Quantitative MRI in obesity & reno-cardiovascular function

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Obesity, Brain Volume and White Matter Microstructure by MRI: A Cross-sectional Study of the UK Biobank.

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ABSTRACT

Background

Obesity has been associated with increased risk of accelerated cognitive decline, and dementia, suggesting underlying neurobiological changes.

Purpose

To investigate the associations between obesity and brain structure (overall and regional brain volumes, and white matter microstructure) assessed by MRI in a sample of the general population.

Materials and methods

Between March 2014 and January 2018, 12,087 participants (53% women; mean age 62 years; range 45-76 years) of the prospective observational UK Biobank study underwent 3T multiparametric (3D T1-weighted, diffusion tensor imaging [DTI]) brain imaging. Total body fat percentage (TBF) was assessed by body impedance. Volumetric measures included brain volume, grey matter volume, white matter volume, volumes of subcortical grey matter structures, and regional cortical volumes. Global and tract-specific microstructure was assessed by fractional anisotropy (FA) and mean diffusivity (MD) using DTI. Linear regression was performed using TBF as determinant and brain measures as outcome variables, and effect estimates are expressed as standardized beta's.

Results

Mean BMI was 26.6 ± 4.4 kg/m^2, mean TBF in men was 24.4 ± 5.5% and 35.5 ± 6.5% in women. In men, TBF was negatively associated with all subcortical grey matter volumes (thalamus, caudate nucleus, putamen, globus pallidus, hippocampus, nucleus accumbens) except amygdala volume. In women, TBF was solely negatively associated with globus pallidus volume. In females and males TBF was positively associated with global FA (females|males: 0.05|0.07 SD change in global FA per SD change in TBF, P<0.001). TBF was negatively associated with global MD in females (-0.07 SD change in global MD per SD change in TBF, P<0.001).

Conclusions

Our findings provide evidence that obesity is associated with smaller subcortical grey matter volumes. In addition, obesity was associated with higher coherence but lower magnitude of white matter microstructure suggesting differential influences of obesity on the geometric organisation of white matter microstructure.

INTRODUCTION

The disease burden of obesity has increased substantially over the last decades, making excess body weight and associated metabolic disorders one of the most challenging public health problems to date (1). The global obesity pandemic has not only led to a greater incidence of cardiovascular disease and type 2 diabetes (2), but has also coincided with a rise in brain diseases, such as accelerated cognitive decline (3), and dementia (4). The metabolic syndrome has been proposed as the shared common component of these different diseases associated with obesity, as it leads to low-grade systemic inflammation affecting various organs, including the liver, pancreas, adipose tissues, and brain via complex intermediate pathways (5).

In obesity, inflammatory responses in the central nervous system (CNS) with subtle glial cell activation, commonly referred to as neuro-inflammation without peripheral immune cells, have been described in different structures, such as the hypothalamus (6). These observations have been supported by preclinical animal studies relating high-fat and high-sugar diet to neuro-inflammatory changes in the brain (7), and post-mortem studies showing higher concentrations of Alzheimer's disease associated hippocampal markers (amyloid beta and tau) in elderly obese patients compared to non-obese patients (8).

Possible detrimental influences of obesity on brain structure can be assessed on a large scale in population-based imaging studies. High field three-dimensional MRI-based volumetric brain metrics allow for the assessment of volumetric differences in regional brain volumes, and diffusion tensor imaging (DTI) for the assessment of global and tract-specific white matter integrity by fractional anisotropy (FA; directional coherence of water molecule diffusion) and mean diffusivity (MD; magnitude of water molecule diffusion) (9). Previous imaging studies in obesity have linked body-mass index (BMI) to lower grey matter volume and white matter integrity (10,11), and to the presence of hypothalamic gliosis in insulin resistance (12). However, structural brain differences in regions that have been implicated to play a role in the regulation of eating behavior (e.g. food-reward circuitry) have also been described in human obesity (13). Studies performed thus far have focused on solely BMI as a measure of obesity and were limited by small sample sizes. Total body fat (TBF) percentage assessed by bio-impedance is a more accurate measure of obesity compared to indirect measurements, such as BMI and waist-hip-ratio (WHR) which may introduce misclassification and bias when estimating the effects of obesity (14).

We hypothesize that TBF is negatively associated with brain volume and microstructural integrity, which could be due to underlying systemic inflammation. Alternatively, lower volume of brain regions or decreased microstructural integrity of tracts involved in the neuronal regulation of the food-reward circuitry might also be associated with obesity.

In this study, we investigated the associations between obesity and brain architecture (overall and regional brain volumes, and white matter microstructure) assessed by MRI in a large study sample of the general population.

MATERIAL AND METHODS

The protocol for this prospective observational study was approved by the National Research Ethics Service Committee reference 11/NW/0382). Written informed consent was obtained from all participants.

