Received: 31 October 2023 | Revised: 9 February 2024 | Accepted: 27 February 2024

DOI: 10.1002/hbm.26654

RESEARCH ARTICLE

WILEY

White adipose tissue distribution and amount are associated with increased white matter connectivity

Liana Okudzhava[1,2] | Stephanie Schulz[1,2] | Elda Fischi-Gomez[3,4,5] | Gabriel Girard[3,6] | Jürgen Machann[7,8,9] | Philipp J. Koch[1,2] | Jean-Philippe Thiran[3,4,5] | Thomas F. Münte[1,2] | Marcus Heldmann[1,2,10]

[1]Department of Neurology, University of Lübeck, Lübeck, Germany

[2]Center of Brain, Behavior and Metabolism, University of Lübeck, Lübeck, Germany

[3]CIBM Center for Biomedical Imaging, Lausanne, Switzerland

[4]Radiology Department, Lausanne University and University Hospital (CHUV), Lausanne, Switzerland

[5]Signal Processing Laboratory (LTS5), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

[6]Department of Computer Science, Université de Sherbrooke, Sherbrooke, Quebec, Canada

[7]Section on Experimental Radiology, Department of Radiology, Eberhard-Karls University, Tübingen, Germany

[8]German Center for Diabetes Research (DZD), Neuherberg, Germany

[9]Institute for Diabetes Research and Metabolic Diseases, Helmholtz Center Munich, University of Tübingen, Tübingen, Germany

[10]Institute of Psychology II, University of Lübeck, Lübeck, Germany

Correspondence
Liana Okudzhava, Department of Neurology, University of Lübeck, Lübeck, Germany.
Email: l.okudzhava@uni-luebeck.de

Funding information
Deutsche Forschungsgemeinschaft; Bundesministerium für Bildung und Forschung, Grant/Award Number: 01GI0925

Abstract

Obesity represents a significant public health concern and is linked to various comorbidities and cognitive impairments. Previous research indicates that elevated body mass index (BMI) is associated with structural changes in white matter (WM). However, a deeper characterization of body composition is required, especially considering the links between abdominal obesity and metabolic dysfunction. This study aims to enhance our understanding of the relationship between obesity and WM connectivity by directly assessing the amount and distribution of fat tissue. Whole-body magnetic resonance imaging (MRI) was employed to evaluate total adipose tissue (TAT), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT), while MR liver spectroscopy measured liver fat content in 63 normal-weight, overweight, and obese males. WM connectivity was quantified using microstructure-informed tractography. Connectome-based predictive modeling was used to predict body composition metrics based on WM connectomes. Our analysis revealed a positive dependency between BMI, TAT, SAT, and WM connectivity in brain regions involved in reward processing and appetite regulation, such as the insula, nucleus accumbens, and orbitofrontal cortex. Increased connectivity was also observed in cognitive control and inhibition networks, including the middle frontal gyrus and anterior cingulate cortex. No significant associations were found between WM connectivity and VAT or liver fat. Our findings suggest that altered neural communication between these brain regions may affect cognitive processes, emotional regulation, and reward perception in individuals with obesity, potentially contributing to weight gain. While our study did not identify a link between WM connectivity and VAT or liver fat, further investigation of the role of various fat depots and metabolic factors in brain networks is required to advance obesity prevention and treatment approaches.

KEYWORDS
adipose tissue, connectome-based predictive modeling, obesity, structural connectivity

1 | INTRODUCTION

The prevalence of obesity has skyrocketed in recent decades, posing a significant global health hazard. Approximately 39% of the world's population is overweight, with around 13% classified as obese (World Health Organization [WHO], 2021). Despite its profound impact on health, obesity is often overlooked as a disease due to limited public awareness and social stigmatization. This is concerning considering its strong association with numerous comorbid conditions, such as hypertension, Type 2 diabetes, metabolic syndrome, cardiovascular disease, and certain cancers (Apovian, 2016). Furthermore, accumulating evidence highlights a heightened risk of cognitive impairment and dementia linked to excessive fat accumulation (Tang et al., 2021). This is supported by consistent structural brain abnormalities associated with excess fat, including gray matter (GM) and white matter (WM) changes (Han et al., 2021). Failing to recognize obesity as a disease and neglecting proper management strategies contribute to the escalating burden of this pandemic worldwide.

Obesity induces pathological alterations, including neuroinflammation, vascular damage, and blood–brain barrier disruption (Karczewski et al., 2022). Chronic low-grade inflammation, a consequence of obesity, releases adipokines and pro-inflammatory cytokines, initiating neuroinflammatory responses in the brain (Salas-Venegas et al., 2022). This disrupts the hypothalamus, a central regulator of appetite, impacting communication between brain regions involved in reward processing, emotional regulation, and cognition (Berthoud et al., 2017). The disturbed balance between appetite and energy consumption contributes to weight gain and obesity. Notably, hypothalamic neuroinflammation plays a role in brain pathology, interacting with non-homeostatic factors like stress, anxiety, depression, and societal influences, shaping structural brain alterations associated with obesity (Lazarevich et al., 2016). Evidence from structural magnetic resonance imaging (MRI) studies indicates GM and WM alterations linked to obesity/overweight (Fernández-Andújar et al., 2021; Kullmann et al., 2015). Elevated body mass index (BMI), an established metric to assess obesity, has been consistently associated with changes in GM volume. The caudate nucleus (Caud), nucleus accumbens (NAc), putamen (Put), and the orbitofrontal cortex (OFC) are assumed to play a key role in regulating and encoding the rewarding properties of stimuli (Camara et al., 2009; Chen et al., 2018). Notably, these regions have shown volumetric reductions in GM associated with increased BMI, suggesting potential deficits in reward processing associated with overweight and obesity (Herrmann et al., 2019). The insular cortex (Ins) is another key structure mediating eating behavior by integrating external sensory and internal homeostatic information related to food stimuli (Frank et al., 2013). Volumetric reductions in the insula further facilitate abnormal eating behavior due to disrupted integration of metabolic hunger/satiety cues on the one hand, and reward-related aspects of food, on the other hand (Herrmann et al., 2019; Smucny et al., 2012). Furthermore, while the link between obesity and cognitive impairment requires further investigation, hippocampal atrophy in individuals suffering from obesity suggests accelerated cognitive decline (Taki et al., 2008). Similarly, GM atrophy in frontal cortical areas, such as the anterior cingulate cortex (ACC) and superior, middle, and inferior frontal gyri (SFG, MFG, IFG), points to weakened inhibition and inadequate reward-driven decision-making (Saruco & Pleger, 2021; Stillman et al., 2017). Intriguingly, in contrast to cortical areas, some studies have revealed an increase in GM volume specifically within subcortical reward structures indicating a complex interplay between cortical and subcortical regions in the context of reward-related neural mechanisms (García-García et al., 2020; Opel et al., 2021).

Obesity-related WM alterations exhibit less consistency in the existing literature. Diffusion-tensor imaging (DTI) is a commonly used technique to assess microstructural WM properties by modeling water diffusion in WM bundles (Soares et al., 2013). Fractional anisotropy (FA) and mean diffusivity (MD) are primary DTI parameters, representing the anisotropy in the directionality of the WM tissue and the overall magnitude of the water diffusion, respectively. Many studies link higher BMI to decreased FA and/or elevated MD in several major WM tracts (Repple et al., 2018; Stanek et al., 2011). A recent meta-analysis revealed lower FA values associated with higher BMI in the genu of the corpus callosum (CC), which connects prefrontal regions (Daoust et al., 2021). This suggests a potential impact on cognitive function and reward processing. Reduced FA has been previously linked to myelin loss in several neurological and psychiatric diseases, but the evidence regarding demyelination in obesity is limited (Alba-Ferrara & de Erausquin, 2013; Kantarci, 2014). On the contrary, several studies do not indicate any significant differences in DTI measures, while other evidence reports a reversed pattern of changes associated with adiposity (Alosco et al., 2014; Birdsill et al., 2017; Dekkers et al., 2019).

