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Obesity

Obesity Is Associated with White Matter Atrophy: A Combined Diffusion Tensor Imaging and Voxel-Based Morphometric Study

Henry K. Karlsson[1], Jetro J. Tuulari[1], Jussi Hirvonen[1], Virva Lepomäki[1], Riitta Parkkola[2], Jaana Hiltunen[3], Jarna C. Hannukainen[1], Minna Soinio[4], Tam Pham[1], Paulina Salminen[5], Pirjo Nuutila[1,4] and Lauri Nummenmaa[1,3,6]

Objective: Little is known about the mechanisms by which obesity influences brain structure. In this study, the obesity-related changes in brain white and gray matter integrity were examined.
Design and Methods: 23 morbidly obese subjects and 22 nonobese volunteers were studied using voxel-based analysis of diffusion tensor imaging and of T1-weighted MRI images. Full-volume statistical parametric mapping analysis was used to compare fractional anisotropy (FA) and mean diffusivity (MD) values as well as gray (GM) and white matter (WM) density between these groups.
Results: Obese subjects had lower FA and MD values and lower focal and global GM and WM volumes than control subjects did. The focal structural changes were observed in brain regions governing reward seeking, inhibitory control, and appetite. Regression analysis showed that FA and MD values as well as GM and WM density were negatively associated with body fat percentage. Moreover, the volume of abdominal subcutaneous fat was negatively associated with GM density in most regions.
Conclusion: These findings imply that changes in GM and WM in obesity may be due to metabolic factors. Atrophy in regions involved in reward processing and appetite control may further promote abnormal reward seeking and eating behavior.

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Introduction

Obesity damages several organs, such as heart, skeletal muscle, and liver. Animal studies suggest that overeating has also many adverse effects on the central nervous system, particularly by increasing its susceptibility to dysfunction and degeneration. Accordingly, obesity is a significant risk factor for neurodegenerative disorders in humans (1). Thus, examining the effects of obesity and the associated adverse metabolic profile on brain structure and functions appears to be a viable strategy in determining how this phenotype predisposes the brain to neurodegenerative disorders.

The reward circuit involves the ventral striatum, amygdala, and several other interconnected brain regions, whereas networks that inhibit reward-seeking include regions such as the dorsolateral prefrontal and orbitofrontal cortices. Functional imaging studies suggest that obesity is characterized by an imbalance in these systems: the reward circuit is overactive to anticipated reward, and inhibitory networks fail to engage control of the reward circuit (2).

Structural changes in these circuits may underlie altered reward processing in obesity. Structural brain imaging studies have established that obese subjects have changes in the aforementioned circuitry. Focal gray matter (GM) reductions in obese versus normal-weight subjects have been reported in regions involved in reward processing (*i.e.*, putamen), behavioral control (i.e., middle frontal gyrus), and the regulation of taste (i.e., inferior frontal operculum and postcentral gyrus) (3).

[1] Turku PET Centre, Turku, Finland. Correspondence: Henry K. Karlsson (hekrka@utu.fi) [2] University of Kiinamyllynkatu 4-8, FIN-20520, Turku, Department of Radiology, Kiinamyllynkatu 4-8, FIN-20520, Turku, Finland [3] Brain Research Unit, O.V. Lounasmaa Laboratory, School of Science, Aalto University [4] University of Turku, Department of Medicine, FIN-00076, Aalto, Finland [5] University of Turku, Department of Surgery, Kiinamyllynkatu 4-8, FIN-20520, Turku, Finland, Kiinamyllynkatu 4-8, FIN-20520, Turku, Finland [6] Department of Biomedical Engineering and Computational Science, School of Science, Aalto University, FIN-00076 Aalto, Finland.

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Furthermore, obese subjects show atrophy in the frontal lobe, anterior cingulate gyrus, hippocampus, and thalamus in comparison with normal-weight subjects (4). Recently, another study established a link between obesity and reduction of amygdala and lateral orbitofrontal cortex volumes (5). Atrophy has previously been explained by diabetes (6), plasma leptin concentration (7), hypercortisolemia (8), hypertension (9), and hyperlipidemia (10). There is also growing evidence that systemic low-grade inflammation might underlie atrophy (5).

