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The interplay between white adipose tissue, adipokines, and structural gray matter changes

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Abstract

The growing global obesity issue emphasizes the importance of understanding its health implications. Previous research has identified consistent alterations in gray matter (GM) volume in connection with obesity. Given the various implications of distinct fat compartments and the potential role of adipose tissue-derived adipokines in brain health, a more detailed investigation of adiposity is required. This study investigates a sample of 65 males with varying body mass indices to explore the relationship between various fat compartments, adipokine levels, and volumetric GM variations, aiming to provide a deeper understanding of the interplay between adiposity, brain structure, and metabolic signals. Whole-body magnetic resonance imaging (MRI) was used to assess total, visceral, and subcutaneous adipose tissue, while MR spectroscopy was performed to capture liver fat content. For the assessment of adipokine levels leptin and adiponectin concentrations were measured, and structural brain images underwent cortical and subcortical segmentation for GM volume and thickness. A predictive modeling approach with leave-one-out cross-validation was used to predict body composition metrics and adipokine levels based on structural GM data. Our investigation revealed diminished GM volume and thickness correlated with elevated leptin levels in areas crucial for appetite regulation, decision-making, and cognitive control, including the anterior insula, orbitofrontal cortex, and anterior cingulate cortex. These findings suggest a potential adverse impact of heightened leptin concentrations on brain health and eating habits. Contrary to expectations, our investigation found no significant relationship between GM volume and any of the measured fat compartments. This result prompts the need for further research to elucidate the relationship between obesity, adipokines, and brain structure.

KEYWORDS
adipokines, gray matter volume, leave-one-out cross-validation, obesity, white adipose tissue

1 | INTRODUCTION

Projections indicate that by 2035 an alarming 51% of the global population might be overweight or obese (Lobstein & Brinsden, 2022). It implies an increase in obesity-related comorbidities and underscores the urgency for effective prevention and treatment strategies to address this pandemic (Chooi et al., 2019). Understanding structural brain changes associated with excess fat and fat-derived endocrine signals may contribute to unraveling the complex health implications of obesity. Volumetric alterations of gray matter (GM) in subcortical reward- and emotion-related areas and cortical regions involved in sensory processing and higher cognitive functions have been found in overweight and obese individuals compared to lean controls (Cho et al., 2021; Kennedy et al., 2016; Pflanz et al., 2022). However, body mass index (BMI, kg/m^2), a widely used obesity metric, has yielded mixed findings with regard to volumetric brain changes. Some obesity studies link lower GM associated with elevated BMI in the caudate nucleus (Caud), nucleus accumbens (NAc), and pallidum (Pall) with impaired reward-driven behaviors (Dekkers et al., 2019), although conflicting reports exist (García-García et al., 2020). Functional MRI (fMRI) consistently shows increased activity in the putamen (Put) and Caud in response to appealing food cues in obese individuals compared to normal-weight participants (Pursey et al., 2014; Rothemund et al., 2007). Moreover, increased functional connectivity in the dorsal striatum aligns with subjective craving scores, predicting BMI gains (Contreras-Rodríguez et al., 2017). Altogether, these findings hint at disruptions in food-related reward processing and an increased incentive salience related to food cues associated with increased fat mass.

In addition, integrative structures, such as the amygdala (Amyg) and insula (Ins) (Chao et al., 2018; Gómez-Apo et al., 2021) have also been implicated in obesity. By exhibiting connections with the hypothalamus, striatum, and prefrontal cortex, the Amyg is believed to integrate sensory, motivational, and homeostatic inputs. This integrative role extends to emotional processing, influencing emotional eating behaviors, such as those induced by anxiety and depression (Izadi & Radahmadi, 2022). Besides, increased Amyg volume has been linked to reduced dietary self-control (Kim et al., 2020). Within this interconnected network, the insular cortex processes a range of sensory cues related to food, including taste, odor, texture, and appearance (Gogolla, 2017). Numerous studies report heightened activity in the Ins during craving for specific foods (Pelchat et al., 2004; Tang et al., 2012). Forming a complex network with striatal regions, Amyg, hypothalamus, and frontal cortex, the Ins integrates different cues involving rewards, interoceptive signals, and emotional cues associated with food consumption. Consequently, reduced insular GM volume in individuals with obesity has been proposed to reflect processing abnormalities with regard to food cues (Herrmann et al., 2019; Shott et al., 2015).

