Investigating obesity-associated brain inflammation using quantitative water content mapping

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Abstract

There is growing evidence that obesity is associated with inflammation in the brain, which could contribute to the pathogenesis of obesity. In humans, it is challenging to detect brain inflammation in vivo. Recently, quantitative magnetic resonance imaging (qMRI) has emerged as a tool for characterising pathophysiological processes in the brain with reliable and reproducible measures. Proton density imaging provides quantitative assessment of the brain water content, which is affected in different pathologies, including inflammation. We enrolled 115 normal weight, overweight and obese men and women (body mass index [BMI] range 20.1-39.7 kg m⁻², age range 20-75 years, 60% men) to acquire cerebral water content mapping in vivo using MRI at 3 Tesla. We investigated potential associations between brain water content with anthropometric measures of obesity, body fat distribution and whole-body metabolism. No global changes in water content were associated with obesity. However, higher water content values in the cerebellum, limbic lobe and sub-lobular region were detected in participants with higher BMI, independent of age. More specifically,
the dorsal striatum, hypothalamus, thalamus, fornix, anterior limb of the internal capsule and posterior thalamic radiation showed the strongest relationship with BMI, independent of age. In a subgroup with available measurements (n = 50), we identified visceral adipose tissue to be the strongest tested link between higher water content values and obesity. Individuals with metabolic syndrome had the highest water content values in the hypothalamus and the fornix. There is accumulating evidence that inflammation of the hypothalamus contributed to obesity-associated insulin resistance in that area. Whether brain inflammation is a cause or consequence of obesity in humans still needs to be investigated using a longitudinal study design. Using qMRI, we were able to detect marked water content changes in young and older obese adults, which is most likely the result of chronic low-grade inflammation.

**KEYWORDS**
cerebral oedema, hypothalamus, inflammation, obesity, quantitative MRI

1 | INTRODUCTION

From 1975 onwards, obesity has tripled worldwide to 650 million,\(^1\) increasing the risk of metabolic syndrome, type 2 diabetes (T2D), coronary heart disease and certain forms of cancer.\(^2,3\) Despite tremendous efforts, an effective cure and the prevention of obesity and T2D have remained elusive. This is partly the result of a multitude of factors that substantially contribute to the pathophysiology of obesity and T2D, including impaired insulin secretion, insulin resistance, inflammation and disproportionate body fat distribution.\(^4\) Particularly central adiposity, a prominent trait of metabolically unhealthy obesity\(^4\) and metabolic syndrome, is a significant source of inflammation.\(^5\) Recent accumulating evidence shows that chronic low-grade inflammation prompts inflammatory processes in the brain, which involves non-neuronal populations such as astrocytes and microglia.\(^6,7\) Moreover, rodent models clearly show that dietary excess can trigger brain inflammation, causing weight gain.\(^7,8\) In humans, less is known about whether obesity is related to inflammation in the brain because it is challenging to detect subclinical brain inflammation in vivo. Thaler et al\(^8\) were the first to describe hypothalamic gliosis in individuals with obesity using T\(_2\)-weighted magnetic resonance imaging (MRI). Subsequently, as a result of technological advances, quantitative MRI has emerged as a tool for characterising pathophysiological processes in the whole brain in vivo with reliable and reproducible measures.\(^9,10\) The initial evidence points to water content alteration contributing to the alterations found in individuals with obesity.\(^11\) Proton density imaging provides a quantitative assessment of the brain water content as a marker of inflammatory processes. The higher water content (ie, increased uptake of fluid can result in local swelling) may compress the distinct local microenvironments, which may finally result in dysfunctional states, accompanying various processes that damage cells.\(^10,12-15\) In the present study, we investigated potential associations between measures of obesity and brain water content using proton density imaging to investigate potential inflammation of the entire brain. We hypothesise that individuals with obesity, especially those with visceral adiposity and metabolic syndrome, will show increased brain water content particularly in the hypothalamus. Based on our cross-sectional design, we cannot differentiate between diet-induced or chronic inflammation.