Significantly less is known about how obesity influences white matter (WM) integrity. High BMI has been associated with the loss of WM integrity in older women (11). One tensor-based morphometric study has found WM reductions atrophy in basal ganglia and corona radiata in obese subjects (4), and another study using voxel-based morphometry found increased WM volumes in the anterior temporal lobe of obese subjects (12).

Studies addressing the integrity of WM tracts using diffusion tensor imaging (DTI) are even fewer, although this biomarker would likely yield a more comprehensive view of WM pathology in obesity. DTI is a method that measures the cellular density, integrity, and directionality of WM tracts, and several different metrics can be computed from the diffusion-weighted images. Fractional anisotropy (FA) is a measure of the directionality of diffusion and provides information on WM tract integrity, whereas mean diffusivity (MD) measures the overall magnitude of diffusion, which can change in many pathological processes. High BMI has been associated with lower WM integrity in right posterior cingulate cortex (13), whereas another study found reduced WM integrity as measured with FA in the genu, splenium, and fornix (14). Recently, decreased FA was observed particularly in the midbrain and brainstem tracts among the obese persons (15).

There is also evidence that obesity together with its comorbid diseases can cause significant changes in the WM tracts. One study found reduced WM integrity in temporal stem, cingulate cortex, frontal lobe, occipital lobe, and cerebral peduncles in obese adolescents with type 2 diabetes (16). In addition, patients with type 2 diabetes have global but predominantly frontal and temporal microstructural WM abnormalities (17), and patients with hypertension have lower FA and higher MD values (18,19).

The Present Study

Because the evidence on the effects of obesity on brain WM integrity remains elusive and because the mechanisms underlying brain atrophy in obesity are poorly understood, we implemented VBM and DTI to test whether morbid obesity is associated with structural changes in the brain. Furthermore, we tested whether brain volume and integrity are associated with metabolic, inflammatory, and cardiovascular variables. We hypothesized that morbidly obese subjects would have atrophy and loss of integrity in brain regions associated with regulation of smell, taste, and behaviour. As adipose tissue is known to produce a low-grade systemic inflammation, imaging biomarkers were expected to be associated with body fat percentage and abdominal adipose tissue volumes.

Methods

Participants

The study protocol was approved by the Ethical Committee of the Hospital District of South-Western Finland and all participants signed ethical committee-approved, informed consent forms. The study was conducted in accordance with the Declaration of Helsinki. We recruited 23 morbidly obese subjects without neurological disease (Table 1). Nine subjects had type 2 diabetes, five had impaired fasting glucose, two had impaired glucose tolerance, and seven had normal glycemic status. The obese subjects were compared with 22 healthy normal-weight or slightly overweight subjects (inclusion criteria for BMI was set between 18 and 27 kg/m^3) without neurological disease who were matched for age, height, and sex with the obese subjects. None of the subjects had eating disorders or severe mental disorders and none abused alcohol. Three healthy volunteers from the DTI analyses and one patient from the VBM analyses had to be excluded because of technical problems with the MRI scanner data storage.

Image acquisition

MR imaging was performed with Philips Gyroscan Intera 1.5 T CV Nova Dual scanner at Turku PET Centre. High-resolution anatomical images (1 mm^3 isotropic resolution) were acquired using a T1-weighted sequence (TR 25 ms, TE 4.6 ms, flip angle 30°, scan time 376 s). For DTI, 32 noncolinear directions of gradients and nondiffusion weighted b0 image were acquired to obtain the whole diffusion tensor, using a single-shot spin-echo echo-planar-imaging sequence (TE 89 ms, TR 5947 ms, 90° flip angle, FOV 240 112 × 112 imaging matrix [reconstructed to 256 × 256], 3 mm slice thickness, 1 mm gap between slices, 36 transverse slices).

To assess the volume of abdominal subcutaneous (SAT) and visceral (VAT) adipose tissue, we acquired the axial T1-weighted dual fast field echo images covering the abdominal area (TE 2.3 and 4.6 ms, TR 120 ms, slice thickness 10 mm without gap). Abdominal subcutaneous and visceral fat was counted from top of liver until the head of femoral bone appeared on both sides, and then were analyzed with the SliceOmatic software version 4.3 (http://www.tomovision.com/products/sliceomatic.htm). Sets of images were opened in SliceOmatic and the borders of adipose tissues were determined. SAT and VAT volumes were calculated automatically using SliceOmatic.