These inconsistencies may be partly attributed to methodological limitations in the DTI approach, particularly the insufficient specificity of the measured parameters and the limited accuracy of WM tract reconstruction (Okudzhava et al., 2022). For instance, FA alterations may reflect various underlying factors such as axonal loss or injury, changes in myelin content, inflammation, or shifts in extracellular and intracellular water concentrations (O'Donnell & Westin, 2011). Interpreting this metric in a biological context is therefore challenging. Moreover, DTI is unable to accurately model the presence of crossing fibers within a voxel, which results in errors when reconstructing WM fibers (Auriat et al., 2015). Therefore, to better understand WM structure in relation to obesity, it is crucial to apply advanced techniques that not only improve the accuracy of fiber reconstruction but also provide biologically interpretable measures. One method that addresses the limitations of crossing fibers is constrained spherical deconvolution (CSD). Moreover, the integration of multishell, multitissue CSD (MSMT-CSD) enhances the precision of fiber orientation estimates within a voxel and reduces the number of spurious peaks (Jeurissen et al., 2014). Additionally, MSMT-CSD-based novel quantitative fiber tracking methods, such as the SIFT2 microstructure-informed tractography method, present valid biologically meaningful measures of WM fiber density (Smith et al., 2015).

When evaluating obesity/overweight, the adequacy of BMI is questionable given its imprecise measurement of the amount and

distribution of body fat. Similarly, measures like waist-to-hip ratio or waist circumference may indicate central (abdominal) obesity but do not differentiate between distinct fat depots. Consequently, the significance of distinguishing between adipose tissue (AT) depots is gaining attention in obesity research due to the profound impact of their metabolic functions. Accumulation of visceral adipose tissue (VAT) in the abdominal area is correlated with insulin resistance and an elevated risk of metabolic dysfunction (Luong et al., 2019). Conversely, subcutaneous adipose tissue (SAT) has been proposed to play a protective role against metabolic syndrome (Porter et al., 2009). A growing body of evidence links the accumulation of VAT to cognitive decline and late-life dementia, making abdominal obesity a potential target for early intervention and prevention strategies (Huang et al., 2022; Ozato et al., 2021). Furthermore, excessive VAT promotes the accumulation of fatty acids in the liver, contributing to nonalcoholic fatty liver disease (Hanlon & Yuan, 2022). Importantly, in contrast to SAT, both liver fat and VAT have been associated with lower GM volume and WM hyperintensities (Boccara et al., 2023; Lee et al., 2021; Weinstein et al., 2018).

To address the scarcity and ambiguity of WM findings, this study aims to explore the interplay between WM connectivity and obesity by using state-of-the-art microstructure-informed tractography and quantifying AT compartments using MRI and MR spectroscopy (MRS). We propose that metabolically more active fat depots will be associated with distinct patterns of WM connectivity alterations, shedding light on the intricate relationship between brain structure, adiposity, and metabolic health.

2 | METHODS

2.1 | Sample

Sixty-five male participants with no history of metabolic, neurological, or psychiatric conditions were recruited from the University of Lübeck participants' pool and via advertisements using online platforms. The participants were between 24 and 61 years old (mean ± SD = 27 ± 9.6), with a BMI ranging between 19 and 41 kg/m^2 (mean ± SD = 28 ± 4.9). The study was designed and conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of the University of Lübeck. All experimental procedures were performed with participants' written informed consent.

Prior to participation, all individuals had to fill out a questionnaire asking about any preexisting neurological or psychiatric conditions. Fasting glucose, glycated hemoglobin (HbA1c), and triglyceride levels were assessed to exclude diabetes and an increased risk for cardiovascular and metabolic diseases. Due to data quality check during data preprocessing, two brain MRI datasets, two whole-body MRI datasets, and two MRS datasets were removed from further analysis resulting in a final sample of 63 subjects. Information on the study participants is summarized in Table 1.

TABLE 1 Sample characteristics.

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

2.2 | Anthropometric measures and Bod Pod

The height and weight of the subjects were measured following overnight fasting on the day of the investigation. BMI was calculated using the formula: BMI = weight (kg)/(height [m])^2.

Body fat percentage was measured with Bod Pod (Life Measurement, Inc.©), which uses air displacement plethysmography to estimate whole-body fat mass and fat-free mass fractions based on the volume and density of the body.

2.3 | MRI and MRS acquisition

MRI and MRS were acquired on a 3T whole-body imager (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) at the Center of Brain Behavior and Metabolism, University of Lübeck, Germany. T1-weighted images were acquired using a 64-channel head coil. A T1 magnetization-prepared rapid gradient-echo sequence was acquired with the following parameters: repetition time (TR): 2300 ms; echo time (TE): 2.43 ms; flip angle: 8°; voxel size: 0.8 × 0.8 × 0.9 mm^3; slice thickness: 0.85 mm.

The diffusion-weighted imaging (DWI) protocol comprised a multi-shell echo-planar two-dimensional sequence with 107 encoding directions and 5 different *b*-values (300, 700, 1000, 2000, and 3000 s/mm^2). A total number of eight *b*0 (b = 0 s/mm^2) volumes were acquired. The protocol included the following parameters: TR: 5300 ms; TE: 108 ms; voxel size: 2 × 2 × 2 mm^3; slice thickness: 2 mm.

Body MRI was acquired applying a T1-weighted turbo spin echo sequence with the following parameters: TR: 600 ms; TE: 8.1 ms; flip angle: 130°; voxel size: 2 × 2 × 10 mm^3; slice thickness: 10 mm. Participants were placed in a prone position with arms extended, the whole-body scans were acquired from fingers to toes. Participants were instructed to hold their breath during the 13-s acquisition time to

minimize breathing artifacts. A total number of 15–20 recordings (5 slices each) was acquired with the table shift set to 10 cm to ensure coverage of the entire body.

In the liver spectroscopy protocol, a single-voxel stimulated-echo acquisition mode localization technique was used with TR: 4000 ms and TE: 11 ms. MRS was performed within a $3 \times 3 \times 2$ cm^3 voxel of interest situated in the posterior part of Segment 7 of the liver avoiding inclusion of blood vessels to optimize the accuracy of metabolic analysis. The measurement was performed in a fasting state to ensure an accurate assessment of the liver lipid concentrations.

2.4 | Brain MRI processing

T1-weighted data was preprocessed and reconstructed using FreeSurfer 6.0.0 (Fischl, 2012). The standard FreeSurfer analysis pipeline includes skull stripping, motion correction, Talairach transformation, intensity normalization, tissue segmentation to classify GM, WM, and cerebrospinal fluid, and subsequent cortical parcellation and subcortical segmentation. Parcellation of cortical areas was performed based on the Desikan–Killiany atlas (Desikan et al., 2006), while the automatic subcortical segmentation atlas (Fischl et al., 2002) was used to obtain segmentations and labels for subcortical structures.