Study population and study design

The UK Biobank Study (www.ukbiobank.ac.uk) is a large population-based cohort including 503,325 individuals between the age of 45 to 69 years (15). The participants were recruited across the United Kingdom for participation in the UK Biobank over a 5-year period beginning in 2006, of which a consecutive subset of participants underwent additional magnetic resonance imaging (MRI) and were included in our study (starting March 2014 until the data release of January 2018). Data collection included extensive baseline data based on questionnaires, anthropometric assessments, biological samples, genetics and imaging data. This research has been conducted using the UK Biobank Resource under Application Number 20666. Questionnaire-based data was used for ethnicity, smoking (never, former, current), frequency of alcohol use, socio-economic status according to the Townsend deprivation index (TDI), self-reported history of diabetes and cardiovascular disease (myocardial infarction, angina pectoris, stroke, and hypertension) diagnosed by doctor, and self-reported medication use for high cholesterol, hypertension or diabetes.

Measures of obesity

Anthropometric measurements were obtained by trained research clinic staff. Weight was measured using the Tanita BC 418 body composition analyzer (Tanita Corporation, Arlington Heights, IL), and height was measured using the wall-mounted SECA 240 height measure (SECA, Hamburg, Germany). BMI was calculated as weight divided by squared height (kg/m^2) and WHR as waist circumference divided by hip circumference. Total body fat (TBF) percentage was estimated with the body composition analyzer using electrical impedance. Healthy weight was defined as BMI between 18 to 25 kg/m^2, overweight as BMI between ≥25 and 30 kg/m², and obesity was defined as BMI ≥30 kg/m².

Brain MRI

All brain imaging data were obtained using a 3T MRI scanner (Siemens Skyra, Siemens Healthcare, Erlangen, Germany) with a standard 32-channel RF receive head coil. Prepro-

cessing was done using FSL (the FMRIB Software Library) packages, version 5.0. Imaging acquisition, processing and imaging analysis for brain volumes and DTI measures of white matter tracts were conducted by the coordinating UK Biobank research team as part of the imaging processing and quality-control pipeline, referred to as FBP (FMRIB's Biobank Pipeline), version 1.0 (16).

Volumetric measures

T1-weighted imaging was performed using a 3D MPRAGE sequence (voxel 1.0 x 1.0 x 1.0 mm, matrix 208 x 256 x 256, IT/RT=880/2000 ms). T1-weighted data were first segmented using FAST (version 4.1, FMRIB's Automated Segmentation Tool), to extract grey matter, white matter, and cerebrospinal fluid (CSF). Subcortical structures were extracted using FIRST (version 5.0, FMRIB's Integrated Registration and Segmentation Tool). Intracranial volume was based on the sum of grey matter, white matter and CSF volumes. We calculated the mean of both hemispheres for each of the bilateral subcortical structures. In addition, to obtain cerebral cortical regional volumes according to the Desikan–Killiany atlas, field-of-view reduced T1-weighted volumes were used to segmented the cortex using default parameters in FreeSurfer, version 5.3 (17). An overview of derived volumetric metrics is given in supplemental figure 1a and supplemental table 1, and an overview of all 49 cortical regions is provided in supplemental table 2 and 3.

Diffusion-tensor imaging

An echo-planar imaging (EPI), single-shot Stejskal-Tanner pulse sequence with TE=92ms was applied to obtain 36 slices (voxel 2.0 x 2.0 x 2.0mm, matrix 104 x 104 x 72) in 50 distinct diffusion-weighted directions (b=1000 and b=2000 s/mm^2). Eigenvectors, eigenvalues and FA were calculated by feeding the b=1000 s/mm^2 shell into the DTI fitting tool DTIFIT (version 2.0, the FSL diffusion tensor fitting program), creating FA and mean diffusivity (MD) outputs. Weighted tract-averaged FA and MD values were acquired for association and commissural fibers, and projection fibers. Global measures of FA and MD were calculated by averaging the diffusion metrics over all white matter tracts of both hemispheres per individual. An overview of derived DTI metrices is given in supplemental figure 1b.

Statistical analysis

Baseline characteristics are expressed as percentage or mean (SD), inter-quartile range (IQR) and range. Multiple linear regression was used to calculate standardized beta coefficients (β), representing the change in SDs in the outcome measure (brain imaging phenotypes) per SD TBF. Complete case analysis was performed, and a one-way multivariate analysis of variance (MANCOVA) was conducted to assess whether one or more mean differences were present between BMI levels (healthy weight, overweight and obese), specific regional brain regional volumes and white matter tracts. Analyses were adjusted

for age, ethnicity, TDI, assessment center (baseline visit and imaging visit), smoking, alcohol frequency, diabetes, and cardiovascular disease. Interaction for sex was evaluated by adding an interaction term TBF × sex. Since sex effects were highly significant for each brain imaging outcome measure ($P<0.001$), sex main effects were also included in the models resulting in separate intercepts for men and women (i.e. respectively β male and β female) (18). Volumetric measures were additionally adjusted for intra-cranial volume, while DTI measures were adjusted for brain volume because of potential confounding of partial volume effects. All statistical analyses were corrected for multiple testing using False Discovery Rate (FDR) (19). Based on the total number of all statistical tests over 13 global and subcortical brain volumes, 49 cortical regional volumes and 19 white matter metrics for FA and MD, the defined *P*-value significance threshold was set to pFDR = 0.023 (Benjamini-Hochberg, at $\alpha=0.05$). Uncorrected *P*-values below this threshold were considered statistically significant (uncorrected *P*-values are presented). All effect size estimates were reported as standardized effect estimates (β) to provide comparable, unit-independent measures of effect for different determinants and outcomes. Analyses were performed in R, using package MANCOVA.RM (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