A consistent finding in obesity-related meta-analyses is a notable decrease in GM in prefrontal regions, including the orbitofrontal cortex (OFC) (Chen et al., 2018, 2020; García-García et al., 2019; Herrmann et al., 2019). Studies demonstrate altered OFC activation during response inhibition tasks in individuals with higher BMI (Batterink et al., 2010). Moreover, irregular activity in the medial prefrontal cortex has been associated with lower reinforcement-based learning performance among obese but not lean participants (Kube et al., 2018). Additionally, the anterior cingulate cortex (ACC) plays a role in body satisfaction and awareness, although its exact contribution to obesity requires further exploration (Preston & Ehrsson, 2016). Taken together, this might imply compromised executive control over eating behavior.

The precision of BMI in assessing obesity and overweight is debated due to its limitations in accurately measuring body fat quantity and distribution. Similarly, while measurements such as waist-to-hip ratio (WHR) or waist circumference (WC) better represent abdominal obesity, they fail to distinguish between specific fat compartments. This separation is relevant due to the varied functions of different fat depots (Luong et al., 2019). For instance, excess visceral adipose tissue (VAT) has been associated with insulin resistance and low-grade inflammation, whereas subcutaneous adipose tissue (SAT) is not that metabolically active (Ibrahim, 2010). Moreover, excess VAT promotes the accumulation of hepatic fat leading to metabolic dysfunction-associated steatotic liver disease (MASLD), which contributes to systemic metabolic dysfunction (Chan et al., 2023; Hanlon & Yuan, 2022). Volumetric reductions in GM and decreased cortical thickness have been observed in connection with visceral adiposity, but not with increased subcutaneous fat (Cho et al., 2021). Additionally, while there is a strong correlation between BMI and VAT, a more pronounced cortical atrophy was observed specifically concerning VAT, indicating its distinct impact on brain structure due to its endocrine and inflammatory characteristics (Veit et al., 2014). Excess accumulation of abdominal fat is accompanied by changes in circulating adipokine levels, such as leptin and adiponectin. High concentrations of leptin, known for its anorexigenic properties, can lead to reduced sensitivity to satiety signals in the hypothalamus, consequently affecting appetite regulation and energy expenditure (Waterson & Horvath, 2015). While adiponectin is involved in glucose and fatty acid metabolism its decreased levels in obesity are associated with chronic inflammation, promoting neuroinflammation and impacting insulin sensitivity (Bloemer et al., 2018). A growing body of evidence highlights the involvement of adipokines in cognitive decline and dementia, indicating a potential link between obesity and accelerated cognitive deficits. For example, while Rajagopalan et al. (2013) reported decreased GM linked to higher leptin levels, other studies have associated increased hippocampal volume with elevated leptin concentrations, proposing a neuroprotective role of leptin (Narita et al., 2009). Previously linked to the pathogenesis of Alzheimer's disease (Kim et al., 2020), decreased adiponectin levels have been correlated with hippocampal atrophy in diabetic patients (Masaki et al., 2012). This suggests a possible involvement of AT derived hormonal signals in the progression of neurodegenerative conditions and cognitive decline, although the exact mechanisms remain understudied.

This study aims to investigate the interplay between various fat compartments, adipokine levels and volumetric GM variations in a sample of male participants covering a broad spectrum of BMI. We hypothesize that metabolically active fat depots, specifically VAT and hepatic fat, will exhibit associations with volumetric GM changes in

critical areas involved in processing sensory and reward cues, along with those linked to executive control. Furthermore, we propose that changes in adiponectin and leptin levels might act as mediators in this relationship.

2 | METHODS

2.1 | Study population

In this study, we used the dataset from Okudzhava et al. (2024). In this cross-sectional study design, 65 male participants, free from any metabolic, neurological, or psychiatric conditions, were recruited from the University of Lübeck's participant pool and through online platform advertisements. The recruited participants had an age range of 24–61 years (mean ± SD = 27 ± 9.6) and a BMI between 19 and 41 kg/m^2 (mean ± SD = 28 ± 4.9). In the normal-weight group, 17 participants had a mean BMI of 22.7 (±1.8) and a mean age of 37.4 years (±9.3). The overweight group comprised 28 participants with a mean BMI of 27.1 (±1.5) and a mean age of 41.5 years (±9.4), while the obese group included 20 participants with a mean BMI of 34.2 (±3.5) and a mean age of 40.0 years (±8.0). The study followed the guidelines outlined in the World Medical Association Declaration of Helsinki and obtained approval from the Ethics Committee of the University of Lübeck. Prior to engaging in experimental procedures, all participants provided written informed consent.