2 | MATERIALS AND METHODS

2.1 | Participants

The study sample consisted of 115 normal weight, overweight and obese adult participants (body mass index [BMI] range 20.1–39.7 kg m\(^{-2}\)) and healthy volunteers. The local ethics committee approved the protocol and informed written consent was obtained from all participants, who were recruited using broadcast emails at the University of Tübingen or through local newspaper advertisement. Participants underwent a thorough medical examination and did not suffer from psychiatric or neurological diseases. To rule out T2D, participants underwent a 75-g oral glucose tolerance test. Peripheral insulin sensitivity,\(^16\) blood pressure and lipid profiles were additionally assessed. Metabolic syndrome was diagnosed in accordance with the International Diabetes Federation criteria.\(^17\) It is defined by central obesity (waist circumference > 94 cm for men, > 80 cm for women) plus any two of the following risk factors: raised triglycerides, reduced high-density lipoprotein cholesterol, raised blood pressure and raised fasting glucose. Participant characteristics are summarised in Table 1 and the Supporting information (Table S1).

2.2 | Data acquisition

Studies were conducted after an overnight fast of at least 10 hours. Whole-brain MRI was obtained by using a 3 Tesla scanner (PRISMA; Siemens, Munich, Germany) with a 20-channel head coil for signal reception and the body coil for excitation. Quantitative cerebral free water (FW) content measurements were estimated based on MR-visible-proton density (PD) with an acquisition time
of 14 minutes. For this purpose, the water content mapping protocol was implemented using the Siemens multi-slice, multi-echo radio frequency (RF)-spoiled gradient recalled echo sequence (GRE). This method was previously validated in multiple cohorts (ranging from healthy controls to patients) using 1.5-T and 3-T MRI.

Two proton-density-weighted (PD-w) GRE images, with interleaved concatenations (32 slices each), were acquired with an acceleration factor of 2 and 24 auto-calibration lines, TR = 1800 ms, TE = 5.8 ms, FA = 40° and bandwidth = 210 Hz per pixel. This led to 64 gap-free transverse slices of 2-mm slice thickness and 1-mm in-plane resolution measured in 6 minutes.

To quantify tissue water content, the PD-w images need to be corrected for (i) the RF field inhomogeneities; (ii) the T2*-contrast; and (iii) the residual T1-contrast. Correction 1 refers to the transmit (B1^+ ) and the receive (B1^−) profile. Estimation of the B1^+ field was performed via a multiple flip angle technique. This technique requires four echo-planar images with different FAs (30°, 60°, 90° and 120°) with a TR of 20 seconds acquired in approximately 1.3 minutes. The B1^− profile is estimated by acquiring two low-resolution GRE scans (TR = 500 ms, TE = 5.8 ms, BW per pixel = 210 Hz and FA = 40°, acquisition time = 30 seconds each) where the body coil was used in place of the receive head array coil for signal reception in the second acquisition.