Multishell DWI data were processed using MRtrix (Tournier et al., 2012). The preprocessing steps of the MRtrix pipeline include distortion correction, motion correction, and eddy current correction aimed to minimize artifacts introduced during acquisition (Andersson & Sotiropoulos, 2016). MSMT-CSD was then applied to estimate the fiber orientation and magnitude of diffusion within each voxel (Jeurissen et al., 2014). Estimated fiber orientation density functions allowed subsequent reconstruction of WM fibers using an Anatomically Constrained Tractography algorithm (Smith et al., 2015). Generated tractograms were further refined with the SIFT2 microstructure-informed tractography method (Smith et al., 2015) allowing for the filtering of false-positive streamlines to improve the biological plausibility of the underlying WM connections. Parcellated FreeSurfer labels and obtained streamline weights representing a measure of WM connectivity strength were further used to construct individual connectomes. Based on previous research, a subset of 17 relevant regions of interests (ROIs) 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), Ins, thalamus (Thal), Caud, Put, pallidum (Pal), hippocampus (Hipp), amygdala (Amyg), NAc. Therefore, a network containing 34 nodes and an additional whole-brain network with 82 nodes were derived resulting in 34×34 and 82×82 symmetrical structural connectivity matrices per participant, respectively. Connectomes were built using a parcellation scheme from the Desikan–Killiany atlas.

2.5 | Body MRI and MRS processing

Segmentation and quantification of total adipose tissue (TAT), VAT, and SAT was carried out using a Matlab-based automatic procedure based on a modified fuzzy c-means algorithm and an extended snake algorithm as described by Würslin et al. (2010). The volumes of AT compartments are calculated by multiplying the number of segmented pixels by the in-plane pixel dimensions and the slice thickness.

Intrahepatic lipid (IHL) content was calculated by integrating water and lipid signals (methylene and methyl) and expressed as a ratio of a lipid signal to the entire signal in the spectrum (Machann et al., 2010).

3 | STATISTICAL ANALYSIS

3.1 | Connectome-based predictive modeling

Connectome-based predictive modeling (CPM) (Shen et al., 2017) was performed to predict individual body composition measures including BMI, fat%, TAT, VAT, SAT, and IHL by the properties of individual connectomes. IHL data underwent a logarithmic transformation to account for its skewed distribution. CPM was performed with a 34-node model comprising the anatomical areas described in the previous section and an 82-node model to assess the generalizability of this CPM approach to the whole-brain network. Six separate multiple linear regression models were built including age as a covariate. Both intrahemispheric and interhemispheric connections were taken into account. Leave-one-out cross-validation (LOOCV) was used to evaluate the model's predictive performance by iteratively training the model on all but one subject in the dataset and testing it on the left-out subject. The process was repeated until the model performance was tested on each subject.

The CPM procedure comprised the following steps: (1) leaving one subject out; (2) selecting edges using partial correlations ($p < .01$) between each edge and body composition measures across remaining subjects; (3) identifying positive and negative networks; (4) summing up significant edges for each subject; (5) fitting a linear regression model using summed up edges as regressors to predict body fat values; (5) applying fitted model parameters to predict body fat values in the left-out subject; (6) repeating the procedure for all iterations of LOOCV.

At the edge selection step, only those edges that significantly correlated with the target variable in all iterations of LOOCV were retained. Following LOOCV, permutation testing with 1000 iterations was performed to determine the statistical significance of the model's predictions. The corresponding permutation p-value signifies the proportion of permutations that are greater or equal to the true prediction.

4 | RESULTS

The MRI-assessed AT metrics were normalized to global body volume and expressed as ratios. Correlations between body composition variables are presented in Figure 1.

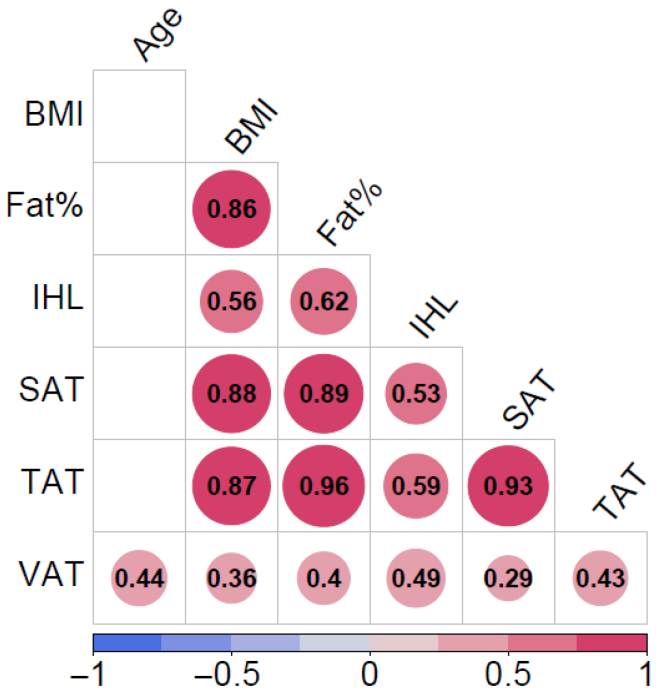

FIGURE 1 Correlations between body composition metrics and age, with correlation strength represented by the correlation coefficient, circle size, and color. Empty boxes indicate the absence of significant correlations. BMI, body mass index; IHL, intrahepatic lipids; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; VAT, visceral adipose tissue.

4.1 | Predicting body composition profiles: 34-node network

Six models were trained to predict body composition profiles (BMI, fat%, TAT, VAT, SAT, IHL). LOOCV revealed four positive models that significantly predicted body composition values. Notably, we did not observe any significant negative networks. Positive networks associated with BMI ($r = .46$; $R^2 = .21$), fat% ($r = .45$; $R^2 = .20$), TAT ($r = .46$; $R^2 = .21$) and SAT ($r = .31$; $R^2 = .10$) were identified (Figure 2). The validity of our findings was confirmed through permutation testing, which yielded the following p-values: BMI ($p = .005$), fat% ($p = .005$), TAT ($p = .001$), and SAT ($p = .047$).

Pairs of GM nodes exhibiting increased connectivity in the BMI model included R Amyg-L FrP, R Ins-R mOFC, R Ins-L rACC, R Ins-R NAc, R rACC-L rACC, and R rMFG- R FrP. Significant edges that contributed to fat% prediction included R Ins-R mOFC, R Ins-R NAc, R NAc-L lOFC, R rACC-L rACC, and rMFG- R FrP. Furthermore, R Ins-R mOFC, R Ins-R NAc, R rACC-L rACC, and rMFG-R FrP nodes were identified with regard to TAT, and finally, R Ins-R mOFC and rMFG-R FrP pairs contributed to SAT prediction. The right insula with the highest nodal degree emerged as a central area significantly associated with predicting fat levels. Additional information on the nodes can be found in the Supplementary Material (Table S1).

4.2 | Predicting body composition profiles: 82-node network

The whole-brain analysis revealed two significant positive models predicting fat% ($r = .40$; $R^2 = .16$) and TAT ($r = .45$; $R^2 = .20$) (Figure S1). The significance of the predictive model was further confirmed by permutation testing which yielded p-values of .013 for fat% and .005 for TAT. No significant negative networks were identified.

Edges that were significantly associated with fat% included R Ins-R mOFC, R Ins-R Caud, R Ins-R NAc, R rACC-L rACC, R rMFG-R FrP, L NAc-L lFG (pars orbitalis), R NAc-L lOFC, and L IPL-L lOccG. A similar network was identified in response to TAT including two additional connections: L SMG-L PCC and R ITG-R PCC. In both networks, the right insula appeared as a main hub contributing to the fat prediction.