Before participating in the study, individuals completed a questionnaire addressing preexisting neurological or psychiatric conditions. During data preprocessing, two whole-body MRI datasets and two MR spectroscopy (MRS) datasets were excluded due to data quality issues, resulting in a sample of 63 subjects. Please note that the analyses involving BMI, BodPod, and adipokine data were conducted on a subset of 65 subjects. Table 1 provides a summary of the study participants' information.

TABLE 1 Descriptive information of the sample.

Variable	Mean	SD	Range
Age (years)	27	9.6	24–61
BMI (kg/m^2)	28	4.9	19.6–41.8
Years of education	15.9	3.04	10–24
Fat (%)	26.9	9.6	4–51
Total fat (L)	31	12.9	13.8–69
Visceral fat (L)	4.4	2.2	1.4–9.2
Subcutaneous fat (L)	10.8	6.4	1.1–29.6
Global body volume (L)	86.6	18.05	62.4–145.2
Total fat ratio (L/L)	0.4	0.07	0.2–0.57
Visceral fat ratio (L/L)	0.05	0.02	0.01–0.09
Subcutaneous fat ratio (L/L)	0.1	0.04	0.02–0.24
Liver fat (%)	3.2	3.0	0.15–14.2
Triglycerides (mg/dL)	121.4	69.3	36–362
HbA1c (%)	5.39	0.23	4.7–6.2
Fasting glucose (mg/dL)	84.5	6.5	78–109
Adiponectin (μg/mL)	6.28	3.7	1.02–17.05
Leptin (ng/mL)	13.04	18.01	0.08–102.1

2.2 | Data acquisition

After an overnight, fast blood samples (20 mL) were collected to assess fasting serum concentrations of leptin and adiponectin. Assessment of fasting glucose, glycated hemoglobin (HbA1c), and triglyceride levels was performed to control for potential cardiovascular and metabolic risks. Subject height and weight were measured, and their BMI was calculated.

Body fat percentage (fat%) was assessed using the Bod Pod (Life Measurement, Inc.©), employing air displacement plethysmography to estimate whole-body fat mass and fat-free mass fractions based on body volume and density.

MRI and MRS data were assessed using a 3T whole-body imager (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) at the University of Lübeck's Center of Brain Behavior and Metabolism (CBBM). T1-weighted images were acquired with a 64-channel head coil using a T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR: 2300 ms; TE: 2.43 ms; flip angle: 8°; voxel size: 0.8 × 0.8 × 0.9 mm^3; slice thickness: 0.85 mm).

For whole-body MRI, a T1-weighted turbo spin echo sequence was applied (TR: 600 ms; TE: 8.1 ms; flip angle: 130°; voxel size: 2 × 2 × 10 mm^3; slice thickness: 10 mm). Participants, positioned prone with arms extended, underwent scans from fingers to toes. Breath-holding instructions during the 13-s acquisition minimized breathing artifacts. A total of 15–20 recordings (five slices each) were acquired with a 10-cm table shift to cover the entire body.

For volume selective proton spectroscopy (^{1}H-MRS) of the liver, a single-voxel stimulated-echo acquisition mode (STEAM) localization technique was employed (TR: 4000 ms; TE: 11 ms). MRS was conducted within a 3 × 3 × 2 cm^3 voxel of interest in the posterior part of liver segment 7, avoiding inclusion of blood vessels for enhanced metabolic analysis accuracy. The measurements were conducted in a fasting state to ensure a precise assessment of intrahepatic lipid (IHL) concentrations.

2.3 | Processing of MRI, MRS, and metabolic data

FreeSurfer 6.0.0 (Fischl, 2012) was used to preprocess and segment T1-weighted data. The standard FreeSurfer analysis pipeline encompassed several steps, including skull stripping, motion correction, Talairach transformation, intensity normalization, and tissue segmentation to classify GM, white matter, and cerebrospinal fluid. Subsequent procedures involved cortical parcellation and subcortical segmentation. Cortical areas were parceled based on the Desikan–Killiany and Destrieux atlases (Desikan et al., 2006; Destrieux et al., 2010), while the automatic subcortical segmentation atlas (Fischl et al., 2002) was applied to obtain segmentations and labels for

subcortical structures. We opted for a ROI-based analysis, to focus on brain areas that have been identified as important hubs for the control of eating behavior by previous studies. A subset of 18 relevant regions of interest (ROIs) was determined as indicated in Okudzhava et al. (2024). The selection included bilateral GM areas, specifically the rostral ACC (rACC), caudal ACC (cACC), rostral MFG (rMFG), caudal MFG (cMFG), SFG, lateral OFC (lOFC), medial OFC (mOFC), frontal pole (FrP), parahippocampal gyrus (PpG), anterior Ins (aIns), posterior Ins (pIns), thalamus (Thal), Caud, Put, Pall, Hipp, Amyg, and NAc.