### TABLE 1 Descriptive statistics

|                          | Mean  | SE    | Minimum | Maximum |
|--------------------------|-------|-------|---------|---------|
| Age (years)              |       |       |         |         |
| Women                    | 51.76 | 2.168 | 24      | 74      |
| Men                      | 43.43 | 1.605 | 20      | 75      |
| All                      | 46.77 | 0.629 | 20      | 75      |
| Body mass index (kg m^-2)|       |       |         |         |
| Women                    | 27.83 | 0.492 | 20.86   | 35.56   |
| Men                      | 26.34 | 0.392 | 20.10   | 39.68   |
| All                      | 26.94 | 0.054 | 20.10   | 39.68   |
| HbA1c (%)                |       |       |         |         |
| Women                    | 5.50  | 0.0477| 4.70    | 6.40    |
| Men                      | 5.40  | 0.0361| 4.40    | 6.40    |
| All                      | 5.44  | 0.054 | 4.40    | 6.40    |
| Fasting glucose (mg dL^-1)|      |       |         |         |
| Women                    | 96.63 | 1.073 | 81.00   | 124.0   |
| Men                      | 94.31 | 0.9014| 79.00   | 123.0   |
| All                      | 95.24 | 1.134 | 79.00   | 124.0   |
| oGTT-derived insulin sensitivity index | | | |
| Women                    | 13.05 | 1.001 | 2.58    | 50.34   |
| Men                      | 13.61 | 0.8083| 2.07    | 34.51   |
| All                      | 13.35 | 0.881 | 2.07    | 50.34   |
| Waist circumference (cm) |       |       |         |         |
| Women                    | 90.06 | 1.597 | 68.00   | 117.0   |
| Men                      | 94.74 | 1.236 | 72.00   | 129.0   |
| All                      | 92.63 | 0.0079| 68.00   | 129.0   |
| Waist to hip ratio       |       |       |         |         |
| Women                    | 0.865 | 0.0074| 0.720   | 0.9700  |
| Men                      | 0.946 | 0.00674| 0.800 | 1.055 |
| All                      | 0.909 | 0.00674| 0.800 | 1.055 |
| Triglyceride (mg dL^-1)  |       |       |         |         |
| Women                    | 111.93| 10.062| 39      | 490     |
| Men                      | 117.02| 7.534 | 48      | 367     |
| All                      | 114.66| 5.843 | 39      | 490     |
| Cholesterol (mg dL^-1)   |       |       |         |         |
| Women                    | 211.20| 6.568 | 140     | 312     |
| Men                      | 198.27| 4.470 | 103     | 366     |
| All                      | 204.27| 2.220 | 103     | 366     |
| HDL-cholesterol (mg dL^-1)|     |       |         |         |
| Women                    | 64.51 | 2.067 | 39      | 100     |
| Men                      | 53.08 | 1.614 | 28      | 97      |
| All                      | 58.38 | 4.325 | 28      | 100     |
| LDL-cholesterol (mg dL^-1)|    |       |         |         |
| Women                    | 126.20| 5.775 | 69      | 179     |
| Men                      | 128.42| 3.673 | 64      | 302     |
| All                      | 127.39| 4.151 | 64      | 302     |
| Fasting free fatty acids (µmol l^-1) |    |       |         |         |
| Women                    | 612.64| 22.244| 99      | 1650    |

### TABLE 1 (Continued)

|                          | Mean  | SE    | Minimum | Maximum |
|--------------------------|-------|-------|---------|---------|
| Men                      | 464.50| 24.366| 147     | 865     |
| All                      | 533.23| 2.273 | 99      | 1650    |
| Systolic blood pressure (mm Hg) |       |       |         |         |
| Women                    | 131.91| 2.148 | 105     | 162     |
| Men                      | 138.93| 1.593 | 110     | 187     |
| All                      | 135.76| 1.922 | 105     | 187     |
| Diastolic blood pressure (mm Hg) |     |       |         |         |
| Women                    | 85.78 | 1.533 | 56      | 111     |
| Men                      | 85.39 | 1.202 | 64      | 115     |
| All                      | 85.57 | 1.685 | 56      | 115     |
| Total adipose tissue (L) |       |       |         |         |
| Women                    | 38.33 | 2.151 | 23.60   | 50.90   |
| Men                      | 29.43 | 1.572 | 11.05   | 60.49   |
| All                      | 32.99 | 0.322 | 11.05   | 60.49   |
| Visceral adipose tissue (L) |     |       |         |         |
| Women                    | 4.02  | 0.4581| 1.69    | 7.46    |
| Men                      | 4.57  | 0.3003| 1.31    | 11.07   |
| All                      | 4.34765| 0.7424| 1.31    | 11.07   |
| Subcutaneous adipose tissue lower extremities | | | |
| Women                    | 14.59550| 0.7033| 7.00   | 20.51   |
| Men                      | 10.92667| 0.5719| 4.74   | 20.71   |
| All                      | 12.39420| 0.5719| 4.74   | 20.71   |

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test.
The correction for the $T_2^*$ contrast was achieved by measuring the $T_2^*$ relaxation time map using a separate RF-spoiled multi-echo 3D-GRE MR acquisition scan, with parameters of TR = 35 ms, FA = 12°, BW per pixel = 510 Hz, TE1 = 2.3 ms, ΔTE = 2.3 ms and eight echoes, acquired in 3.4 minutes (2-mm slice-thickness, 1-mm in-plane resolution). Assuming an exponential decay of the 3D-GRE, this dataset allows an estimation of the $T_2^*$ decay constant and correction of the signal decay present in the PD-weighted scan.