5 | DISCUSSION

In the present study, we investigated the relationship between structural WM connectivity and the quantity of various AT compartments in a sample of healthy male subjects using a connectome-based machine learning approach. Our findings reveal that body composition metrics, specifically BMI, fat%, TAT, and SAT, can be successfully predicted based on the properties of individual WM connectomes. Interestingly, no significant associations between WM connectivity and VAT or IHL were found contrary to our initial expectations based on their association with metabolic dysfunctions and inflammation.

Alterations in connectivity patterns in 34-node network analysis have been observed between R Ins and R mOFC, and R FrP and R rMFG, as well as bilateral rACC, and R Ins and R NAc. Additionally, interhemispheric connections related to BMI and fat% include L FrP-R Amyg and L rACC-R Ins, and L lOFC-R NAc, respectively. The whole-brain analysis confirmed the robustness of our results. It identified a similar set of connections highlighting the replicability of our results within the broader context of the entire brain network. Additional connections identified in this analysis include posterior cingulate (PCC) connectivity with the temporal lobe, accumbens—inferior frontal, and parietal—occipital interactions. Observed findings expand upon existing knowledge on brain connectivity in obesity signifying increased WM fiber density between these regions linked to elevated body fat.

The Ins is known to be involved in appetite regulation and processing sensory aspects of food. Receiving afferent projections, Ins processes homeostatic signals related to energy status and integrates them with gustatory, somatosensory, and olfactory aspects of food. It then relays this converged information to higher-order cortical structures, a part of the executive control network regulating planning, decision-making, inhibitory control, and cognitive flexibility (De Araujo et al., 2020). Numerous task-based functional MRI (fMRI) studies highlight abnormal insular activation in response to high-calorie versus low-calorie foods in individuals with obesity (Frank et al., 2012; Stoeckel et al., 2008). Moreover, evidence from resting-state fMRI

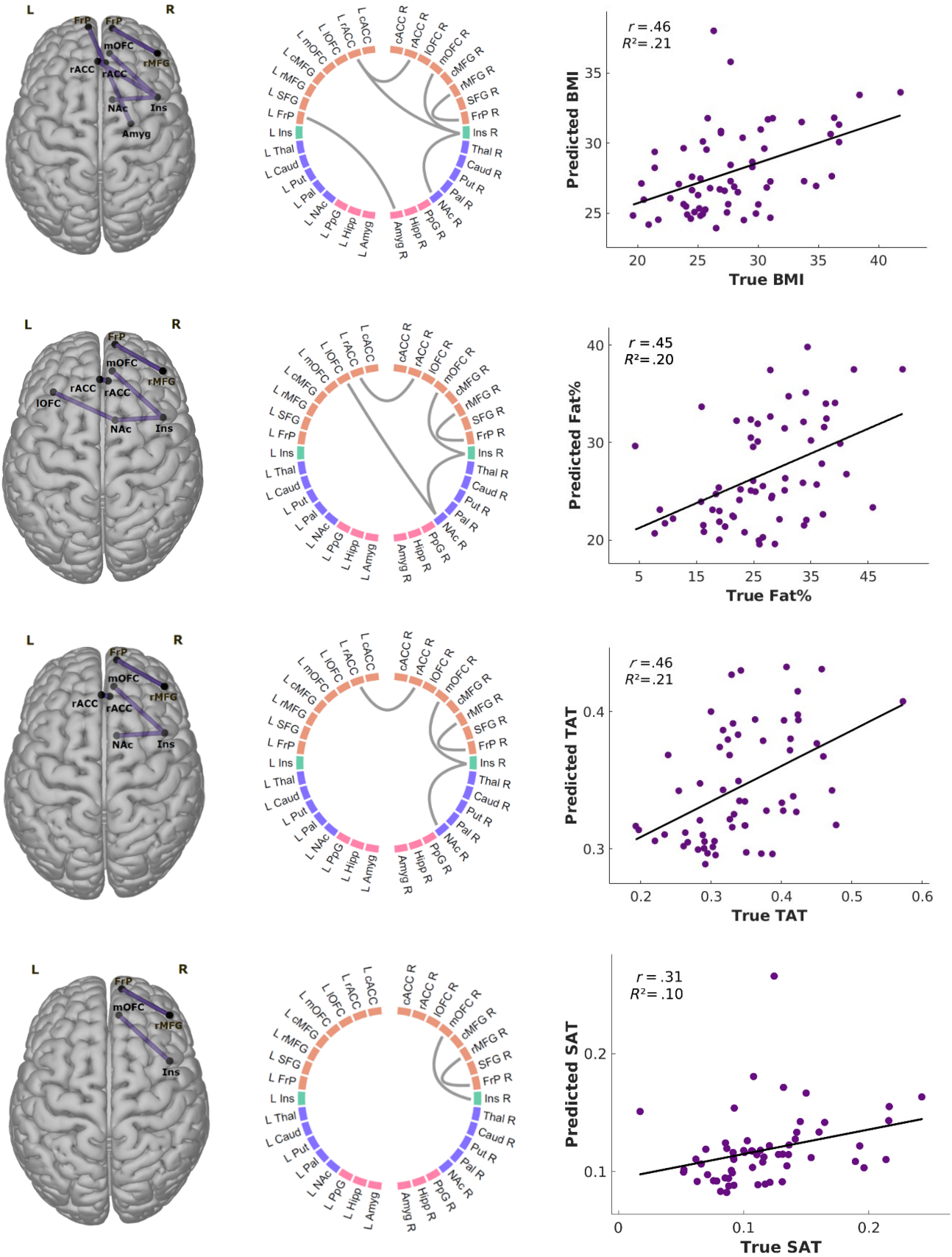

FIGURE 2 Thirty-four-node-based significant positive networks predicting BMI (1), fat% (2), TAT (3), SAT (4). Amyg, amygdala; cACC, caudal anterior cingulate cortex; Caud, caudate nucleus; cMFG, caudal middle frontal gyrus; BMI, body mass index; FrP, frontal pole; Ins, insular cortex; Hipp, hippocampus; lOFC, lateral orbitofrontal cortex; L, left; mOFC, medial orbitofrontal cortex; NAc, nucleus accumbens; Pal, pallidum; PpG, parahippocampal gyrus; Put, putamen; SFG, superior frontal gyrus; R, right; rACC, rostral anterior cingulate cortex; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; Thal, thalamus.

underscores decreased insular connectivity suggesting impaired signaling with regard to food-related interoceptive signals on the one hand, and reward-driven inhibitory regulation on the other (Parsons et al., 2022). This suggests that an interoceptive awareness system might override reward-based decision-making and inhibition, further enabling reward-seeking behavior that results in overeating. Interestingly, our findings reveal significant connectivity changes between Ins and key components of the reward network—mOFC and NAc. The NAc, a part of the ventral striatum, plays a crucial role in nonhomeostatic feeding (Kenny, 2011). Current theories on the role of NAc in obesity and overeating are linked to "wanting" and "liking" aspects of food intake (Morales & Berridge, 2020). Specifically, incentive-sensitization theory suggests that individuals vulnerable to obesity and binge-eating disorders may exhibit heightened "wanting" for food, while "liking" remains unaffected. Neuroimaging studies supporting this perspective reveal activation patterns similar to those seen in drug addiction when individuals prone to overeating are exposed to food cues (Devoto et al., 2018). Moreover, increased NAc volume in overweight individuals has been linked to heightened reward sensitivity and potential predisposition to weight gain (García-García et al., 2020; Samara et al., 2021).