Post-processing of whole-body images for segmentation and quantification of fat compartments was performed applying an automatic segmentation algorithm based on Matlab (The MathWorks, version 7.5.0) as described in Würslin et al. (2010). Areas of AT and lean tissue were automatically calculated, separation of VAT and other adipose tissue depots was automatically performed between femoral head and thoracic diaphragm using an extended snake algorithm. Hepatic lipid content was calculated by calculating the ratio of lipid signal (methylene + methyl) and water plus lipid signal as described in Machann et al. (2006).

The assessment of leptin concentrations in fasted serum samples was conducted with sandwich immunoassay using Quantikine ELISA kits (R&D Systems, Minneapolis, MN, USA) with a sensitivity of 7.8 pg/mL and an assay range of 15.6–1000 pg/mL. Serum adiponectin levels were assessed using Quantikine ELISA kits (R&D Systems, Minneapolis, MN, USA) with a sensitivity of 0.891 ng/mL and an assay range of 3.9–250 ng/mL. Each assessment was replicated to enhance precision and control for inter-assay variability, with subsequent averaging of replicated values.

2.4 | Statistical analysis

The Connectome-Based Predictive Modeling (CPM) toolbox (Shen et al., 2017) was used for predictions of body composition variables (BMI, fat%, total adipose tissue (TAT), VAT, SAT, and IHL) and metabolic measures (leptin, adiponectin) utilizing individual GM volume and thickness data. Notably, CPM toolbox, originally developed for functional and structural connectome data, demonstrated flexibility in handling alternative data formats. Rather than inputting $M \times M \times N$ connectivity matrices, where M represents the number of nodes and N represents the number of subjects, the parameters of the MATLAB-based toolbox could be adjusted to accommodate $M \times 1 \times N$ dimensions. This adjustment would enable the input of vectors of data across subjects instead of matrices. In our study, vectors of GM volume values per subject were utilized as input, highlighting the adaptability of the CPM toolbox beyond connectome applications and enabling robust predictions.

The predictive modeling employed a 36-node model encompassing the anatomical regions listed above. Eight distinct multiple linear regression models were constructed to account for collinearity issues across adipokine and fat metrics. Age was incorporated as a covariate for body composition variables, and both age and fat%—for metabolic variables. TAT, VAT, and SAT were expressed as ratios to body global volume (in liters) to account for variations in body size. IHL, leptin, and adiponectin data underwent logarithmic transformation due to the skewed distribution and the presence of outliers. Model predictive performance was assessed using leave-one-out cross-validation (LOOCV), wherein the model iteratively trained on all subjects but one, subsequently testing on the excluded subject. The process repeated until each subject's model performance was evaluated. In addition to volumetric values, cortical thickness measurements for the cortical ROIs were also included in the analysis resulting in GM vectors with 58 values per subject.

The following procedure was implemented to construct the predictive model: in each iteration, one subject was excluded from the dataset. Edges were then selected based on partial correlations ($p < .05$) with body composition and metabolic measures across the remaining subjects. Positive and negative networks were identified, and significant edges were accumulated for each individual. Subsequently, we formulated a linear regression model, utilizing the aggregated edges as regressors to predict outcome variables. The fitted model parameters were then applied to forecast outcome variables in the excluded subject. This entire process was systematically repeated for all iterations of LOOCV.

During the edge selection phase, only edges displaying significant correlation with the target variable in every LOOCV iteration were retained. Following LOOCV, a robust assessment of the model's predictions was conducted through permutation testing with 1000 iterations. This testing determined the statistical significance of the model's predictions, with the corresponding permutation p-value indicating the proportion of permutations equal to or greater than the true prediction. The schematic of the predictive modeling procedure is illustrated in Figure 1.

3 | RESULTS

The mean and SD of leptin levels for the normal-weight, overweight, and obese groups were 3.1 ng/mL (±3.3), 5.8 ng/mL (±4.7), and 31.7 ng/mL (±22.9), respectively. For adiponectin levels, the corresponding values were 9.03 μg/mL (±5.0), 5.9 μg/mL (±3.1), and 4.5 μg/mL (±2.3). Prior to group comparisons, adipokine data was assessed for normality within each BMI group. The analysis using the Wilcoxon signed-rank test with Bonferroni correction revealed significant differences in leptin concentrations between the normal-weight and obese ($p < .001$), as well as between the overweight and obese BMI groups ($p < .001$). A pairwise t-test with Bonferroni correction was performed to compare adiponectin concentrations across groups indicating significant differences between normal-weight and overweight ($p = .009$), and overweight and obese groups ($p = .003$). These results are illustrated in Figure 2.