VBM methods

Structural images were analyzed with SPM5 (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm/). The SPM5 software enables automated spatial normalization, tissue classification, and radio-frequency bias correction to be combined within the segmentation step (20). Moreover, the tissue classification technique employed in VBM in SPM5 is known to produce highly replicable results (21). Cut-off of spatial normalization was 25 mm, medium (0.01) affine regularization was used, and the protocol involved 16 nonlinear iterations. Following normalization and segmentation into GM and WM, a modulation step was incorporated to take into account volume changes caused by spatial normalization that can cause certain brain regions to shrink or expand. This was done by multiplying the voxel values in the segmented images by the Jacobian determinants from the spatial normalization step. The segmented, normalized, and modulated GM and WM images were smoothed using a Gaussian kernel of 10 mm FWHM, and entered into between-group comparisons (healthy controls vs. obese patients) using GLM (22). An absolute threshold mask was set at 0.1 to avoid possible edge effects around the border between GM and WM. Total intracranial volume was entered into the models as a regressor of no interest to account for any gross differences in total brain volume

TABLE 1 Characteristics of the participants

	Obese subjects ($n = 23$)		Nonobese subjects ($n = 22$)		
	M	SD	M	SD	*P*
Age (years)	47.30	8.90	46.45	9.45	0.758
Sex (female/male)	18 / 5		15 / 7		0.445
Weight (kg)	122.44	11.85	71.21	10.78	**<0.001**
Height (cm)	168.36	7.14	171.88	9.41	0.163
BMI (kg/m^2)	43.17	3.74	24.02	2.28	**<0.001**
Percentage of fat (%)	47.29	7.47	30.50	6.04	**<0.001**
Abdominal subcutaneous adipose tissue volume (dm^3)	21.33	4.48	5.09[a]	1.98[a]	**<0.001**
Abdominal visceral adipose tissue volume (dm^3)	4.44	1.28	1.97[a]	0.71[a]	**<0.001**
HbA1c (%)	5.97	0.68	5.38	0.41	**0.001**
Systolic blood pressure (mm Hg)	136.26	18.64	126.45	12.66	**0.046**
Diastolic blood pressure (mm Hg)	86.78	9.53	80.91	8.84	**0.038**
Leucocytes (E^9/L)	6.00	1.38	4.68	1.16	**0.022**
uCRP (mg/L)	4.74	4.22	1.08[a]	0.71[a]	**0.005**
LDL-cholesterol (mmol/L)	2.38	0.65	2.70	0.89	0.182
HDL-cholesterol (mmol/L)	1.25	0.21	1.76	0.49	**<0.001**
Triglycerides (mmol/L)	1.37	0.46	0.85	0.41	**<0.001**
Total GM volume (cm^3)	686.01	68.65	725.06	70.14	0.066
Total WM volume (cm^3)	489.40	55.05	496.59	51.13	0.653
BDI-II score	7.83[b]	5.92[b]	2.75[b]	4.28[b]	**0.016**

Last column indicates significant between-groups differences, significant differences are shown in boldface.
[a]In the control group, adipose tissue volumes and uCRP were acquired only from eight subjects.
[b]The BDI-II scores were acquired from 18 obese and 12 nonobese subjects.

across subjects. Similarly, effects of age and gender on brain volume were controlled by modeling them as regressors of no interest. Statistical threshold was set at $p < 0.05$, FWE corrected at the cluster level while controlling for nonstationarity in VBM analysis as proposed by Hayasaka et al. (23). Additional significant clusters were explored at $p < 0.001$ (uncorrected).

DTI methods

Diffusion weighted (DW) images were processed with FDT analysis package in FSL (www.fmrib.ox.ac.uk/fsl) software. First, the DW images were corrected for movements and eddy currents (24), and nonbrain structures were removed using Brain Extraction Tool (25). Next, the diffusion tensors, FA and MD images were computed using FDT toolbox implemented in FSL (26). FA and MD images were analyzed in SPM5. Images were normalized to the MNI space using linear and nonlinear transformations, smoothed with a Gaussian kernel of 10 mm full-width half-maximum (FWHM), and entered into between-group comparisons (healthy control subjects vs. obese patients) using GLM (22) in SPM5. Effects of age and gender on FA and MD were modelled as regressors of no interest. Statistical threshold was set at $T > 3.30$ and $P < 0.05$; FWE corrected at the cluster level. Additionally, potential smaller effects were explored using an uncorrected threshold of $P < 0.001$.