The role of OFC in integrating sensory, emotional, and cognitive information to assign a value to reward stimuli is well established (Seabrook & Borgland, 2020). Research involving rats with OFC lesions showed they did not reduce their response to food cues after food devaluation, emphasizing the OFC's role in maintaining knowledge about reward value (Pickens et al., 2005). Rats exposed to a palatable diet displayed similar behavior, suggesting obesogenic diets might affect this mechanism (Reichelt et al., 2014). In lean individuals, an fMRI study revealed decreased responses to devalued stimuli in the OFC and Amyg, while maintaining responses to non-devalued items (Gottfried et al., 2003). The evidence of increased OFC resting connectivity (Parsons et al., 2022) and volumetric reductions in the obese population (Chen et al., 2018; Raji et al., 2010) combined with our findings of altered OFC connectivity may thus indicate inadequate food representation in obese individuals due to altered reward devaluation, promoting food overconsumption.

Furthermore, our investigation revealed aberrant connectivity in key components of the cognitive control and inhibition network, including FrP, rMFG, and rACC. A weaker MFG activation was correlated with a greater delay discounting in women with obesity, indicating heightened impulsivity towards immediate rewards (Stoeckel et al., 2013). Moreover, reduced activation during complex monetary tasks predicted greater subsequent weight gain (Kishinevsky et al., 2012). Anterior Ins and ACC are major elements of the salience network, implicated in detecting and prioritizing stimuli from both the external environment and internal states. Resting-state functional connectivity changes in the salience network have been identified in obese individuals, although the direction of these changes varies (Moreno-Lopez et al., 2016; Wijngaarden et al., 2015). Additionally, obesity-related changes in functional connectivity strength between the salience and executive function networks, particularly prefrontal areas, propose impaired integration of information about the body's internal state, external cues, and cognitive control mechanisms (Borowitz et al., 2020).

In line with these findings, DTI studies consistently demonstrate FA reductions in the genu of CC, projecting to frontal areas including OFC, FrP, and rMFG (Daoust et al., 2021; Kullmann et al., 2015). Moreover, alterations in diffusion metrics in the body of CC, connected to ACC and Ins, have been reported (Xu et al., 2013). This convergence emphasizes the complementary nature of functional and structural findings.

Intriguingly, our main findings are predominantly located in the right hemisphere. Alonso-Alonso and Pascual-Leone (2007) proposed that the right hemisphere dysfunction, primarily right PFC, could hold a central role in the dysregulation of top-down control of behavior, contributing to obesity development. While this hypothesis did not receive widespread acceptance, recent meta-analyses indicate GM and WM changes in the right hemisphere, with reduced OFC volume and decreased FA in the genu of CC linked to higher BMI (Chen et al., 2020; Daoust et al., 2021). These findings emphasize the potential relevance of hemispheric lateralization in obesity, encouraging further investigation.

In contrast to the results discussed, parts of our hypotheses—specifically, the anticipated association between WM and VAT or IHL—could not be confirmed. The lack of findings may originate from the predominantly minor metabolic fluctuations within our sample, potentially hindering the identification of associated WM pathology. Further potential explanations might be due to methodological limitations that are addressed in the following section. In our study, the robust association between WM changes and SAT was observed predominantly because SAT displayed strong correlations with BMI, fat%, and TAT reflecting a specific body composition trend. Our results suggest that in our cohort, total body composition metrics reflect brain changes the best, and further metabolic investigation is required to delineate the relationship between connectivity and specific AT depots.

6 | LIMITATIONS

Several limitations need to be taken into consideration in our study. First, our research primarily focuses on brain regions associated with hedonic and reward-related processes, which may not fully encompass the interplay between homeostatic and non-homeostatic factors in obesity regulation. Second, due to its small size and intricate localization, accurately segmenting the hypothalamus proved challenging, limiting our ability to explore its role. Third, with a sample size of 63 subjects, there is a heightened risk of overfitting, potentially affecting predictions. Fourth, our cross-sectional study design may not capture the complete temporal dynamics of brain connectivity changes related to specific fat compartments, highlighting the need for future longitudinal research. Lastly, our sample lacks adequate age and sex/gender diversity, limiting the generalizability of our findings to a broader demographic range. This is significant given that men exhibit a stronger association between brain abnormalities and excess fat compared to women. This is

attributed to sex hormones potentially delineating distinct implications for future interventions (Subramaniapillai et al., 2022).

7 | PERSPECTIVES

The ultimate goal of uncovering the complex relationship between brain structure and function and body composition is to pave the way for the development of effective and accessible intervention strategies for obesity. It is important to note that there is no one-size-fits-all treatment for obesity (Li et al., 2023). To address this complexity, it is crucial to evaluate different obesity phenotypes, such as normal weight obesity, metabolically obese normal weight, metabolically healthy obese, and metabolically unhealthy obese individuals. Furthermore, psycho-behavioral phenotypes based on individual reward sensitivity, cognitive control abilities, and mood and emotion regulation can help identify individual biomarkers for preventive measures (Camacho-Barcia et al., 2023). In future studies, it is essential to prioritize a comprehensive assessment of fat distribution and quantity. Exploring these relationships in larger samples should be emphasized, reducing the risk of overfitting and enabling more accurate predictive outcomes. Importantly, expanding existing knowledge could be achieved by using more sensitive tools for finer brain segmentation, such as the hypothalamus, providing a more holistic understanding of brain structure in obesity (Billot et al., 2020). Brown AT stands out as a new promising target due to its role in burning excess fat. Enhancing brown fat activation and promoting the "browning" of white adipocytes could lead to improvements in glucose and lipid metabolism, as well as insulin resistance in obese and diabetic individuals (Liu et al., 2022). Understanding the interplay between AT compartments, their temporal dynamic, and their interactions with metabolic and hormonal factors is essential for pinpointing dysfunctional brain networks in obesity. Incorporating these aspects can offer valuable insights into obesity prevention and treatment.

8 | CONCLUSION

Our study highlights the relationship between structural brain connectivity and body composition metrics, emphasizing the role of non-homeostatic brain regions in regulating eating behavior. Detailed assessment of obesity phenotypes should further be considered to untangle this complex relationship and enable tailored treatments, ultimately leading to better health outcomes and a more sustainable healthcare system.

AUTHOR CONTRIBUTIONS

L.O. acquired and analyzed the data and drafted the manuscript and figures. S.S. acquired the data. E.F.G. supervised the data analysis. G.G. supervised the data analysis. J.M. analyzed the whole-body MR data. P.J.K. contributed to the development of the analysis pipeline. J.P.T. provided tools for data analysis and supervised the process. T.F.M. conceived and designed the study and drafted and revised the manuscript. M.H. conceived and designed the study and drafted and revised the manuscript.

ACKNOWLEDGEMENTS

We would like to thank all participants for their participation. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

This work was supported by the Deutsche Forschungsgemeinschaft through the Graduiertenkolleg 1957 "Adipocyte—Brain Crosstalk". Supported in part by a grant (01GI0925) from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.).

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.