In the UK Biobank 22,059 participants out of 502,616 individuals participating in the full cohort underwent brain imaging, of which 14,515 participants had fully segmented T1-weighted brain MRI scans with derived volumetric outcome measures and 12,857 participants had both volumetric and quantified DTI outcome measures available at the data release of 30th January 2018 (22). After exclusion of participants with missing data regarding covariates used in the regression models (n=656) and outliers (n=114), the final population consisted of 12,087 individuals (**Fig. 1**). Mean age was 62 ± 7.3 years (range 45-76 years) and 53% were women. An overview of the baseline characteristics is provided in **Table 1**.

General associations of obesity and sex with brain structure

General overall MANCOVA was performed prior to conducting multiple linear regression analysis to assess the presence of multivariate of obesity on brain structure. MANCOVA showed that mean differences between BMI levels (healthy weight, overweight, and obese) and brain MRI outcome measures including both global and subcortical brain volumes (Pillai's Trace=0.063, F=20, df=36, $P<0.001$) and specific cortical regions (Pillai's Trace=0.088, F=7, df=147, $P<0.001$) were present. For white matter integrity, MANCOVA

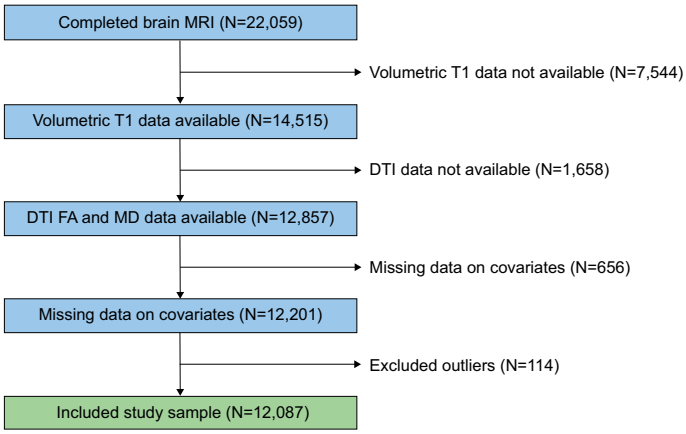

Figure 1. Flow diagram of UK Biobank study. DTI; Diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity.

showed that mean differences between categorical BMI levels and specific white matter tracts were present for both FA based (Pillai's Trace=0.061, F=15, df=45, *P*<0.001) as well as for MD based metrics (Pillai's Trace=0.056, F=14, df=45, *P*<0.001). Tests for TBF × sex interaction were highly significant (*P*<0.001) in the MANCOVA models for global and subcortical brain volumes, cortical regional volumes, and for both FA and MD based metrics. Therefore, all subsequent analyses were performed reporting slopes for males and females.

Total body fat and brain volumetric imaging data

An overview of means and SDs of all global and subcortical grey matter structures are presented in **Table 2** for men and women separately. Means and SDs of regional cortical volumes in the whole study sample and in men and women separately are presented in Supplemental Table 2. TBF was negatively associated with almost all subcortical grey matter volumes except for amygdala volume in men, while in women only globus pallidus volume (-0.06 change in SD [95% CI -0.09, -0.03] per SD change in TBF) was significantly associated with TBF in the adjusted analysis (**Table 3, Figure 2**). Of the subcortical volumes that were associated with TBF in men, the association between TBF and globus pallidus volume was most pronounced (β:-0.13 [95% CI -0.17, -0.10] per SD change in TBF), which was significantly larger than the association between TBF and globus pallidus volume in women (difference between men and women: *P*=0.001). To illustrate, per SD increase in TBF the globus pallidus volume was 27.2 mm^3 smaller in men (mean globus pallidus volume in men: 1857 ± 209 mm^3). In women, this was associated with 11.2 mm^3 smaller volumes (mean globus pallidus volume in women: 1706 ± 187 mm^3).

Positive associations were found for TBF and overall brain volume (0.04 change in SD [95% CI 0.02, 0.06] per SD change in TBF), grey matter volume (0.03 change in SD [95%

Table 1. Characteristics of the included participants of the UK Biobank

Characteristic	Study sample (n=12,087) % or mean ± SD
Age (years)	62.0 ± 7.3
Sex (% women)	53
Ethnicity (% whites)	97
Townsend deprivation index	-2.0 ± 2.6
Smoking, Former (%)	33
Smoking, Current (%)	6
Alcohol, ≥3 drinks per week (%)	13
Diabetes diagnosed by doctor (%)	3
CVD diagnosed by doctor (%)*	21
Use of statines (%)	24
Use of antihypertensives (%)	10
Use of insulin (%)	0.2
Body mass index (kg/m²)	26.6 ± 4.4
Men	27.2 ± 4.0
Women	26.1 ± 4.7
Waist-hip-ratio	0.86 ± 0.08
Men	0.92 ± 0.06
Women	0.81 ± 0.06
Total body fat (%)	30.3 ± 8.2
Men	24.4 ± 5.5
Women	35.5 ± 6.5
Healthy weight (%)	39
Men	29
Women	48
Overweight weight (%)	43
Men	52
Women	35
Obese (%)	18
Men	19
Women	17

Data are shown as percentage, or mean ± standard deviation (SD). Healthy weight was defined as BMI 18-25 kg/m², overweight as BMI ≥25-30 kg/m², and obese as BMI≥30kg/m². CVD, cardiovascular disease was defined as myocardial infarction, angina pectoris, stroke and hypertension diagnosed by doctor.