Correction (c) required quantification of $T_1$ relaxation time. This was performed using the two-point technique. This requires an extra $T_1$-weighted GRE scan, which was acquired with TR = 500 ms, TE = 5.8 ms, FA = 90° and BW per pixel = 210 Hz. Sixty-four transverse slices were acquired in two concatenations in 1.7 minutes.

For all sequences, the same orientation and field of view were used. The details about the parameters and the processing steps are provided in Abbas et al. The free water content was estimated using in-house MATLAB (Mathworks, Natick, MA, USA) algorithms.

Additionally, to identify obesity-associated differences in cerebral blood flow arterial spin labelling was used, as described previously. Accordingly, pulsed arterial spin labelling images were obtained with a PICORE-Q2TIPS (proximal inversion with control for off-resonance effects—quantitative imaging of perfusion by using a single subtraction) sequence using a frequency offset corrected inversion pulse and echo-planar imaging readout for acquisition.

### 2.3 Data processing

#### 2.3.1 Estimation of the relaxation parameters and total free water content

Following the $T_1$, $T_2^*$ and transmit/receiver profiles corrections, the PD-weighted scan cannot yet be treated as a quantitative water content map because it requires further correction for receiver bias profile maps. This is achieved by exploiting the linear relationship between corrected PD-weighted contrast and $T_1$ relaxation time in certain brain regions (60 ms > $T_2^* > 50$ ms).

Finally, the calibration of the bias-free water content map was performed using a robust and reliable approach. It uses the regions within cerebrospinal fluid based on $T_1$, $T_2^*$ thresholds and its stability in terms of transmit profile. The calibration factor was then computed via the weighted average across the stable regions.

All quantitative free water content and $T_1$ maps were normalised using SPM12.

#### 2.3.2 Cerebral blood flow quantification

Image preprocessing was performed using ASLTEX 

With accurate CBF quantification (mL x 100g\(^{-1}\) x min\(^{-1}\)), we used an M0 map to quantify the perfusion on each voxel.

### 2.3.3 Body fat assessment by whole-body MRI

On a separate day, a subgroup (n = 50) underwent whole-body MRI to assess body fat distribution of the participants. These MRI examinations were performed on a 1.5-T whole-body imager (Magnetom Sonata; Siemens Healthineers, Erlangen, Germany). A whole-body imaging protocol was used to record a set of 90-120 $T_1$-weighted axial slices. This approach enabled quantification of body volume, total adipose tissue (TAT) and total mass of specific fat depots such as subcutaneous (s.c. adipose tissue of the lower extremities (SCAT\(_{LE}\) ranging from feet to femoral heads, and visceral adipose tissue (VAT) via an automated segmentation algorithm, applying fuzzy clustering and orthonormal snakes.

### 2.4 Statistical analysis

Region-of-interests (ROIs) were selected from the Wake Forest Pickatlas to extract quantitative FW values of 11 brain lobes (temporal, sub-lobar, pons, parietal, occipital, midbrain, medulla, limbic, frontal-temporal space, frontal lobe and parts of the cerebellum within the field of view during data acquisition) and seven subcortical regions: bilateral thalamus, dorsal and ventral striatum, amygdala, hippocampus, and the lateral and medial hypothalamus. ROIs of white matter tracts were selected from the JHU-DTI based white matter atlases (JHU-ICBM labels 1 mm) to extract quantitative FW values of 48 white matter tracts. Additionally, FW values of total grey (GM) and white matter (WM) were extracted for the calculation of ratios (FW values displayed in the Supporting information, Table S2). In total, 66 ratios were created to compare the mean quantitative FW values within the ROIs with total grey matter or white matter tissue as a control region. Correlation analysis was performed between the 66 ratios and BMI, presence of the metabolic syndrome and MR-based body fat distribution (visceral adipose tissue and non-VAT tissue). Non-parametric bivariate correlations and partial correlations with Spearman rho was used for analysis in SPSS, version 25 (IBM Corp., Armonk, NY, USA).