ORCID

Liana Okudzhava https://orcid.org/0000-0002-4522-9920
Elda Fischi-Gomez https://orcid.org/0000-0002-6506-2128

REFERENCES

Alba-Ferrara, L. M., & de Erausquin, G. A. (2013). What does anisotropy measure? Insights from increased and decreased anisotropy in selective fiber tracts in schizophrenia. *Frontiers in Integrative Neuroscience*, *7*, 39601. https://doi.org/10.3389/FNINT.2013.00009/BIBTEX

Alonso-Alonso, M., & Pascual-Leone, A. (2007). The right brain hypothesis for obesity. *JAMA*, *297*(16), 1819–1822. https://doi.org/10.1001/JAMA.297.16.1819

Alosco, M. L., Stanek, K. M., Galioto, R., Korgaonkar, M. S., Grieve, S. M., Brickman, A. M., Spitznagel, M. B., & Gunstad, J. (2014). Body mass index and brain structure in healthy children and adolescents. *International Journal of Neuroscience*, *124*(1), 49–55. https://doi.org/10.3109/00207454.2013.817408

Andersson, J. L. R., & Sotiropoulos, S. N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *NeuroImage*, *125*, 1063–1078. https://doi.org/10.1016/J.NEUROIMAGE.2015.10.019

Apovian, C. (2016). *Obesity: definition, comorbidities, causes, and burden*. https://ajmc.com/journals/supplement/2016/impact-obesity-interventions-managed-care/obesity-definition-comorbidities-causes-burden?p=3

Auriat, A. M., Borich, M. R., Snow, N. J., Wadden, K. P., & Boyd, L. A. (2015). Comparing a diffusion tensor and non-tensor approach to white matter fiber tractography in chronic stroke. *NeuroImage: Clinical*, *7*, 771–781. https://doi.org/10.1016/J.NICL.2015.03.007

Berthoud, H. R., Münzberg, H., & Morrison, C. D. (2017). Blaming the brain for obesity: Integration of hedonic and homeostatic mechanisms. *Gastroenterology*, *152*(7), 1728–1738. https://doi.org/10.1053/J.GASTRO.2016.12.050

Billot, B., Bocchetta, M., Todd, E., Dalca, A. V., Rohrer, J. D., & Iglesias, J. E. (2020). Automated segmentation of the hypothalamus and associated subunits in brain MRI. *NeuroImage*, *223*, 117287. https://doi.org/10.1016/J.NEUROIMAGE.2020.117287

Birdsill, A. C., Oleson, S., Kaur, S., Pasha, E., Ireton, A., Tanaka, H., & Haley, A. (2017). Abdominal obesity and white matter microstructure in midlife. *Human Brain Mapping*, *38*(7), 3337–3344. https://doi.org/10.1002/hbm.23576

Boccara, E., Golan, S., & Beeri, M. S. (2023). The association between regional adiposity, cognitive function, and dementia-related brain changes: A systematic review. *Frontiers in Medicine*, *10*, 1160426. https://doi.org/10.3389/fmed.2023.1160426

Borowitz, M. A., Yokum, S., Duval, E. R., & Gearhardt, A. N. (2020). Weight-related differences in salience, default mode, and executive function network connectivity in adolescents. *Obesity*, *28*(8), 1438–1446. https://doi.org/10.1002/OBY.22853

Camacho-Barcia, L., Lucas, I., Miranda-Olivos, R., Jiménez-Murcia, S., & Fernández-Aranda, F. (2023). Applying psycho-behavioural phenotyping in obesity characterization. *Reviews in Endocrine and Metabolic Disorders*, *24*(5), 871–883. https://doi.org/10.1007/S11154-023-09810-8

Camara, E., Rodriguez-Fornells, A., Ye, Z., & Münte, T. F. (2009). Reward networks in the brain as captured by connectivity measures. *Frontiers in Neuroscience*, *3*, 350–362. https://doi.org/10.3389/NEURO.01.034.2009/BIBTEX

Chen, E. Y., Eickhoff, S. B., Giovannetti, T., & Smith, D. V. (2020). Obesity is associated with reduced orbitofrontal cortex volume: A coordinate-based meta-analysis. *NeuroImage: Clinical*, *28*, 102420. https://doi.org/10.1016/J.NICL.2020.102420

Chen, E. Y., Murray, S., Giovannetti, T., & Smith, D. V. (2018). Reduced gray matter volume in the orbitofrontal cortex is associated with greater body mass index: A coordinate-based meta-analysis. *bioRxiv*, 359919. https://doi.org/10.1101/359919

Daoust, J., Schaffer, J., Zeighami, Y., Dagher, A., García-García, I., & Michaud, A. (2021). White matter integrity differences in obesity: A meta-analysis of diffusion tensor imaging studies. *Neuroscience and Biobehavioral Reviews*, *129*(July), 133–141. https://doi.org/10.1016/j.neubiorev.2021.07.020

De Araujo, I. E., Schatzker, M., & Small, D. M. (2020). Rethinking food reward. *Annual Review of Psychology*, *71*, 139–164. https://doi.org/10.1146/ANNUREV-PSYCH-122216-011643

Dekkers, I. A., Jansen, P. R., & Lamb, H. J. (2019). Obesity, brain volume, and white matter microstructure at MRI: A cross-sectional UK biobank study. *Radiology*, *291*(3), 763–771. https://doi.org/10.1148/radiol.2019181012

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/J.NEUROIMAGE.2006.01.021

Devoto, F., Zapparoli, L., Bonandrini, R., Berlingeri, M., Ferrulli, A., Luzi, L., Banfi, G., & Paulesu, E. (2018). Hungry brains: A meta-analytical review of brain activation imaging studies on food perception and appetite in obese individuals. *Neuroscience and Biobehavioral Reviews*, *94*, 271–285. https://doi.org/10.1016/j.neubiorev.2018.07.017

Fernández-Andújar, M., Morales-García, E., & García-Casares, N. (2021). Obesity and gray matter volume assessed by neuroimaging: A systematic review. *Brain Sciences*, *11*(8), 999. https://doi.org/10.3390/brainsci11080999

Fischl, B. (2012). FreeSurfer. *NeuroImage*, *62*(2), 774–781. https://doi.org/10.1016/J.NEUROIMAGE.2012.01.021

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., Van Der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355. https://doi.org/10.1016/S0896-6273(02)00569-X

Frank, S., Kullmann, S., & Veit, R. (2013). Food related processes in the insular cortex. *Frontiers in Human Neuroscience*, *7*, 499. https://doi.org/10.3389/FNHUM.2013.00499

Frank, S., Linder, K., Kullmann, S., Heni, M., Ketterer, C., Çavuşoğlu, M., Krzeminski, A., Fritsche, A., Häring, H. U., Preissl, H., Hinrichs, J., & Veit, R. (2012). Fat intake modulates cerebral blood flow in homeostatic and gustatory brain areas in humans. *The American Journal of Clinical Nutrition*, *95*(6), 1342–1349. https://doi.org/10.3945/AJCN.111.031492

García-García, I., Morys, F., & Dagher, A. (2020). Nucleus accumbens volume is related to obesity measures in an age-dependent fashion. *Journal of Neuroendocrinology*, *32*(12), e12812. https://doi.org/10.1111/jne.12812

Gottfried, J. A., O'Doherty, J., & Dolan, R. J. (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science (New York, N.Y.)*, *301*(5636), 1104–1107. https://doi.org/10.1126/SCIENCE.1087919

Han, Y. P., Tang, X., Han, M., Yang, J., Cardoso, M. A., Zhou, J., & Simó, R. (2021). Relationship between obesity and structural brain abnormality: Accumulated evidence from observational studies. *Ageing Research Reviews*, *71*, 101445. https://doi.org/10.1016/J.ARR.2021.101445

Hanlon, C. L., & Yuan, L. (2022). Nonalcoholic fatty liver disease: The role of visceral adipose tissue. *Clinical Liver Disease*, *19*(3), 106–110. https://doi.org/10.1002/CLD.1183

Herrmann, M. J., Tesar, A., Beier, J., Berg, M., & Warrings, B. (2019). Grey matter alterations in obesity: A meta-analysis of whole-brain studies. *Obesity Reviews*, *20*(3), 464–471. https://doi.org/10.1111/obr.12799