3.1 | Body composition and adipokine predictions with CPM

The analysis involved training eight separate models to predict body composition metrics and adipokines using age as a confounding

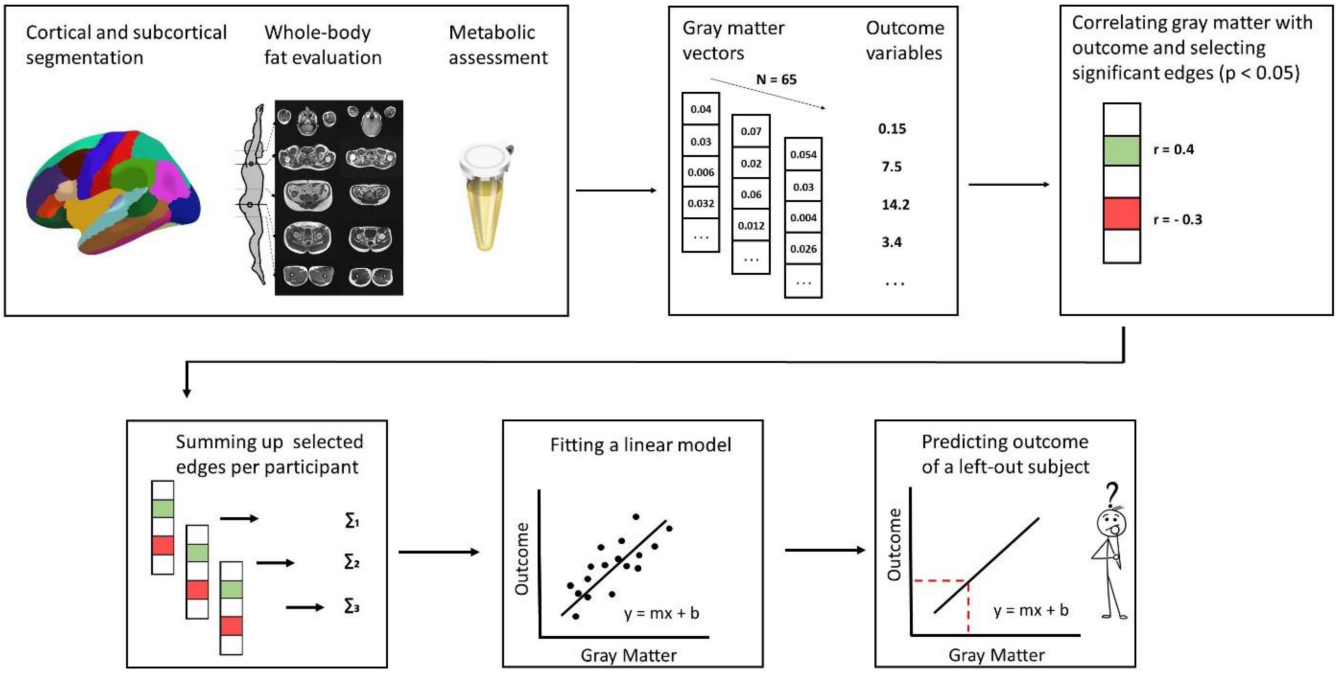


FIGURE 1 Schematic of the adapted CPM procedure.