CI 0.010, 0.05] per SD change in TBF) and white matter volume (0.05 change in SD [95% CI 0.02, 0.07] per SD change in TBF) in women. In men, a positive association was found with white matter volume, but this was not significant after multiple testing correction (*P*=0.050). Analysis of cortical regional volumes found 21 out of 49 tested regions to be significantly associated with TBF in females of which all but two showed a positive

Table 2. Distributions of different MRI outcome measures for females and males separately

MRI outcome measures	Females (n=6,381)	Males (n=5,706)
Volume	Mean (SD)	Mean (SD)
Brain volume (mm^3)	$1.11 \cdot 10^6$ ($8.87 \cdot 10^4$)	$1.23 \cdot 10^6$ ($1.00 \cdot 10^5$)
Grey matter (mm^3)	$5.94 \cdot 10^5$ ($4.75 \cdot 10^4$)	$6.41 \cdot 10^5$ ($5.27 \cdot 10^4$)
White matter (mm^3)	$5.17 \cdot 10^5$ ($4.71 \cdot 10^4$)	$5.88 \cdot 10^5$ ($5.44 \cdot 10^4$)
Brain stem (mm^3)	$2.17 \cdot 10^4$ ($2.24 \cdot 10^3$)	$1.17 \cdot 10^6$ ($1.11 \cdot 10^5$)
CSF (mm^3)	$2.92 \cdot 10^4$ ($1.25 \cdot 10^4$)	$6.16 \cdot 10^5$ ($5.53 \cdot 10^4$)
Thalamus (mm^3)	$7.41 \cdot 10^3$ ($6.24 \cdot 10^2$)	$5.50 \cdot 10^5$ ($6.18 \cdot 10^4$)
Caudate nucleus (mm^3)	$3.35 \cdot 10^3$ ($3.75 \cdot 10^2$)	$3.62 \cdot 10^3$ ($4.17 \cdot 10^2$)
Putamen (mm^3)	$4.61 \cdot 10^3$ ($4.72 \cdot 10^2$)	$5.08 \cdot 10^3$ ($5.53 \cdot 10^2$)
Pallidus (mm^3)	$1.71 \cdot 10^3$ ($1.87 \cdot 10^2$)	$1.86 \cdot 10^3$ ($2.09 \cdot 10^2$)
Hippocampus (mm^3)	$3.77 \cdot 10^3$ ($3.78 \cdot 10^2$)	$3.98 \cdot 10^3$ ($4.56 \cdot 10^2$)
Amygdala (mm^3)	$1.20 \cdot 10^3$ ($1.89 \cdot 10^2$)	$1.34 \cdot 10^3$ ($2.25 \cdot 10^2$)
Accumbens (mm^3)	$4.43 \cdot 10^2$ ($9.48 \cdot 10^1$)	$4.73 \cdot 10^2$ ($1.08 \cdot 10^2$)
Subcortical (mm^3)	$2.25 \cdot 10^4$ ($1.71 \cdot 10^3$)	$2.43 \cdot 10^4$ ($2.01 \cdot 10^3$)
DTI tract – Fractional anisotropy		
Mean Global FA	$4.49 \cdot 10^{-1}$ ($1.35 \cdot 10^{-2}$)	$4.53 \cdot 10^{-1}$ ($1.38 \cdot 10^{-2}$)
Mean FA of Commissural fibers	1.04 ($3.81 \cdot 10^{-2}$)	1.05 ($4.04 \cdot 10^{-2}$)
Mean FA of Association fibers	$3.21 \cdot 10^{-1}$ ($1.19 \cdot 10^{-2}$)	$3.24 \cdot 10^{-1}$ ($1.23 \cdot 10^{-2}$)
Mean FA of Projection fibers	$4.45 \cdot 10^{-1}$ ($1.28 \cdot 10^{-2}$)	$4.51 \cdot 10^{-1}$ ($1.30 \cdot 10^{-2}$)
DTI tract – Mean diffusivity		
Mean Global MD	$8.11 \cdot 10^{-4}$ ($2.25 \cdot 10^{-5}$)	$8.14 \cdot 10^{-4}$ ($2.35 \cdot 10^{-5}$)
Mean MD of Commissural fibers	$1.73 \cdot 10^{-3}$ ($6.62 \cdot 10^{-5}$)	$1.74 \cdot 10^{-3}$ ($6.95 \cdot 10^{-5}$)
Mean MD of Association fibers	$6.02 \cdot 10^{-4}$ ($1.93 \cdot 10^{-5}$)	$6.05 \cdot 10^{-4}$ ($1.99 \cdot 10^{-5}$)
Mean MD of Projection fibers	$8.02 \cdot 10^{-4}$ ($2.21 \cdot 10^{-5}$)	$8.05 \cdot 10^{-4}$ ($2.31 \cdot 10^{-5}$)