Results

Morbidly obese subjects had smaller GM and WM volumes focally in several brain regions compared to nonobese control subjects, as revealed by the VBM analysis (Figure 1, Tables S-1 and S-2). Gray matter density was significantly lower in frontal lobes that govern executive functions (right inferior frontal gyrus), temporal lobes subserving long-term memory, auditory, speech, and vision processing (inferior temporal gyri, right middle temporal gyri), somatosensory (left postcentral gyrus) and occipital visual cortices (occipital gyri). WM density was lower in the limbic regions governing emotional functions (insular region, amygdala) and under superior and middle temporal lobes. GM and WM volumes were not larger in obese versus nonobese control subjects in any brain region.

Analysis of DW data revealed decreased cellular density, integrity, and tract directionality in more specific areas of the brain. Obese subjects had lower FA values in corticospinal tracts, mamillary bodies, optic radiations, corpus callosum, and right inferior occipito-frontal fascicle, and lower MD values in both uncinate fascicles and inferior occipito-frontal fascicles (Figure 2, Tables S-3 and S-4). Even though we statistically controlled the gender effect in both VBM and DTI analyses, we also performed the DTI analyses using only female participants. This essentially replicated the results from the mixed-gender sample. The clusters were at similar foci, yet T values were slightly larger than in the mixed-gender sample. Finally, we sought to determine whether clinical variables were associated with the observed abnormalities in brain structure. Furthermore, because obese and nonobese subjects differed in various metabolic parameters as well as BDI-II scores (Table 1), we specifically sought to determine which of these variables best predicts the obesity-related abnormities in brain structure. To this end, we extracted

