159:105580.
16. Nilsson IAK, Thams S, Lindfors C, Bergstrand A, Cullheim S, Hökfelt T, et al. Evidence of hypothalamic degeneration in the anorectic anx/anx mouse. Glia. 2011;59:45–57.
17. Berner LA, Brown TA, Lavender JM, Lopez E, Wierenga CE, Kaye WH. Neuroendocrinology of reward in anorexia nervosa and bulimia nervosa: Beyond leptin and ghrelin. Mol Cell Endocrinol. 2018;497:110320–110320.
18. Steward T, Miranda-Olivos R, Soriano-Mas C, Fernández-Aranda F. Neuroendocrinological mechanisms underlying impulsive and compulsive behaviors in obesity: a narrative review of fMRI studies. Rev Endocr Metab Disord. 2019;20:263–72.

19. Ceccarini G, Pelosini C, Paoli M, Tyutyusheva N, Magno S, Gilio D, et al. Serum levels of adiponectin differentiate generalized lipodystrophies from anorexia nervosa. J Endocrinol Invest. 2024;47:1881–6.
20. Misra M, Klibanski A. Endocrine Consequences of Anorexia Nervosa. Lancet Diabetes Endocrinol. 2014;2:581–92.
21. Paslakis G, Agüera Z, Granero R, Sánchez I, Riesco N, Jimenez-Murcia S, et al. Associations between neuropsychological performance and appetite-regulating hormones in anorexia nervosa and healthy controls: Ghrelin's putative role as a mediator of decision-making. Mol Cell Endocrinol. 2019;497:110441–110441.
22. Misra M, Miller KK, Kuo K, Griffin K, Stewart V, Hunter E, et al. Secretory dynamics of ghrelin in adolescent girls with anorexia nervosa and healthy adolescents. Am J Physiol Endocrinol Metab. 2005;289:E347–356.
23. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S, Stewart AJ et al. Leptin and obesity: role and clinical implication. Front Endocrinol 2021;12. https://doi.org/10.3389/fendo.2021.585887.
24. Monteleone P, Fabrazzo M, Tortorella A, Martiadis V, Serritella C, Maj M. Circulating ghrelin is decreased in non-obese and obese women with binge eating disorder as well as in obese non-binge eating women, but not in patients with bulimia nervosa. Psychoneuroendocrinology. 2005;30:243–50.
25. Rouach V, Bloch M, Rosenberg N, Gilad S, Limor R, Stern N et al. The acute ghrelin response to a psychological stress challenge does not predict the post-stress urge to eat. Psychoneuroendocrinology 2007. https://doi.org/10.1016/j.psyneuen.2007.04.010.
26. Billot B, Bocchetta M, Todd E, Dalca AV, Rohrer JD, Iglesias JE. Automated segmentation of the hypothalamus and associated subunits in brain MRI. NeuroImage. 2020;223:117287.
27. Alzaid H, Simon JJ, Brugnara G, Vollmuth P, Bendszus M, Friederich H. Hypothalamic subregion alterations in anorexia nervosa and obesity: association with appetite-regulating hormone levels. Int J Eat Disord. 2024;57:581–92.
28. Brown SSG, Westwater ML, Seidlitz J, Ziauddeen H, Fletcher PC. Hypothalamic volume is associated with body mass index. NeuroImage Clin. 2023;39:103478.
29. Seitz J, Konrad K, Herpertz-Dahlmann B. Extend, pathomechanism and clinical consequences of brain volume changes in anorexia nervosa. Curr Neuropharmacol. 2018;16:1164–73.
30. First MB, Williams JBW, Karg RS, Spitzer RL Structured clinical interview for DSM-5 research version. Am Psychiatr Assoc Wash DC 2015.
31. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59:0–0.
32. Garner DM Eating Disorder Inventory-2. Odessa: Psychological Assessment Resources; 1991.
33. Garner DDM Inventario de Trastornos de la Conducta Alimentaria (EDI-2). Madrid: TEA ediciones; 1998.
34. Derogatis LR SCL-90-R: Symptom Checklist-90-R. Administration, Scoring and Procedures Manuall—II for the Revised Version. Towson: Clinical Psychometric Research; 1994.
35. Derogatis LR SCL-90-R. Cuestionario de 90 síntomas-Manual. Madrid: TEA Editorial; 2002.
36. Billot B, Greve DN, Puonti O, Thielscher A, Van Leemput K, Fischl B, et al. SynthSeg: Segmentation of brain MRI scans of any contrast and resolution without retraining. Med Image Anal. 2023;86:102789.
37. Rodrigues L, Bocchetta M, Puonti O, Greve D, Londe AC, França M, et al. High-resolution segmentations of the hypothalamus and its subregions for training of segmentation models. Sci Data. 2024;11:940.
38. Godet A, Fortier A, Bannier E, Coquery N, Val-Laillet D. Interactions between emotions and eating behaviors: main issues, neuroimaging contributions, and innovative preventive or corrective strategies. Rev Endocr Metab Disord. 2022;23:807–31.
39. Collantoni E, Meneguzzo P, Tenconi E, Manara R, Favaro A. Small-world properties of brain morphological characteristics in Anorexia Nervosa. PloS One. 2019;14:e0216154.
40. Camacho-Barcia L, Giel KE, Jiménez-Murcia S, Pitti JÁ, Micali N, Lucas I, et al. Eating disorders and obesity: bridging clinical, neurobiological, and therapeutic perspectives. Trends Mol Med. 2024;30:361–79.
41. Himmerich H, Lewis YD, Conti C, Mutwalli H, Karwautz A, Sj"gren JM. et al.World Federation of Societies of Biological Psychiatry (WFSBP) guidelines update 2023 on the pharmacological treatment of eating disorders.World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry 2023;24:643–706.
42. He M, Zhang Q, Deng C, Wang H, Lian J, Huang X-F. Hypothalamic histamine H1 receptor-AMPK signaling time-dependently mediates olanzapine-induced hyperphagia and weight gain in female rats. Psychoneuroendocrinology. 2014;42:153–64.
43. Milos G, Antel J, Kaufmann L-K, Barth N, Koller A, Tan S, et al. Short-term metreleptin treatment of patients with anorexia nervosa: rapid on-set of beneficial cognitive, emotional, and behavioral effects. Transl Psychiatry. 2020;10:303.
44. Bahnsen K, Wronski M-L, Keeler JL, King JA, Preusker Q, Kolb T, et al. Differential longitudinal changes of hippocampal subfields in patients with anorexia nervosa. Psychiatry Clin Neurosci. 2024;78:186–96.
45. Korek E, Krauss H, Gibas-Dorna M, Kupsz J, Piątek M, Piątek J. Fasting and postprandial levels of ghrelin, leptin and insulin in lean, obese and anorexic subjects. Przeglad Gastroenterol. 2013;8:383–9.
46. Wu Y-K, Watson HJ, Del Re AC, Finch JE, Hardin SL, Dumain AS, et al. Peripheral biomarkers of anorexia nervosa: a meta-analysis. Nutrients. 2024;16:2095.
47. Delhanty PJD, Neggers SJ, van der Lely AJ. Mechanisms in endocrinology: Ghrelin: the differences between acyl- and des-acyl ghrelin. Eur J Endocrinol. 2012;167:601–8.
48. Gómez-Apo E, Mondragón-Maya A, Ferrari-Díaz M, Silva-Pereyra J. Structural brain changes associated with overweight and obesity. J Obes. 2021;2021:6613385.
49. Thaler JP, Yi C-X, Schur EA, Guyenet SJ, Hwang BH, Dietrich MO, et al. Obesity is associated with hypothalamic injury in rodents and humans. J Clin Invest. 2012;122:153–62.