CSF, cerebral spinal fluid; FA, fractional anisotropy; MD, mean diffusivity.

association between TBF and specific cortical regional volume (Supplemental table 3). Negative associations were found for temporal fusiform anterior cortex and ventral striatum in women. In men, 19 out of 49 regions were found to be associated with TBF of which the majority was negatively associated. Six cortical regional volumes were significantly associated with TBF in both males and females (temporal fusiform anterior cortex, ventral striatum, percuneous cortex, occipital pole, and cuneal cortex). Sensitivity analysis in healthy weight individuals (BMI 18–25 kg/m²) showed similar associations for global volumes, subcortical grey matter volumes, and cortical regional volumes after adjustment and multiple comparisons correction (Supplemental table 4). An example of T1-weighted brain MRI scans of two UK biobank participants with low and high body fat percentage respectively is given in **Figure 3**.

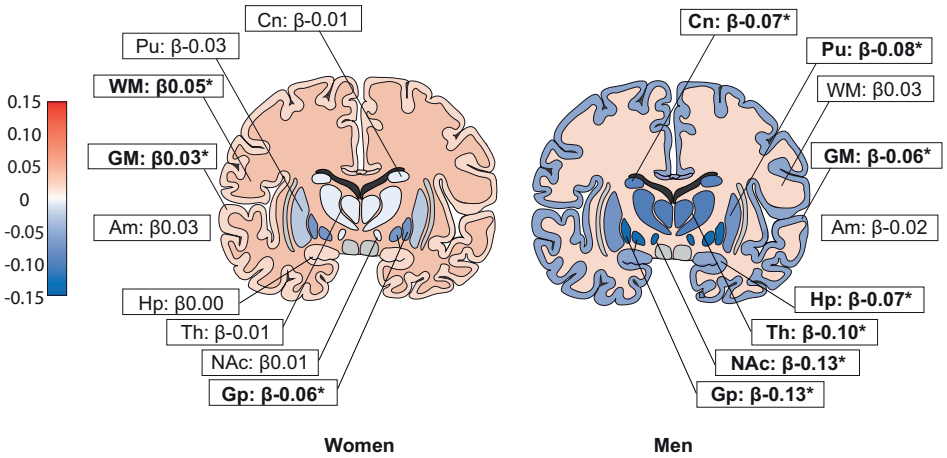

Figure 2. Overview of observed standardized regression coefficients (β) for the associations between total body fat and specific brain regions for men and women. Standardized regression coefficients reflect the SD change in regional brain volume per SD (=6.5% in women and 5.5% in men) change in total body fat. Example of interpretation, in men per SD increase in TBF globus pallidus volume was 27.2 mm^3 lower, and in women per SD increase in TBF globus pallidus volume was 11.2 mm^3 lower. *Significant after FDR correction (threshold pFDR=0.023). Results were adjusted for age, ethnicity, Townsend deprivation index, assessment center (baseline visit and imaging visit), smoking, alcohol use, diabetes, cardiovascular disease, and intra-cranial volume. Am, amygdala; Cn, caudate nucleus; GM, grey matter; Gp, globus pallidus; Hp, hippocampus; NAc, nucleus accumbens; Pu, putamen; Th, thalamus; WM, white matter.

Total body fat and white matter integrity

An overview of means and SDs of global FA and MD for the whole study sample and for men and women separately, is presented in table 2 and means of SDs of tract-specific FA and MD are presented in supplemental table 2. After adjustment for potential confounding variables, TBF was positively associated with global FA in both men (0.07 change in SD [95% CI 0.03, 0.11] per SD change in TBF) and women (0.05 change in SD [95% 0.02, 0.08] per SD change in TBF) (**Table 4, Figure 4**). TBF was not associated with FA of commissural fibers in either men or women. Significant positive associations were found for FA of the majority of both association and projection fibers in men and women. In women, TBF was negatively associated with global MD (-0.07 change in SD [95% CI -0.10,-0.05] per SD change in TBF). However, in men the association between TBF and global MD did not reach statistical significance (*P*=0.09). Negative associations with TBF were found for commissural fibers, association fibers, and projection fibers in men and women. Sensitivity analyses in healthy weight individuals (BMI 18–25 kg/m^2) only showed similar associations compared to the whole study sample for global FA and MD, and tract-specific DTI measures (Supplemental Table 4).