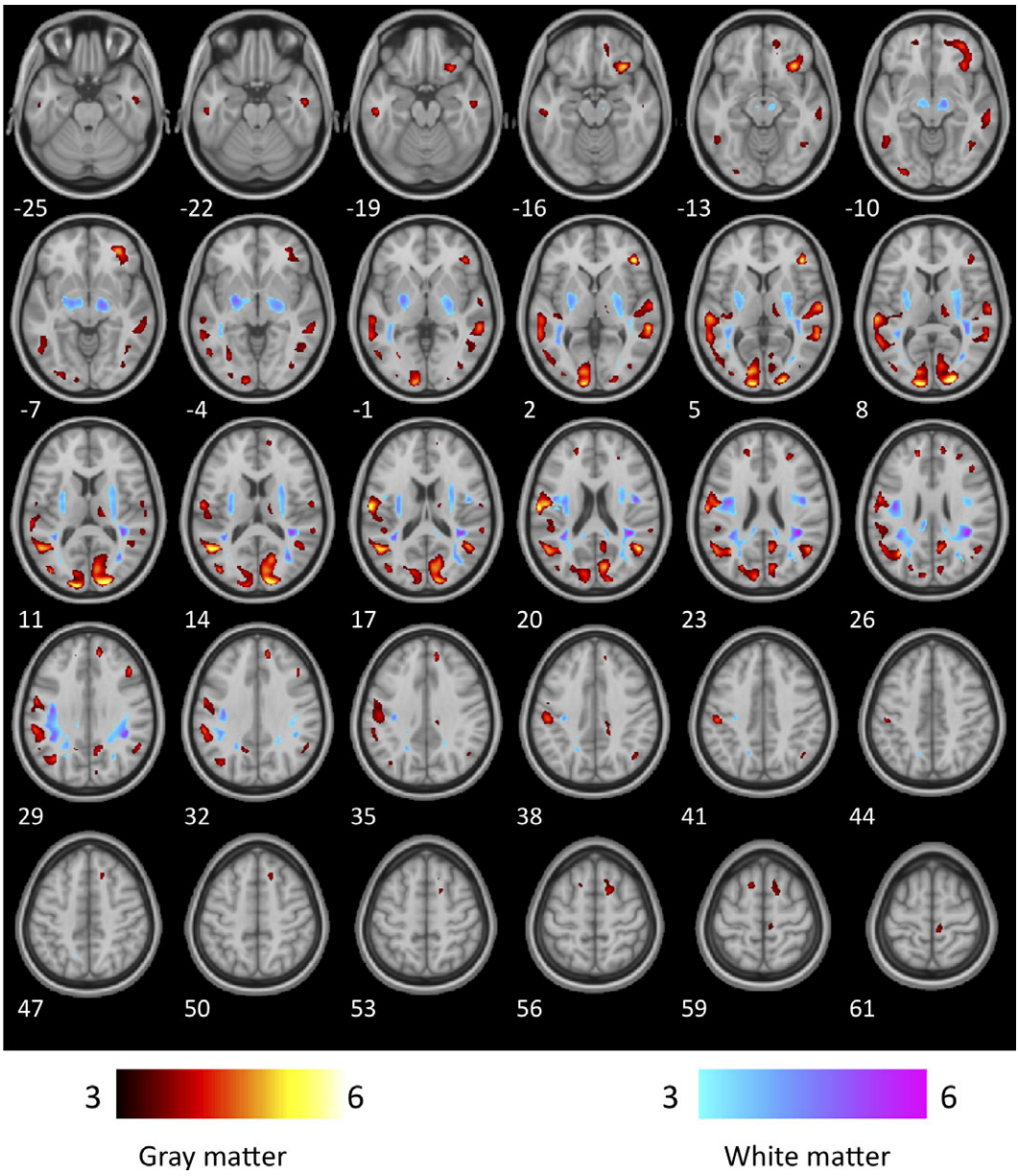

FIGURE 1 Regions with decreased gray (red to yellow) and white (turquoise to pink) matter volumes in obese vs. non-obese subjects. The data are thresholded at $P < 0.001$, uncorrected, for visual inspection.

ROI data from the clusters reported in Supporting tables 1–4 and correlated the GM and WM densities as well as FA and MD values with BMI, percentage of fat, abdominal adipose tissue volumes, HbA1c, systolic blood pressure, diastolic blood pressure, cholesterol levels, and BDI-II scores. First, we found a linear negative association between BMI and measures of brain structure across the whole BMI range (Figure 3). Second, we found that the changes in brain structure were mainly associated with percentage of fat, and that triglycerides had a minor contribution in some regions. Also, SAT volume correlated negatively with regional GM volume. HbA1c, systolic blood pressure, or diastolic blood pressure were not associated with altered brain structure. BDI-II scores were associated with FA values in optic radiations and callosal bodies, but we did not find association between these scores and GM and WM densities.

Discussion

The present data show for the first time that obesity has adverse effects on WM composition of the brain, as revealed by both traditional volumetric measurements (VBM) as well as measurements of WM microstructure (DTI), and confirms that these changes are associated with body fat percentage. Obesity was associated with reductions in both local and global GM and WM volumes, as well