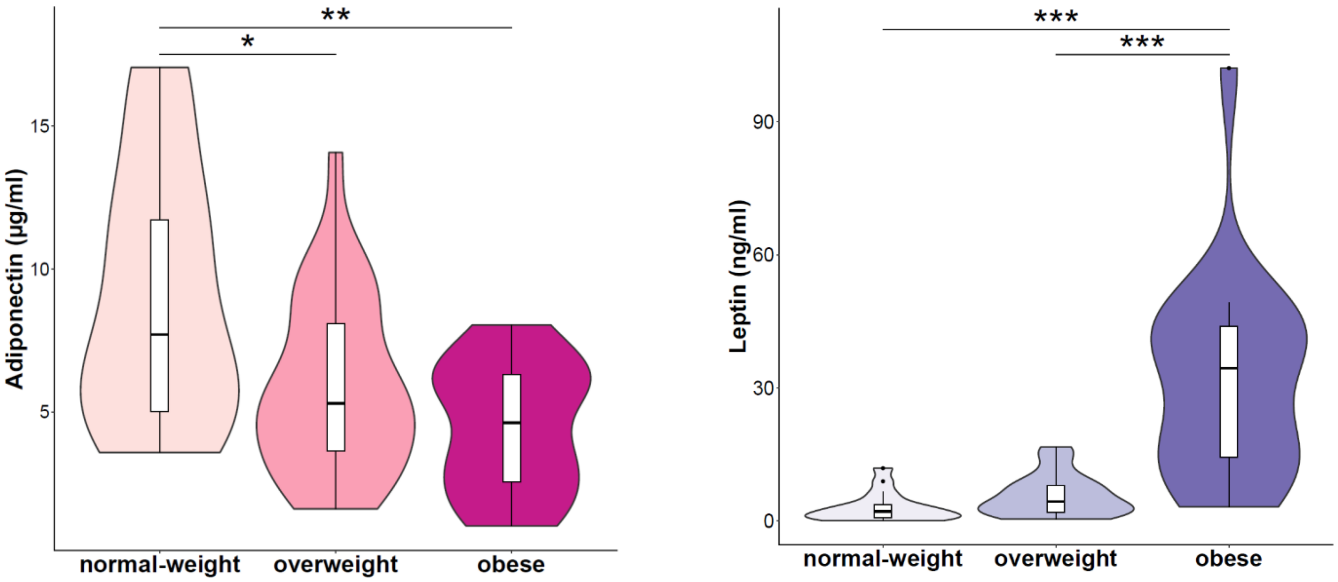


FIGURE 2 Adiponectin and leptin concentrations across BMI groups.

variable for body composition models, and both age and total fat % for adipokine models. Correlations between all target variables are presented in Figure 3. LOOCV consistently revealed a negative association ($p < .05$) between GM volume and cortical thickness, and transformed leptin data across all folds, establishing a model that effectively predicted leptin values after adjusting for age and years of education ($r = 0.37$; $R^2 = 0.14$). Additionally, reduced cortical thickness and volume were identified with regard to elevated leptin levels after correcting for age, years of education, and total fat % ($r = 0.35$; $R^2 = 0.12$). Areas of reduced GM volume linked to age- and years of education-corrected leptin included right rACC and reduced cortical thickness was observed in bilateral aIns. Age-, years of education- and fat %-corrected model identified reductions in the left mOFC volume and right aIns thickness. These findings are presented in Figure 4. The robustness of this relationship was validated through permutation testing, obtaining p-values of .003 for the first and 0.003 for the second leptin model. No significant models were identified with regard to any of the body composition measurements and adiponectin.

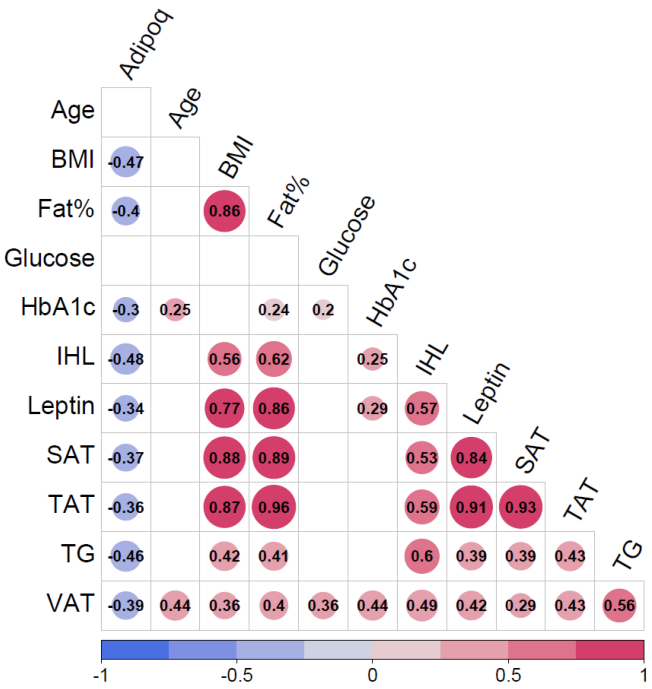
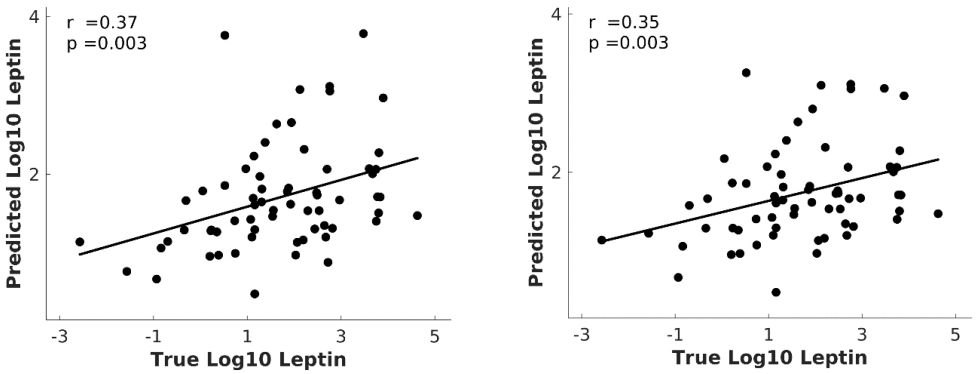