Huang, X., Wang, Y. J., & Xiang, Y. (2022). Bidirectional communication between brain and visceral white adipose tissue: Its potential impact on Alzheimer's disease. *eBioMedicine*, *84*, 104263. https://doi.org/10.1016/J.EBIOM.2022.104263

Jeurissen, B., Tournier, J. D., Dhollander, T., Connelly, A., & Sijbers, J. (2014). Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. *NeuroImage*, *103*, 411–426. https://doi.org/10.1016/J.NEUROIMAGE.2014.07.061

Kantarci, K. (2014). Fractional anisotropy of the fornix and hippocampal atrophy in Alzheimer's disease. *Frontiers in Aging Neuroscience*, *6*(OCT), 112849. https://doi.org/10.3389/FNAGI.2014.00316/BIBTEX

Karczewski, J., Zielińska, A., Staszewski, R., Eder, P., Dobrowolska, A., & Souto, E. B. (2022). Obesity and the brain. *International Journal of Molecular Sciences*, *23*(11), 6145. https://doi.org/10.3390/IJMS23116145

Kenny, P. J. (2011). Reward mechanisms in obesity: New insights and future directions. *Neuron*, *69*(4), 664–679. https://doi.org/10.1016/J.NEURON.2011.02.016

Kishinevsky, F. I., Cox, J. E., Murdaugh, D. L., Stoeckel, L. E., Cook, E. W., & Weller, R. E. (2012). fMRI reactivity on a delay discounting task predicts weight gain in obese women. *Appetite*, *58*(2), 582–592. https://doi.org/10.1016/J.APPET.2011.11.029

Kullmann, S., Schweizer, F., Veit, R., Fritsche, A., & Preissl, H. (2015). Compromised white matter integrity in obesity. *Obesity Reviews*, *16*(4), 273–281. https://doi.org/10.1111/obr.12248

Lazarevich, I., Irigoyen Camacho, M. E., Velázquez-Alva, M. D. C., & Zepeda Zepeda, M. (2016). Relationship among obesity, depression, and emotional eating in young adults. *Appetite*, *107*, 639–644. https://doi.org/10.1016/J.APPET.2016.09.011

Lee, H., Seo, H. S., Kim, R. E. Y., Lee, S. K., Lee, Y. H., & Shin, C. (2021). Obesity and muscle may have synergic effect more than independent effects on brain volume in community-based elderly. *European Radiology*, *31*(5), 2956–2966. https://doi.org/10.1007/S00330-020-07407-2

Li, G., Hu, Y., Zhang, W., Wang, J., Ji, W., Manza, P., Volkow, N. D., Zhang, Y., & Wang, G. J. (2023). Brain functional and structural magnetic resonance imaging of obesity and weight loss interventions.

Molecular Psychiatry, *28*(4), 1466–1479. https://doi.org/10.1038/s41380-023-02025-y

Liu, X., Zhang, Z., Song, Y., Xie, H., & Dong, M. (2022). An update on brown adipose tissue and obesity intervention: Function, regulation and therapeutic implications. *Frontiers in Endocrinology*, *13*, 1065263. https://doi.org/10.3389/FENDO.2022.1065263

Luong, Q., Huang, J., & Lee, K. Y. (2019). Deciphering white adipose tissue heterogeneity. *Biology*, *8*(2), 1–14. https://doi.org/10.3390/biology8020023

Machann, J., Thamer, C., Stefan, N., Schwenzer, N. F., Kantartzis, K., Häring, H. U., Claussen, C. D., Fritsche, A., & Schick, F. (2010). Follow-up whole-body assessment of adipose tissue compartments during a lifestyle intervention in a large cohort at increased risk for type 2 diabetes. *Radiology*, *257*(2), 353–363. https://doi.org/10.1148/radiol.10092284

Morales, I., & Berridge, K. C. (2020). "Liking" and "wanting" in eating and food reward: Brain mechanisms and clinical implications. *Physiology & Behavior*, *227*, 113152. https://doi.org/10.1016/J.PHYSBEH.2020.113152

Moreno-Lopez, L., Contreras-Rodriguez, O., Soriano-Mas, C., Stamatakis, E. A., & Verdejo-Garcia, A. (2016). Disrupted functional connectivity in adolescent obesity. *NeuroImage: Clinical*, *12*, 262–268. https://doi.org/10.1016/J.NICL.2016.07.005

O'Donnell, L. J., & Westin, C. F. (2011). An introduction to diffusion tensor image analysis. *Neurosurgery Clinics of North America*, *22*(2), 185–196. https://doi.org/10.1016/J.NEC.2010.12.004

Okudzhava, L., Heldmann, M., & Münte, T. F. (2022). A systematic review of diffusion tensor imaging studies in obesity. *Obesity Reviews*, *23*(3), e13388. https://doi.org/10.1111/OBR.13388

Opel, N., Thalamuthu, A., Milaneschi, Y., Grotegerd, D., Flint, C., Leenings, R., Goltermann, J., Richter, M., Hahn, T., Woditsch, G., Berger, K., Hermesdorf, M., McIntosh, A., Whalley, H. C., Harris, M. A., MacMaster, F. P., Walter, H., Veer, I. M., Frodl, T., … Dannlowski, U. (2021). Brain structural abnormalities in obesity: Relation to age, genetic risk, and common psychiatric disorders: Evidence through univariate and multivariate mega-analysis including 6420 participants from the ENIGMA MDD working group. *Molecular Psychiatry*, *26*(9), 4839–4852. https://doi.org/10.1038/s41380-020-0774-9

Ozato, N., Saitou, S., Yamaguchi, T., Katashima, M., Misawa, M., Jung, S., Mori, K., Kawada, H., Katsuragi, Y., Mikami, T., & Nakaji, S. (2021). Association between visceral fat and brain structural changes or cognitive function. *Brain Sciences*, *11*(8), 1036. https://doi.org/10.3390/BRAINSCI11081036/S1

Parsons, N., Steward, T., Clohesy, R., Almgren, H., & Duehlmeyer, L. (2022). A systematic review of resting-state functional connectivity in obesity: Refining current neurobiological frameworks and methodological considerations moving forward. *Reviews in Endocrine and Metabolic Disorders*, *23*(4), 861–879. https://doi.org/10.1007/s11154-021-09665-x

Pickens, C. L., Saddoris, M. P., Gallagher, M., & Holland, P. C. (2005). Orbitofrontal lesions impair use of cue-outcome associations in a devaluation task. *Behavioral Neuroscience*, *119*(1), 317–322. https://doi.org/10.1037/0735-7044.119.1.317

Porter, S. A., Massaro, J. M., Hoffmann, U., Vasan, R. S., O'Donnel, C. J., & Fox, C. S. (2009). Abdominal subcutaneous adipose tissue: A protective fat depot?, *32*, 1068–1075. https://doi.org/10.2337/dc08-2280

Raji, C. A., Ho, A. J., Parikshak, N. N., Becker, J. T., Lopez, O. L., Kuller, L. H., Hua, X., Leow, A. D., Toga, A. W., & Thompson, P. M. (2010). Brain structure and obesity. *Human Brain Mapping*, *31*(3), 353–364. https://doi.org/10.1002/hbm.20870

Reichelt, A. C., Morris, M. J., & Westbrook, R. F. (2014). Cafeteria diet impairs expression of sensory-specific satiety and stimulus-outcome learning. *Frontiers in Psychology*, *5*, 103842. https://doi.org/10.3389/FPSYG.2014.00852