Correlations were considered significant if they survived a threshold of $P \leq 0.0007$ ($P = 0.05$ corrected for number of ROIs; n = 66). To estimate the effect size of the relationship between BMI and the change in quantitative FW, the linear coefficient (slope) was calculated. In a similar vein, baseline quantitative cerebral blood flow was extracted for each region of interest and correlated with measures of obesity.

### 3 RESULTS

#### 3.1 Higher water content with increasing BMI in grey and white matter regions

In our sample of 115 adults, no significant associations of global water content of the brain with measures of obesity were observed.
Alternatively, we observed regional specific associations (Figure 1). Of the different brain lobes, the cerebellum and sub-lobular region (which includes striatal regions and hypothalamus) showed higher cerebral free water content values with increasing BMI independent of age and sex (cerebellum: 40, P < 0.0007; sub-lobular: 40, P < 0.0007). Further region of interests, namely the lateral hypothalamus (40 = 0.439, P < 0.0007) (Figure 2), dorsal striatum (40 = 0.394, P < 0.0007) and thalamus (40 = 0.441, P < 0.0007), showed a significant positive relationship with BMI independent of age and sex (Table 2). The BMI-correlated increase in FW amounted to 0.006 (p.u.) per BMI point (calculated slope). Furthermore, FW values of white matter tracts showed a significant positive association with BMI independent of age and sex, most significantly for the fornix (40 = 0.419, P < 0.0007) (Figure 2), left anterior limb of the internal capsule (40 = 0.334, P < 0.0007) and right posterior thalamic radiation (40 = 0.346, P < 0.0007) (Table 2).

3.2 | Individuals with metabolic syndrome display increased hypothalamic and thalamic water content values

We divided the sample of 115 individuals into three groups: individuals with metabolic syndrome (13 women and 18 men), individuals with central obesity who did not fulfill diagnostic criteria for metabolic syndrome (23 women and 12 men) and healthy non-obese individuals (10 women, 39 men). We identified the highest water content values in the hypothalamus (40 = 0.344, P < 0.0007), thalamus (40 = 0.327, P < 0.0007) and fornix (40 = 0.357, P < 0.0007) in individuals with metabolic syndrome adjusted for age and sex (Figure 3).

3.3 | Individuals with higher visceral fat content or lower s.c. adipose tissue mass display increased free water content

In a subgroup with available measurements (n = 50), we investigated the association between water content values and MR-based fat distribution SCATLE and VAT independent of the amount of TAT. The most significant associations were found for the lateral hypothalamus water content with VAT (40 = 0.440, P = 0.001) and SCATLE (40 = −.532, P < 0.0007) independent of the amount of TAT and with the right posterior thalamic radiation (for VAT: 40 = 0.479, for SCATLE: 40 = −.518, P < 0.0007), left tapetum (for VAT: 40 = 0.556, for SCATLE: 40 = −.402, P < 0.0007) and right tapetum (for VAT: 40 = 0.566, P < 0.0007; for SCATLE: 40 = −0.452, P = 0.001). Hence, individuals with more visceral and less s.c. fat in the lower extremities showed the highest water content (for details, see the Supporting information, Table S3). After adjusting for sex and age, correlations did not remain significant (P > 0.05, uncorrected).

3.4 | No significant association between baseline cerebral blood flow and obesity