ACKNOWLEDGEMENTS

We thank the CERCA Programme/Generalitat de Catalunya for institutional support. We also extend our gratitude to the Institut d'Investigació Biomèdica de Bellvitge (IDIBELL) and the Center for Research in Molecular Medicine and Chronic Diseases (CiMUS).

AUTHOR CONTRIBUTIONS

EC: Conceptualization, Investigation, Methodology, Data curation, Writing-original draft. RM-O: Conceptualization, Investigation, Methodology, Data curation, Writing-original draft. SU: Investigation, Methodology, Data curation, Writing-original draft. IB: Conceptualization, Investigation, Methodology, Data curation. ST: Investigation, Data curation. CD: Investigation, Data curation. NV: Data collection. RL-U: Data collection. FG-P: Data collection. S.J.-M.: Funding acquisition. CS-M: Conceptualization, Methodology, Writing-original draft, Supervision, and review; FF-A: Conceptualization, Investigation, Project administration, Funding acquisition, Writing-original draft, Supervision, and review.

FUNDING

This manuscript and research were supported by grants from the Instituto de Salud Carlos III (ISCIII) (FORTALECE Program of the Ministerio de Ciencia e Innovación (FORT23/00032 and FIS PI20/00132) and co-funded by FEDER funds/European Regional Development Fund (ERDF), a way to build Europe. CIBERObn and CIBERSAM are both initiatives of ISCIII. Additional support was received from the Delegación del Gobierno para el Plan Nacional sobre Drogas (2021I031) and the Ministerio de Ciencia e Innovación (grant PID2021-124887OB-I00). Further funding was provided by AGAUR-Generalitat de Catalunya (2021-SGR-00824 and 2021-SGR-01017), the European Union's Horizon 2020 research and innovation program under Grant agreement no. 847879 (PRIME/H2020, Prevention and Remediation of Insulin Multimorbidity in Europe), the European Union's Horizon Europe research and innovation program under grant agreement No 101080219 (eprObes Project) and Biorexia (EPPermed 2024-618). The Institute of Neurosciences of the University of Barcelona is a María de Maeztu Unit of Excellence CEX2021-001159-M of the Ministry of Science and Innovation of Spain. Fernando Fernandez-Aranda also received partial support from ICREA under the ICREA Academia program-2024.

COMPETING INTERESTS

FFA and SJM received consultancy honoraria from Novo Nordisk. The rest of the authors have nothing to disclose.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41398-025-03708-6.

Correspondence and requests for materials should be addressed to Fernando Fernández-Aranda.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2025