FIGURE 3 Interactions between metabolic measures, fat measurements and age. Significant correlations are indicated by colored circles with correlation coefficients, whereas empty boxes represent non-significant correlations. Adipoq, adiponectin; BMI, body mass index; HbA1c, glycated hemoglobin; IHL, intrahepatic lipids; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; TG, triglycerides; VAT, visceral adipose tissue.

4 | DISCUSSION

In this study, we aimed to examine the alterations in GM volume and cortical thickness linked to various measures of body composition and adipokine levels. Our findings revealed robust predictive patterns, indicating that structural GM properties can forecast variations in adipokine concentrations. We identified diminished GM volume and thickness in brain areas crucial for appetite regulation, decision-making and cognitive control, including mOFC, aIns and rACC, correlating with elevated leptin levels. Importantly, the association between leptin and mOFC, as well as aIns, persisted after adjusting for total body fat, highlighting a distinct influence of leptin on brain structure independently from body fat.

Notably, the thinning of the insular cortex associated with heightened leptin concentrations suggests a potential adverse impact on brain health, contributing to alterations in eating habits. This thinning could stem from disrupted leptin signaling to the brain, affecting the dynamic interaction between these areas and leading to structural changes with insular cortex. As the central hub for processing internal body signals related to food, alterations in this region may contribute to shifts in food-related perceptions and behaviors. Previous studies have established a connection between insular atrophy and heightened leptin levels, correlating with increased feelings of hunger (Smucny et al., 2012). Additionally, elevated leptin levels appear to trigger a greater response in Ins when exposed to high-calorie foods, indicating an exaggerated sensitivity to appetizing food stimuli (Jastreboff et al., 2014). These findings propose a potential



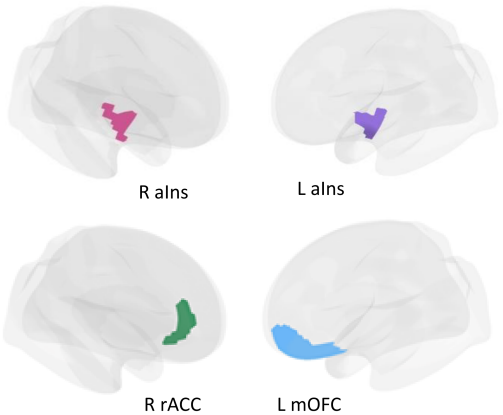


FIGURE 4 Predictions of leptin (on the left: corrected for age and years of education; on the right: corrected for age, years of education, and total fat %). Visualized are the GM areas contributing to the predictions including bilateral aIns, right rACC and left mOFC. L, left; R, right.

mechanism by which leptin could influence brain structure and responsiveness to food cues.

While volumetric changes associated with obesity in reward processing areas, particularly OFC, have been explored previously, the relationship with appetite-related hormones remains understudied. In contrast to our findings, Turan and colleagues reported an increase in mOFC correlated with elevated leptin levels in adolescents with obesity (Turan et al., 2021). However, this correlation might suggest differences in brain development related to age, indicating distinct underlying neural mechanisms in adolescents compared to those seen in adults. The majority of existing obesity literature in adult samples reports volumetric decrease in OFC (Chen et al., 2020). Lesions in OFC, crucial for encoding and updating reward expectations, have been associated with reward devaluation (Howard & Kahnt, 2021; Reber et al., 2017). Functional studies further reveal enhanced activation in OFC in obese individuals, even in a satiated state, compared to lean controls, suggesting disrupted reward-related processing of food in this region (Seabrook & Borgland, 2020). Additionally, reduced ACC volume has been correlated with excess body fat and associated with higher impulsivity traits (Wang et al., 2017). This aligns with the tendency to favor immediate smaller rewards over delayed larger rewards, highlighting impaired reward processing and decision-making (Liu et al., 2022). Moreover, being part of the salience network alongside aIns, structural changes in ACC might contribute to altered attentional mechanisms and disrupted integration of internal and external information related to food cues (Steward et al., 2019).