Based on the arterial spin labelling measure, we identified no significant differences between cerebral blood flow of the different brain regions and BMI, presence of the metabolic syndrome or MR-based body fat distribution (P > 0.05) (data not shown). The mean ± SD cerebral blood flow value of the total grey matter was 33.12 ± 0.79 mL × 100 g−1 × min−1.
| Anatomical regions                  | BMI   | Age  | Sex  | BMI_{adj} for age and sex |
|-----------------------------------|-------|------|------|--------------------------|
| Region-of-interests/total grey matter ratio |       |      |      |                          |
| Amygdala                          |       |      |      |                          |
| Correlation coefficient           | 0.013 | -0.150 | 0.137 | 0.06                     |
| P value (two-sided)               | 0.891 | 0.110 | 0.143 | 0.524                    |
| Dorsal striatum                   |       |      |      |                          |
| Correlation coefficient           | 0.422 | 0.446 | -0.052 | 0.394                    |
| P value (two-sided)               | < 0.0007 | < 0.0007 | .578 | < 0.0007§                 |
| Hippocampus                       |       |      |      |                          |
| Correlation coefficient           | 0.282 | 0.232 | 0.055 | 0.269                    |
| P value (two-sided)               | 0.002 | 0.013 | 0.563 | 0.004                    |
| Lateral hypothalamus              |       |      |      |                          |
| Correlation coefficient           | 0.461 | 0.558 | -0.033 | 0.439                    |
| P value (two-sided)               | < 0.0007 | < 0.0007 | 0.731 | < 0.0007§                 |
| Medial hypothalamus               |       |      |      |                          |
| Correlation coefficient           | 0.291 | 0.634 | 0.026 | 0.262                    |
| P value (two-sided)               | 0.002 | < 0.0007 | 0.781 | 0.005                    |
| Thalamus                          |       |      |      |                          |
| Correlation coefficient           | 0.460 | 0.659 | -0.236 | 0.441                    |
| P value (two-sided)               | < 0.0007 | < 0.0007 | .011 | < 0.0007§                 |
| Ventral striatum                  |       |      |      |                          |
| Correlation coefficient           | 0.189 | 0.042 | 0.005 | 0.188                    |
| P value (two-sided)               | 0.044 | 0.658 | 0.955 | 0.046                    |
| Talairach Daemon lobes/total grey matter ratio |       |      |      |                          |
| Cerebellum (anterior part)        |       |      |      |                          |
| Correlation coefficient           | 0.463 | 0.281 | -0.091 | 0.434                    |
| P value (two-sided)               | < 0.0007 | 0.002 | 0.331 | < 0.0007§                 |
| Frontal temporal space            |       |      |      |                          |
| Correlation coefficient           | -0.159 | 0.082 | 0.194 | -0.152                   |
| P value (two-sided)               | 0.090 | 0.384 | 0.038 | 0.109                    |
| Frontal                           |       |      |      |                          |
| Correlation coefficient           | -0.054 | 0.306 | -0.121 | -0.131                   |
| P value (two-sided)               | 0.570 | 0.001 | 0.196 | 0.166                    |
| Limbic                            |       |      |      |                          |
| Correlation coefficient           | 0.355 | 0.185 | -0.181 | 0.316                    |
| P value (two-sided)               | < 0.0007 | 0.048 | 0.053 | 0.001                    |
| Midbrain                          |       |      |      |                          |
| Correlation coefficient           | 0.329 | 0.508 | -0.196 | 0.263                    |
| P value (two-sided)               | < 0.0007 | < 0.0007 | 0.036 | 0.005                    |
| Occipital                         |       |      |      |                          |
| Correlation coefficient           | -0.154 | -0.466 | 0.166 | -0.063                   |
| P value (two-sided)               | 0.100 | < 0.0007 | 0.076 | 0.507                    |
| Parietal                          |       |      |      |                          |
| Correlation coefficient           | 0.014 | -0.155 | -0.198 | 0.010                    |
| P value (two-sided)               | 0.884 | 0.098 | 0.034 | 0.917                    |

(Continues)
| Anatomical regions              | BMI     | Age  | Sex  | BMI_{adj} for age and sex |
|--------------------------------|---------|------|------|---------------------------|
| Pons                           |         |      |      |                           |
| Correlation coefficient        | 0.271   | 0.175| 0.021| 0.258                     |
| P value (two-sided)            | 0.003   | 0.061| 0.825| 0.006                     |
| Sub lobar                      |         |      |      |                           |
| Correlation coefficient        | 0.446   | 0.575| −0.132| 0.420                     |
| P value (two-sided)            | < 0.0007| < 0.0007| 0.159| < 0.0007§                 |
| Temporal                      |         |      |      |                           |
| Correlation coefficient        | −0.045  | −0.229| −0.109| −0.026                    |
| P value (two-sided)            | 0.630   | 0.014| 0.246| 0.781                     |