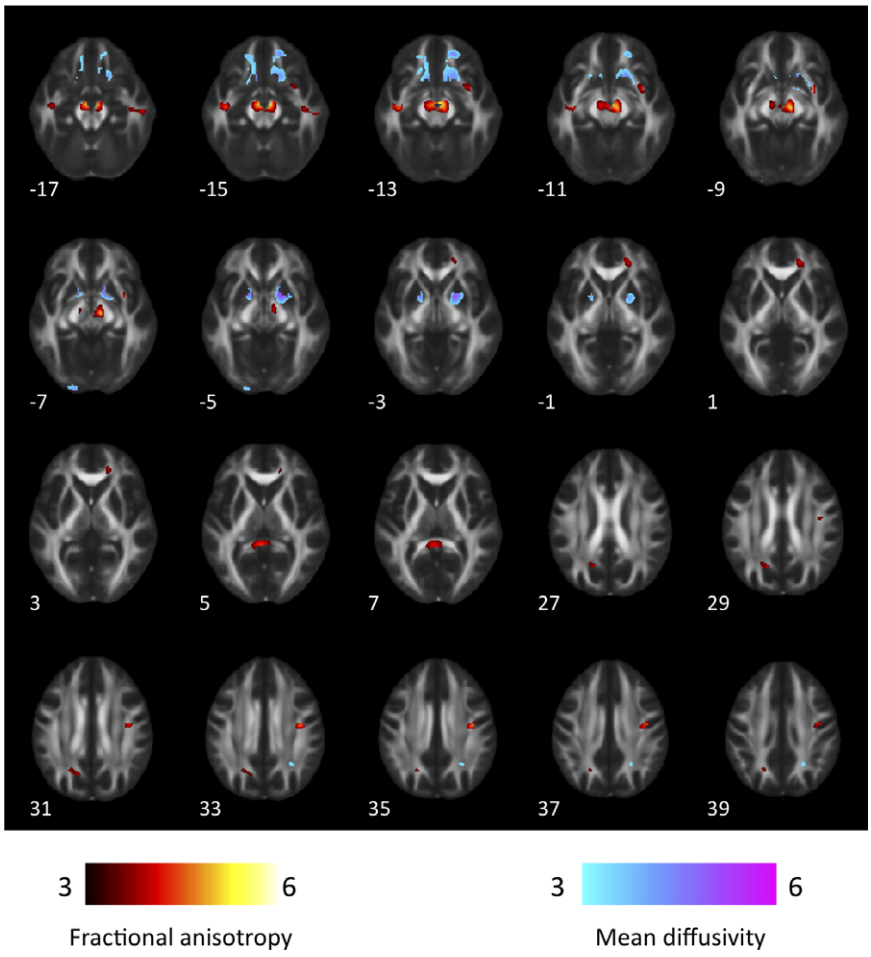

FIGURE 2 Regions with decreased FA (red to yellow) and MD (turquoise to pink) values in obese vs. non-obese subjects. The data are thresholded at $P < 0.001$, uncorrected, for visual inspection.

as lowered FA and MD values in numerous cortical and limbic regions. Most importantly, the focal obesity-related structural changes were observed in brain regions governing reward seeking, inhibitory control and appetite, suggesting that such morphological changes in the reward circuit could underlie excessive food consumption in obesity.

Obesity-related structural changes in inhibition, reward, and somatosensory systems

VBM analysis revealed global GM and WM reductions in both hemispheres of obese patients. Nonetheless, specific structural changes were found in areas previously associated with behavioral processing and appetite. GM densities were significantly smaller in obese individuals in right inferior frontal gyrus and left postcentral gyrus, both associated with the regulation of taste (3). Moreover, right inferior frontal gyrus is connected with inhibitory control (27). This corroborates findings of previous VBM studies of GM in obesity (3). These abnormalities may be the key factors behind unhealthy eating behavior. Additional reductions in GM were also observed in the primary visual cortex.

Obesity was also associated with changes of WM density, particularly in the insular and amygdalar regions. Insular cortex is known to be involved in taste recognition (28), and prior PET and fMRI studies have linked insula to processing pleasantness of external food cues (29). Insula also maintains homeostatic state controlling motivational and hedonic signals. Recent work also points that somatosensory signaling in the insula may contribute significantly to addiction, particularly with urges to consume the drug of abuse (30). These data suggest that impaired processing of the somatosensory signals—particularly those associated with energy balance—might contribute significantly to weight increase.

The amygdala is a core component of the reward circuit, and it has a central role in affective evaluation of the sensory inputs (31). Numerous functional imaging studies have established that it shows consistent responses to visual presentations of foods (32). Consequently, lowered WM density in the amygdalar region emphasizes the possible connection between obesity and elevated reward sensitivity, which may be because of structural changes in the associated brain regions.

Voxel-based analysis of the DTI data revealed that obesity was associated with lowered FA and MD values, which reflect cell abnormalities such as demyelination, axonal changes, and neuronal losses.