Interestingly, none of the measured fat compartments demonstrated a significant relationship with GM volume, despite their strong correlation with leptin. Although permutation testing did not yield significance, all fat measurements indicated positive correlations with bilateral Caud volume across all LOOCV folds. Additionally, VAT exhibited positive correlations with NAc, Put and Amyg volumes. This consistent expansion of subcortical limbic structures suggests hyperactivity in reward- and emotion processing areas indicating heightened sensitivity for palatable foods (Bernardes et al., 2018; Morales & Berridge, 2020; Opel et al., 2021).

Furthermore, partial correlations revealed an inverse relationship between total fat and BMI with right aIns thickness. This aligns with TAT and BMI displaying the strongest correlations with leptin levels, although this finding was not validated by permutation testing. Notably, existing evidence reports insular thinning associated with increased adiposity (Bernardes et al., 2018; Wang et al., 2017). While this relationship might be mediated by elevated leptin levels in obesity, as indicated in the present study, further investigation is needed to fully elucidate the mechanisms involved. Our previous investigation of WM connectivity using the same dataset, revealed altered connectivity among cortical and subcortical brain structures, with the right Ins acting as a central hub (Okudzhava et al., 2024). In line with these findings, the observed GM patterns in the present study provide valuable complementary evidence, offering additional insights into the interplay between brain structure and adiposity.

Intriguingly, VAT is the only fat compartment exhibiting a negative correlation with rMFG. Prior studies have linked VAT to GM deficits in frontal and temporal areas, attributing this to its inflammatory properties and insulin resistance (Benedict et al., 2012; Ozato et al., 2021). Consequently, abdominal obesity is suggested as a risk factor for cognitive decline. In their meta-analysis, Herrmann et al. (2019) indicated consistent volumetric reduction in MFG associated with excess body fat, although this relationship was not specific to abdominal fat. In individuals with obesity, aberrant activation in regions like MFG within the default mode network has been linked to compromised working memory (Syan et al., 2019). Notably, structural GM abnormalities often relate more to visceral rather than subcutaneous fat, although conflicting evidence exists (Pflanz et al., 2022; Raji et al., 2023). The observed negative correlations between adiponectin, fat metrics, and leptin in our study align with previous findings; however, no correlations with volumetric patterns were identified. This is intriguing, given that a decrease in its concentration has been linked to adverse effects on brain health. Reduced adiponectin concentrations are directly linked to reduced insulin sensitivity, and insulin resistance has been associated with cortical GM decrease (Lu et al., 2021). One limitation of our study is the absence of measurements for insulin sensitivity. The lack of findings related to adiponectin could be attributed to the relatively short duration of inflammatory processes, possibly indicating a predominantly insulin-sensitive profile in our sample, potentially mitigating risks to brain health. Moreover, the cross-sectional design limits our ability to infer temporal changes in brain structure concerning fat accumulation and metabolic variations, emphasizing the necessity for longitudinal studies. Furthermore, our sample size of 65 subjects increases the risk of overfitting, impacting the accurate prediction of values for unseen participants. The application of LOOCV with this sample size may remain susceptible to outliers. For example, correlations detected in 64 out of 65 folds fail to meet the edge selection criteria, resulting in their exclusion from subsequent analysis. A larger sample size would enhance stability against such variations. Besides, our current methodology assumes a linear relationship between variables, potentially overlooking more complex patterns. Lastly, our sample lacks diversity in age and sex/gender representation, restricting the broader applicability of our findings.

5 | PERSPECTIVES

Investigating GM alterations in obesity not only reveals neurological impacts but also offers insights into potential avenues for targeted interventions. In future studies, prioritizing comprehensive assessments of fat distribution and quantity, along with metabolic evaluations, becomes crucial for understanding dysfunctional brain networks. The observed link between abdominal obesity, adipokines, and Alzheimer's disease and cognitive decline further emphasizes the broader implications of adipokines, extending beyond energy homeostasis. Exploring psycho-behavioral phenotypes can further help identify individual biomarkers, potentially enhancing the precision of preventive measures (Camacho-Barcia et al., 2023). This comprehensive approach may enhance our understanding of obesity's multifaceted impact on brain health.

AUTHOR CONTRIBUTIONS

L. O.: data acquisition, analysis, manuscript drafting, and figure creation. S. S.: data acquisition. V. P.: analysis of metabolic data. H. O.: provision of tools for metabolic analysis and coordination of the process, manuscript revision. E. F. G. and G. G.: supervision of data analysis. J. M.: analysis of whole-body MR data. J. P. T.: provision of tools for data analysis and supervision of the process. T. F. M.: conception and design of the study, manuscript revision. M. H.: conception and design of the study, manuscript revision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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