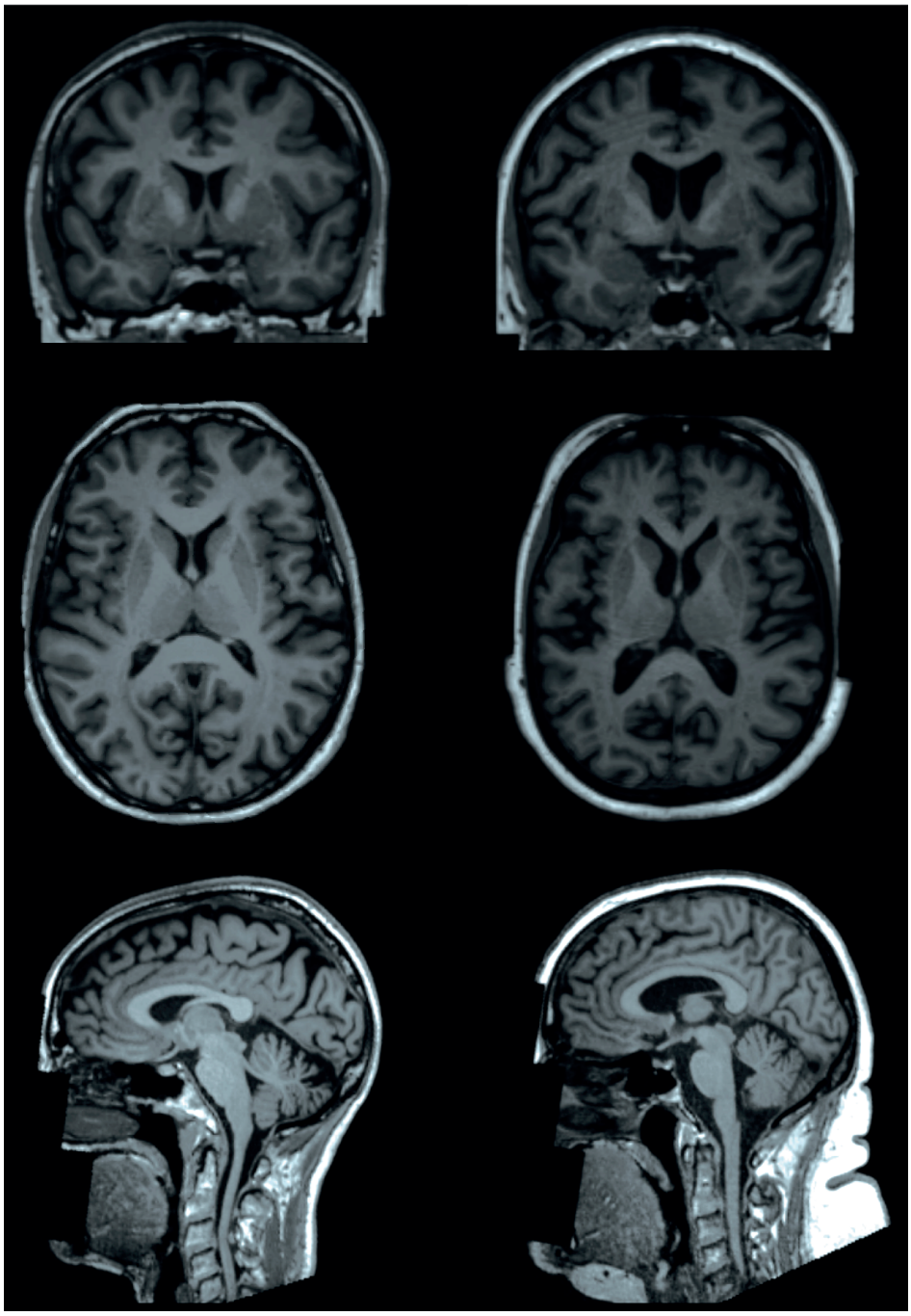

Figure 3. Example of T1-weighted brain MRI scans (coronal, axial and sagittal plane) of two UK biobank participants (both female and 65 years old), one with a body fat percentage of 13% (left) and one with a body fat percentage of 49% (right) showing lower volumes of subcortical gray matter structures in the individual with higher total body fat percentage.

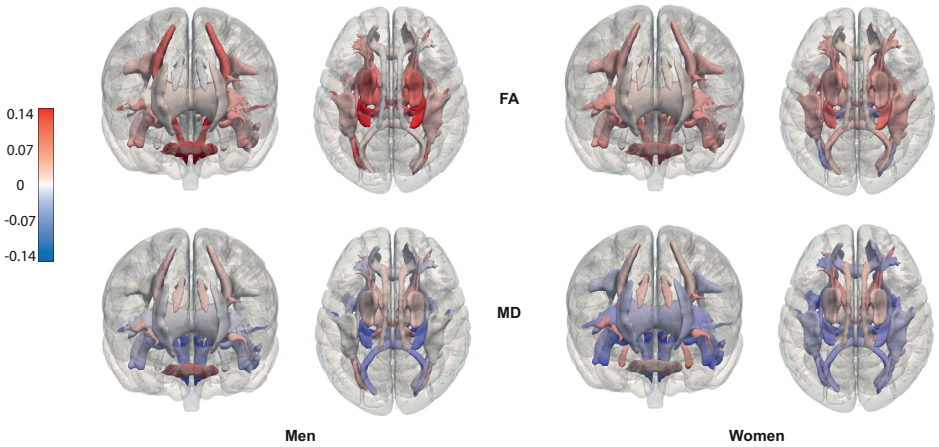

Figure 4. Overview of observed standardized regression coefficients (β) for the associations between total body fat and FA (upper) and MD (lower) based DTI tracts for men and women. Standardized regression coefficients reflect the SD change in FA and MD respectively per SD (=6.5% in women and 5.5% in men) change in total body fat.