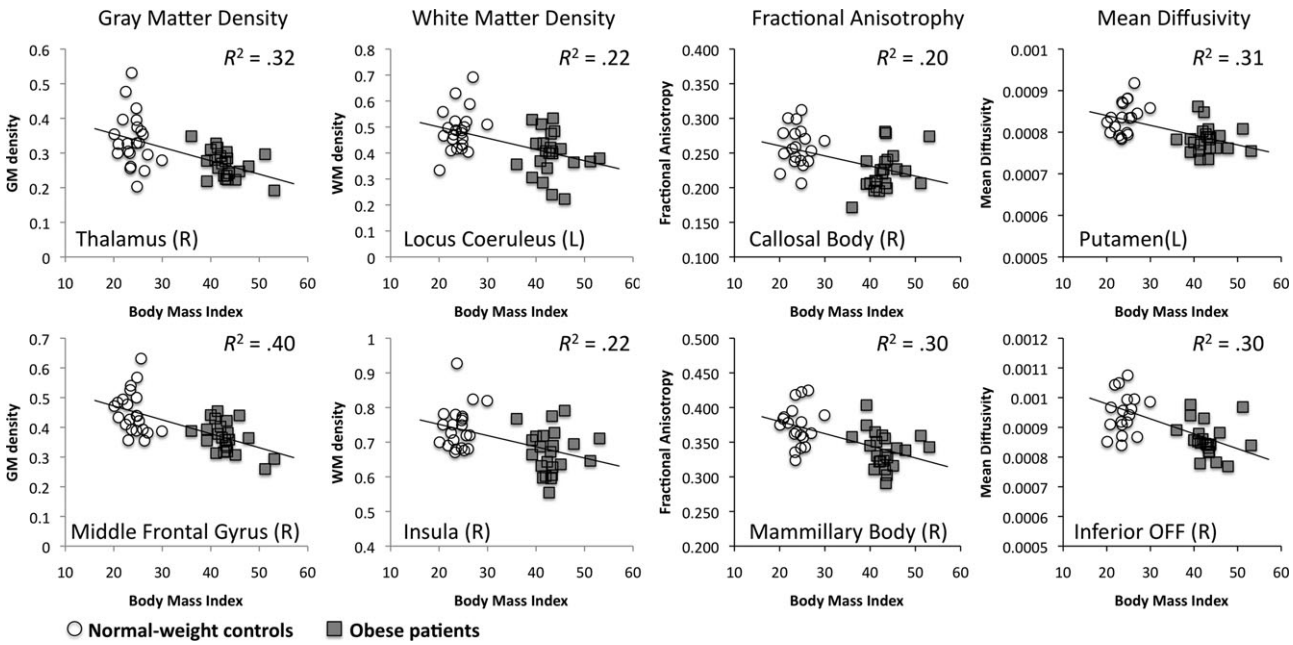

FIGURE 3 Scatterplots with least-squares regression lines illustrating the linear relationship between WM and GM density as well as FA and MD values in selected regions. Note: OFF = Occipito-Frontal Fascicle.

FA is a measure of the directionality of diffusion and provides information on WM tract integrity. Decreased FA values indicate damage in WM tracts (i.e., axonal loss or demyelination) or more disordered WM and fiber structure, as is typically observed, for example, in multiple sclerosis (33). In our study, FA reductions in obese persons were found in corticospinal tracts, mamillary bodies, optic radiations, corpus callosum, and right inferior occipito-frontal fascicle, whereas MD reductions were observed in both uncinate fascicles and inferior occipito-frontal fascicles.

Unlike FA values, which are higher in coherent WM, MD values are higher where water diffusion is less restricted by fibers and structure. In a more general sense, they reflect tissue functioning at the cellular level. Prior studies have observed lowered MD values in ischemic stroke (34), a condition influencing alterations in WM energy metabolism at cellular level. In a similar vein, it is possible that the lowered MD values in obesity might reflect dysfunctional energy metabolism in the WM. As these changes were observed mainly in the frontal cortical regions associated with inhibitory control, it is possible that they may underlie problems in appetite control. Altogether these findings from the DTI suggest that although obesity influences focal WM volumes, it also influences the integrity of the WM tracts, which implies that obesity may actually influence the connectivity of large-scale neural networks involved in reward and cognitive control, which may ultimately lead to altered energy intake. Future studies implementing probabilistic tractography are nevertheless needed to confirm this possibility.

Recent evidence suggests that the obesity-related changes in the brain WM may be different for women and men. Mueller et al. (35) found that increased BMI may cause myelin degeneration in the anterior part of corpus callosum only in women, although the marker that suggests axonal degeneration did not show differences between women and men throughout the corpus callosum. We also ran our analyses separately for women, but the clusters found in female-only subsample were essentially the same as those in the mixed-gender analysis. However, it is possible that lack of power prevented us from observing gender differences in the brain structure.