JHU-ICBM labels/total white matter ratio

| Middle cerebellar peduncle     |         |      |      |                           |
| Correlation coefficient        | 0.250   | −0.128| 0.203| 0.318                     |
| P value (two-sided)            | 0.007   | 0.173| 0.030| 0.001                     |
| Pontine crossing tract         |         |      |      |                           |
| Correlation coefficient        | 0.199   | 0.078| 0.065| 0.204                     |
| P value (two-sided)            | 0.033   | 0.410| 0.489| 0.030                     |
| Genu of corpus callosum        |         |      |      |                           |
| Correlation coefficient        | 0.188   | 0.473| 0.021| 0.136                     |
| P value (two-sided)            | 0.044   | < 0.0007| 0.821| 0.151                     |
| Body of corpus callosum        |         |      |      |                           |
| Correlation coefficient        | 0.271   | 0.542| −0.060| 0.214                     |
| P value (two-sided)            | 0.003   | < 0.0007| 0.521| 0.023                     |
| Splenium of corpus callosum    |         |      |      |                           |
| Correlation coefficient        | 0.217   | 0.176| 0.051| 0.206                     |
| P value (two-sided)            | 0.020   | 0.060| 0.590| 0.028                     |
| Fornix                         |         |      |      |                           |
| Correlation coefficient        | 0.431   | 0.375| 0.029| 0.419                     |
| P value (two-sided)            | < 0.0007| < 0.0007| 0.759| < 0.0007§                 |
| Corticospinal tract, right     |         |      |      |                           |
| Correlation coefficient        | 0.109   | −0.081| 0.056| 0.135                     |
| P value (two-sided)            | 0.247   | 0.388| 0.551| 0.155                     |
| Corticospinal tract, left      |         |      |      |                           |
| Correlation coefficient        | 0.025   | 0.008| 0.030| 0.029                     |
| P value (two-sided)            | 0.789   | 0.928| 0.751| 0.759                     |
| Medial lemniscus, right        |         |      |      |                           |
| Correlation coefficient        | 0.246   | 0.133| 0.009| 0.235                     |
| P value (two-sided)            | 0.008   | 0.158| 0.923| 0.012                     |
| Medial lemniscus, left         |         |      |      |                           |
| Correlation coefficient        | 0.200   | 0.138| −0.048| 0.177                     |
| P value (two-sided)            | 0.032   | 0.141| 0.610| 0.060                     |
| Inferior cerebellar peduncle, right |         |      |      |                           |
| Correlation coefficient        | 0.347   | 0.182| −0.118| 0.316                     |
| P value (two-sided)            | < 0.0007| 0.052| 0.211| 0.001                     |

(Continues)
### TABLE 2 (Continued)

| Anatomical regions                        | BMI  | Age  | Sex   | BMI_adj for age and sex |
|-------------------------------------------|------|------|-------|-------------------------|
| Inferior cerebellar peduncle, left        | 0.176| 0.268| -0.139| 0.120                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | 0.060| 0.004| 0.138 | 0.205                   |
| Superior cerebellar peduncle, right       | 0.152| 0.270| 0.112 | 0.136                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | 0.105| 0.004| 0.234 | 0.151                   |
| Superior cerebellar peduncle, left        | 0.053| 0.281| 0.082 | 0.022                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | 0.571| 0.002| 0.382 | 0.816                   |
| Cerebral peduncle, right                  | 0.197| 0.275| -0.044| 0.156                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | 0.035| 0.003| 0.642 | 0.098                   |
| Superior cerebellar peduncle, left        | 0.111| 0.256| -0.163| 0.049                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | 0.238| 0.006| 0.082 | 0.608                   |
| Anterior limb of internal capsule, right  | 0.305| 0.356| -0.024| 0.270                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | < 0.0007| < 0.0007| 0.161 | 0.002                   |
| Anterior limb of internal capsule, left   | 0.345| 0.309| 0.067 | 0.334                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | < 0.0007| 0.001| 0.478 | < 0.0007§               |
| Posterior limb of internal capsule, right | 0.333| 0.475| -0.283| 0.257                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | < 0.0007| < 0.0007| 0.002 | 0.006                   |
| Retrolenticular part of internal capsule, right | 0.298| 0.384| 0.159 | 0.301                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | 0.001| < 0.0007| 0.090 | 0.001                   |
| Retrolenticular part of internal capsule, left | 0.019| 0.076| -0.172| -0.020                  |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | 0.842| 0.420| 0.067 | 0.833                   |
| Anterior corona radiata, right            | 0.036| 0.369| -0.216| -0.063                  |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | 0.706| < 0.0007| 0.020 | 0.507                   |
| Anterior corona radiata, left             | 0.263| 0.444| -0.057| 0.211                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | 0.005| < 0.0007| 0.547 | 0.025                   |
| Superior corona radiata, right            | 0.133| 0.580| -0.141| 0.023                   |
| Correlation coefficient                   |      |      |       |                         |
| P value (two-sided)                       | 0.156| < 0.0007| 0.132 | 0.806                   |