DISCUSSION

Using large-scale multiparametric imaging data from 12,087 individuals from the UK Biobank study, we examined whether obesity was associated with brain morphology and microstructural integrity. In our study, we showed that sex-differences are present with regard to negative associations of TBF with regional subcortical grey matter volumes, including the globus pallidus and caudate nucleus, which have been associated with the reward circuitry of food-related stimuli (20). Our effect estimates are provided as standardized beta's meaning that, for example, per SD increase in TBF resulted in 0.13 SD lower globus pallidus volume (corresponding to 27.2 mm^3) in men, and 0.06 SD lower globus pallidus volume (corresponding to 11.2 mm^3) per SD increase in TBF in women. A possible explanation of previously described associations between obesity and lower grey matter volume (21) could be based on potential adverse effects of low grade systemic inflammation in obesity preferentially affecting grey matter volume over white matter volume (22). This has been supported by previous findings from the Framingham Heart study showing that several inflammatory biomarkers linked to obesity have also been associated with lower brain volume (23), and preclinical evidence linking high fat diet to neuroinflammatory changes and neurodegeneration (24). In addition, insulin resistance has been implicated as a possible pathway of cognitive impairment and neuroimaging findings in type 2 diabetes and Alzheimer's disease (25).

Aside from obesity influencing brain structure, a reverse direction of associations could be also possible via a neuronal influence on body weight regulation and eating behavior. Lower grey matter volume of mainly frontal and limbic brain areas in obesity suggest that

Table 2. Multiple linear regression results for total body fat and brain volumes

a. Global volumes	Brain volume	Grey matter	White matter	Brain stem	CSF			
Adjusted TBF (female; SD 6.6%)†	**0.04; 0.02,0.06; *P*=0.001**	**0.03; 0.01,0.05; *P*=0.02**	**0.05; 0.02,0.07; *P*=<0.001***	-0.01; -0.04,0.02; *P*=0.36	-0.02; -0.05,0.00; *P*=0.07			
Adjusted TBF (male; SD 5.5%)†	-0.01; -0.04,0.02; *P*=0.52	**-0.06; -0.09,-0.03; *P*<0.001***	0.03; 0.00,0.06; *P*=0.050	**-0.10; -0.13,-0.06; *P*<0.001***	**0.07; 0.04,0.11; *P*<0.001***			
b. Subcortical GM volumes	All	Thalamus	Caudate nucleus	Putamen	Globus Pallidus	Hippocampus	Amygdala	Nucleus accumbens
Adjusted TBF (female; SD 6.6%)†	-0.01; -0.04,0.02; *P*=0.23	-0.01; -0.03,0.02; *P*=0.55	-0.01; -0.04,0.02 *P*=0.38	**-0.03; -0.05,0.00; *P*=0.03**	**-0.06; -0.09,-0.03; *P*<0.001***	0.00; -0.03,0.03; *P*=0.93	0.03; 0.00,0.06; *P*=0.06	0.01; -0.02,0.03; *P*=0.69
Adjusted TBF (male; SD 5.5%)†	**-0.11; -0.14,-0.07; *P*<0.001***	**-0.10; -0.13,-0.06; *P*<0.001***	**-0.07; -0.11,-0.03; *P*<0.001***	**-0.08; -0.11,-0.04; *P*<0.001***	**-0.13; -0.17,-0.10; *P*<0.001***	**-0.07; -0.11,-0.04; *P*<0.001***	-0.02; -0.06,0.02; *P*=0.38	**-0.13; -0.17,-0.10; *P*<0.001***

Whole study sample n=12,087; females n=6,381, males n=5,706. Standardized regression coefficients (β), with corresponding 95% confidence intervals and uncorrected P-values are shown. Standardized regression coefficients reflect the SD change in regional brain volume per SD (=6.5% in women and 5.5% in men) change in TBF. *Significant after FDR correction (threshold pFDR=0.023). Adjusted model includes: age, ethnicity, TDI, assessment center (baseline visit and imaging visit), smoking, alcohol use, diabetes, cardiovascular disease, and intra-cranial volume. CSF, cerebral spinal fluid; TBF, total body fat; TDI, Townsend deprivation index. †P for interaction of TBF and sex, in adjusted model <0.001. TBF (female) (per SD=6.5%)†, TBF (male) (per SD=5.5%)†

Table 3. Multiple linear regression results for total body fat and global and tract specific FA

Mean FA of DTI tracts	Global FA	Commissural fibers	Assocation fibers	Projection fibers
Adjusted TBF (female; SD 6.6%)†	**0.05; 0.02,0.08; *P*=0.001***	0.02; -0.01,0.04; *P*=0.11	0.03; 0.00,0.06; *P*=0.027	**0.07; 0.04,0.10; *P*<0.001***
Adjusted TBF (male; SD 5.5%)†	**0.07; 0.03,0.11; *P*=<0.001***	0.01; -0.03,0.05; *P*=0.51	**0.05; 0.01,0.08; *P*=0.009***	**0.11; 0.07,0.14; *P*<0.001***
Mean MD of DTI tracts	Global MD	Commissural fibers	Assocation fibers	Projection fibers
Adjusted TBF (female; SD 6.6%)†	**-0.07; -0.10,-0.05; *P*<0.001***	**-0.05; -0.08,-0.02; *P*=0.001***	**-0.07; -0.10,-0.04; *P*<0.001***	**-0.07; -0.10,-0.04; *P*<0.001***
Adjusted TBF (male; SD 5.5%)†	-0.03; -0.07,0.01; *P*=0.09	**-0.05; -0.09,-0.01; *P*=0.01***	-0.04; -0.08,-0.00; *P*=0.03	-0.01; -0.04,0.03; *P*=0.07