Body fat percentage is associated with brain atrophy

Obesity causes metabolic changes in body, especially oxidative stress, which may cause brain-volume reductions. Our regression analyses confirmed that body fat percentage is the critical factor explaining brain-volume reductions. Adipose tissue produces low-grade systemic inflammatory response, and inflammatory responses produced by adipose tissue are likely to have a strong effect on brain volume (36). Indeed, inflammatory factors such as adipokines, cytokines, and chemokines generated by adipose tissue (37) may be the key elements behind these brain-volume reductions. The effect of inflammatory factors may harm neural tracts as well as GM areas, which might in turn result in cognitive changes and habituation to overeating. These results are in line with recent findings, especially Cazettes et al. (5), which found the correlation between obesity-mediated inflammation and reduced brain integrity. Of note, obese and control groups differed significantly in uCRP and leukocytes, and uCRP and fat percent were also significantly correlated ($r = 0.39$, $p = 0.032$), highlighting the possible role of adipose tissue-related inflammation as the possible mechanism underlying brain atrophy associated with obesity.

To specify the role of adipose tissue in brain atrophy, we measured abdominal fat volumes from most of our subjects, and established an association between abdominal subcutaneous fat and GM

atrophy. On the contrary, visceral fat was not associated with GM and WM atrophy or lowered FA and MD values. This finding conflicts with one previous study, showing an association between brain volume reductions and visceral but not subcutaneous fat volumes (38). These mixed findings may partly be because of not only the different imaging methods, but also the differences in the study groups: Our study subjects were significantly younger, and among the younger obese patients the distribution of fat volume—and consequently the pattern of associations with brain atrophy—may be different.

We were also able to rule out a number of other possible mechanisms for obesity-related brain atrophy. Type 2 diabetes has previously been associated with brain atrophy (6), and some of our obese patients had type 2 diabetes and were using oral medication. However, although the study groups differed significantly in HbA1c, no correlation between brain-volume and elevated blood sugar was found in our regression analysis. Our sample size did not allow comparisons between obese subjects with and without diabetes, thus this issue needs to be clarified in future studies. Second, it is possible that brain atrophy is caused by cardiovascular risk factors, such as hypertension, as shown earlier with elderly people (39). We did not find significant relation between volume-reductions and elevated blood pressure. Some of our obese patients used medication for hypertension, which may confound the association between cardiovascular and brain data to some extent. Cholesterol profile abnormalities may also have some effect on WM integrity, as shown earlier (10). In line with this previous study, we found that high triglyceride levels associate with GM and WM atrophy in some brain regions.

We also tested for the possible connection between depression and obesity-related changes in the brain. Although the obese group had significantly higher BDI-II scores, no correlation between BDI-II scores and BMI, body fat percentage, or adipose tissue volumes was found. Moreover, there was no association between BDI-II scores and GM and WM density, but higher BDI-II scores were associated to lowered FA values in both optic radiations and callosal bodies implicating a possible connection between depression and damage to WM tracts in the aforementioned areas.

Conclusion

We show that adipose tissue is the critical factor underlying brain atrophy associated with morbid obesity. Focal reductions associated with obesity were observed in brain circuits governing inhibition, reward, and appetite control in the brain, which could implicate abnormalities in energy balance regulation. Nonetheless, it is still not known whether these differences in brain structure between obese and normal-weight persons either precede obesity or occur as a consequence of obesity. It is possible that these abnormalities reflect vulnerability endophenotypes that increase the risk of developing obesity. But alternatively, it is also possible that these structural changes reflect neurodegeneration because of overeating. Few prospective studies have investigated this potential causal link. In a recent one-year follow-up study, VBM analysis showed that the abnormalities in the regional GM volumes may increase the risk for future weight gain (40). In the same study, WM changes were proposed to be secondary to weight gain. One explanation might be that there is vicious circle in relation with brain abnormalities and adiposity: obese persons may have certain innate vulnerability to overeating, which could be seen particularly in focal GM abnormalities, and consequential accumulation of adipose tissue and growing systemic inflammation furthermore causes more global changes especially in WM tracts but also in GM. In the future, longitudinal studies investigating the effects of weight loss on obese person brains are needed to test for these alternative explanations. Moreover, the clarification of the actual cellular mechanisms behind the brain changes is needed in order to design therapies against brain atrophy and cognitive decline. O

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