Repple, J., Opel, N., Meinert, S., Redlich, R., Hahn, T., Winter, N. R., Kaehler, C., Emden, D., Leenings, R., Grotegerd, D., Zaremba, D., Bürger, C., Förster, K., Dohm, K., Enneking, V., Leehr, E. J., Böhnlein, J., Karliczek, G., Heindel, W., … Dannlowski, U. (2018). Elevated body-mass index is associated with reduced white matter integrity in two large independent cohorts. *Psychoneuroendocrinology*, *91*, 179–185. https://doi.org/10.1016/j.psyneuen.2018.03.007

Salas-Venegas, V., Flores-Torres, R. P., Rodríguez-Cortés, Y. M., Rodríguez-Retana, D., Ramírez-Carreto, R. J., Concepción-Carrillo, L. E., Pérez-Flores, L. J., Alarcón-Aguilar, A., López-Díazguerrero, N. E., Gómez-González, B., Chavarría, A., & Konigsberg, M. (2022). The obese brain: Mechanisms of systemic and local inflammation, and interventions to reverse the cognitive deficit. *Frontiers in Integrative Neuroscience*, *16*, 798995. https://doi.org/10.3389/FNINT.2022.798995/FULL

Samara, A., Li, Z., Rutlin, J., Raji, C. A., Sun, P., Song, S. K., Hershey, T., & Eisenstein, S. A. (2021). Nucleus accumbens microstructure mediates the relationship between obesity and eating behavior in adults. *Obesity*, *29*(8), 1328–1337. https://doi.org/10.1002/OBY.23201

Saruco, E., & Pleger, B. (2021). A systematic review of obesity and binge eating associated impairment of the cognitive inhibition system. *Frontiers in Nutrition*, *8*, 609012. https://doi.org/10.3389/FNUT.2021.609012/BIBTEX

Seabrook, L. T., & Borgland, S. L. (2020). The orbitofrontal cortex, food intake and obesity. *Journal of Psychiatry & Neuroscience*, *45*(5), 304–312. https://doi.org/10.1503/jpn.190163

Shen, X., Finn, E. S., Scheinost, D., Rosenberg, M. D., Chun, M. M., Papademetris, X., & Constable, R. T. (2017). Using connectome-based predictive modeling to predict individual behavior from brain connectivity. *Nature Protocols*, *12*(3), 506–518. https://doi.org/10.1038/NPROT.2016.178

Smith, R. E., Tournier, J. D., Calamante, F., & Connelly, A. (2015). SIFT2: Enabling dense quantitative assessment of brain white matter connectivity using streamlines tractography. *NeuroImage*, *119*, 338–351. https://doi.org/10.1016/j.neuroimage.2015.06.092

Smucny, J., Cornier, M. A., Eichman, L. C., Thomas, E. A., Bechtell, J. L., & Tregellas, J. R. (2012). Brain structure predicts risk for obesity. *Appetite*, *59*(3), 859–865. https://doi.org/10.1016/J.APPET.2012.08.027

Soares, J. M., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging. *Frontiers in Neuroscience*, *7*(7), 31. https://doi.org/10.3389/fnins.2013.00031

Stanek, K. M., Grieve, S. M., Brickman, A. M., Korgaonkar, M. S., Paul, R. H., Cohen, R. A., & Gunstad, J. J. (2011). Obesity is associated with reduced white matter integrity in otherwise healthy adults. *Obesity*, *19*(3), 500–504. https://doi.org/10.1038/oby.2010.312

Stillman, C. M., Weinstein, A. M., Marsland, A. L., Gianaros, P. J., & Erickson, K. I. (2017). Body-brain connections: The effects of obesity and behavioral interventions on neurocognitive aging. *Frontiers in Aging Neuroscience*, *9*, 115. https://doi.org/10.3389/fnagi.2017.00115

Stoeckel, L. E., Murdaugh, D. L., Cox, J. E., Cook, E. W., & Weller, R. E. (2013). Greater impulsivity is associated with decreased brain activation in obese women during a delay discounting task. *Brain Imaging and Behavior*, *7*(2), 116–128. https://doi.org/10.1007/S11682-012-9201-4

Stoeckel, L. E., Weller, R. E., Cook, E. W., Twieg, D. B., Knowlton, R. C., & Cox, J. E. (2008). Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *NeuroImage*, *41*(2), 636–647. https://doi.org/10.1016/J.NEUROIMAGE.2008.02.031

Subramaniapillai, S., Suri, S., Barth, C., Maximov, I. I., Voldsbekk, I., van der Meer, D., Gurholt, T. P., Beck, D., Draganski, B., Andreassen, O. A., Ebmeier, K. P., Westlye, L. T., & de Lange, A. M. G. (2022). Sex- and age-specific associations between cardiometabolic risk and white matter brain age in the UK biobank cohort. *Human Brain Mapping*, *43*(12), 3759–3774. https://doi.org/10.1002/HBM.25882

Taki, Y., Kinomura, S., Sato, K., Inoue, K., Goto, R., Okada, K., Uchida, S., Kawashima, R., & Fukuda, H. (2008). Relationship between body mass

index and gray matter volume in 1,428 healthy individuals. *Obesity*, *16*(1), 119–124. https://doi.org/10.1038/oby.2007.4

Tang, X., Zhao, W., Lu, M., Zhang, X., Zhang, P., Xin, Z., Sun, R., Tian, W., Cardoso, M. A., Yang, J., Simó, R., Zhou, J. B., & Stehouwer, C. D. A. (2021). Relationship between central obesity and the incidence of cognitive impairment and dementia from cohort studies involving 5,060,687 participants. *Neuroscience & Biobehavioral Reviews*, *130*, 301–313. https://doi.org/10.1016/J.NEUBIOREV.2021.08.028

Tournier, J. D., Calamante, F., & Connelly, A. (2012). MRtrix: Diffusion tractography in crossing fiber regions. *International Journal of Imaging Systems and Technology*, *22*(1), 53–66. https://doi.org/10.1002/IMA.22005

Weinstein, G., Zelber-Sagi, S., Preis, S. R., Beiser, A. S., DeCarli, C., Speliotes, E. K., Satizabal, C. L., Vasan, R. S., & Seshadri, S. (2018). Association of nonalcoholic fatty liver disease with lower brain volume in healthy middle-aged adults in the Framingham study. *Journal of the American Medical Association Neurology*, *75*(1), 97. https://doi.org/10.1001/JAMANEUROL.2017.3229

Wijngaarden, M. A., Veer, I. M., Rombouts, S. A. R. B., van Buchem, M. A., Willems van Dijk, K., Pijl, H., & van der Grond, J. (2015). Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. *Behavioural Brain Research*, *287*, 127–134. https://doi.org/10.1016/J.BBR.2015.03.016

World Health Organization. (2021). Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Würslin, C., Machann, J., Rempp, H., Claussen, C., Yang, B., & Schick, F. (2010). Topography mapping of whole body adipose tissue using a fully automated and standardized procedure. *Journal of Magnetic Resonance Imaging*, *31*(2), 430–439. https://doi.org/10.1002/JMRI.22036

Xu, J., Li, Y., Lin, H., Sinha, R., & Potenza, M. N. (2013). Body mass index correlates negatively with white matter integrity in the fornix and corpus callosum: A diffusion tensor imaging study. *Human Brain Mapping*, *34*(5), 1044–1052. https://doi.org/10.1002/hbm.21491

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Okudzhava, L., Schulz, S., Fischi-Gomez, E., Girard, G., Machann, J., Koch, P. J., Thiran, J.-P., Münte, T. F., & Heldmann, M. (2024). White adipose tissue distribution and amount are associated with increased white matter connectivity. *Human Brain Mapping*, *45*(5), e26654. https://doi.org/10.1002/hbm.26654