Whole study sample n=12,087; females n=6,381, males n=5,706. Standardized regression coefficients (β), with corresponding 95% confidence intervals and uncorrected *P*-values are shown. Standardized regression coefficients reflect the SD change in regional brain volume per SD (=6.5% in women and 5.5% in men) change in TBF. *Significant after FDR correction (threshold pFDR=0.023). Adjusted model includes: age, ethnicity, TDI, assessment center (baseline visit and imaging visit), smoking, alcohol use, diabetes, cardiovascular disease, and intra-cranial volume. FA, fractional anisotropy; MD, mean diffusivity; TBF, total body fat; TDI, Townsend deprivation index. †P for interaction of TBF and sex, in adjusted model <0.001. TBF (female) (per SD=6.6%)†, TBF (male) (per SD=5.5%)†

regulation of eating behavior could be influenced by altered inhibitory control via lower grey matter volume in these areas and affected signaling pathways of the cortico-limbic tract (26). Altered inhibitory control in obesity shares clinical overlap and vulnerability with substance addiction (20), which has been supported by functional imaging showing lower levels of striatal dopamine receptors in obesity (similar to addiction) (27), and different brain responses to food-related stimuli in obese individuals compared to non-obese individuals (28). In our study no associations were found for TBF and amygdala volume, which had also not shown differences in brain responses to food stimuli between obese and non-obese individuals in functional imaging studies (28).

Lower microstructural integrity of several white matter tracts, such as callosal and limbic tracts have been described previously (29). In contrast, we found that increases in total body fat percentages were linked to higher levels of white matter microstructure assessed by FA. In addition, negative associations were found between body fat and MD. This means that body fat percentage, as a measure of general obesity, was associated with higher coherence and with a lower magnitude of water diffusion. This suggests that associations between obesity and white matter microstructural integrity are opposite to previously described findings in ageing (9).

Our findings are *not* consistent with previous studies that showed negative associations between high BMI and FA (30). The reason for this is unknown. However differences may

be methodological (e.g. voxel based approach, higher scan resolution). Prior studies compared healthy weight versus obese individuals whereas our study evaluated total body fat percentage as a continuous variable. However, previous reported significant differences in DTI metrics in obesity might also stem from false-positive findings as the lower statistical power of these studies (sample sizes ranging between 15 to 499 individuals (30)) increases the likelihood of overestimating effect sizes, leading to a lower reproducibility of results (31).

It has been suggested that obese men are more susceptible to mild cognitive impairment than obese women (32), which has been supported by previous observations indicating greater brain atrophy in obese men compared to obese women (10). In our study, we found significant interaction between TBF and sex, and stronger negative associations between volumes of subcortical grey matter structures for total body fat in men compared to women. A possible explanation for these findings might be a relative protective effect of estrogen on the metabolic syndrome (33). Sex-differences for associations between TBF and DTI were less pronounced but also present for effect estimates of global and tract specific measures showing the same directions in males and females but different strengths of associations.

Our study has some limitations. Although growing evidence indicates that obesity adversely affects the CNS and cognitive functioning, our observational cross-sectional design precludes causal inference. Additionally, our study solely focused on brain architecture as we did not assess associations with cognitive functioning. Since laboratory measurements (e.g. HbA1c, serum glucose etc.) were not available at the time of our study and questionnaire data on physical exercise and medication use were only available for a limited subset, these were not taken into account in our analysis and could be a source of possible residual confounding. In addition to these limitations, we note that although multiple associations were shown to be significant, the observed effect estimates are small. The large sample size of the study enabled us to detect these subtle associations between obesity measures and brain structure. These modest associations may be expected given that our study was performed in the general population, which also included non-obese individuals.

More research is needed to assess changes in brain architecture in obesity over time, and metabolic influences such as insulin-resistance (25) and metabolic responses to fasting/exercise and eating/resting conditions (34). Further research is needed to investigate to what extent a greater amount of visceral adipose tissue (via a low grade systemic metabolic inflammation) leads to detrimental effects on brain structure and cognitive functioning above and beyond measures of general obesity (35). In addition, more functional brain imaging studies (e.g. nuclear metabolic studies, and arterial spin labelling) are warranted, as altered brain metabolism and cerebral hypoperfusion have been

hypothesized as possible underlying pathophysiological pathways of the adverse effects of obesity on cognitive functioning.

Our findings provide further evidence that obesity is associated with smaller subcortical grey matter volumes. In addition, obesity was associated with higher coherence but lower magnitude of white matter microstructure in our study, which provides insights into the potential influences of obesity on the geometric organization of white matter microstructure. Future research is needed to evaluate whether stringent weight reduction and treatment of obesity related metabolic disorders also benefit the potential neurological consequences of obesity.

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