(Continues)
| Anatomical regions                                      | BMI     | Age     | Sex     | BMIadj for age and sex |
|--------------------------------------------------------|---------|---------|---------|------------------------|
| Superior corona radiata, left                          | 0.137   | 0.582   | -0.228  | 0.011                  |
| Correlation coefficient                                | 0.146   | < 0.0007| 0.014   | 0.910                  |
| P value (two-sided)                                    |         |         |         |                        |
| Posterior corona radiata, right                        | 0.180   | 0.495   | 0.206   | 0.167                  |
| Correlation coefficient                                | 0.054   | < 0.0007| 0.027   | 0.077                  |
| P value (two-sided)                                    |         |         |         |                        |
| Posterior corona radiata, left                         | -0.037  | 0.333   | 0.001   | -0.100                 |
| Correlation coefficient                                | 0.691   | < 0.0007| 0.991   | 0.293                  |
| P value (two-sided)                                    |         |         |         |                        |
| Posterior thalamic radiation, right                    | 0.310   | 0.565   | 0.207   | 0.340                  |
| Correlation coefficient                                | 0.001   | < 0.0007| 0.026   | < 0.0007§              |
| P value (two-sided)                                    |         |         |         |                        |
| Posterior thalamic radiation, left                     | 0.100   | 0.580   | 0.054   | 0.019                  |
| Correlation coefficient                                | 0.288   | < 0.0007| 0.566   | 0.844                  |
| P value (two-sided)                                    |         |         |         |                        |
| Sagittal stratum, right                               | 0.213   | 0.363   | 0.218   | 0.218                  |
| Correlation coefficient                                | 0.022   | < 0.0007| 0.019   | 0.020                  |
| P value (two-sided)                                    |         |         |         |                        |
| Sagittal stratum, left                                | 0.066   | 0.308   | 0.017   | 0.021                  |
| Correlation coefficient                                | 0.481   | 0.001   | 0.856   | 0.826                  |
| P value (two-sided)                                    |         |         |         |                        |
| External capsule, right                                | -0.050  | -0.179  | 0.200   | 0.010                  |
| Correlation coefficient                                | 0.598   | 0.056   | 0.032   | 0.920                  |
| P value (two-sided)                                    |         |         |         |                        |
| External capsule, left                                 | -0.003  | -0.231  | 0.114   | 0.054                  |
| Correlation coefficient                                | 0.974   | 0.013   | 0.226   | 0.568                  |
| P value (two-sided)                                    |         |         |         |                        |
| Cingulum (cingulate gyrus), right                      | 0.030   | 0.048   | -0.044  | 0.016                  |
| Correlation coefficient                                | 0.749   | 0.610   | 0.638   | 0.864                  |
| P value (two-sided)                                    |         |         |         |                        |
| Cingulum (cingulate gyrus), left                       | -0.027  | -0.027  | -0.004  | -0.024                 |
| Correlation coefficient                                | 0.775   | 0.771   | 0.964   | 0.802                  |
| P value (two-sided)                                    |         |         |         |                        |
| Cingulum (hippocampus), right                         | 0.256   | -0.105  | 0.210   | 0.321                  |
| Correlation coefficient                                | 0.006   | 0.264   | 0.025   | 0.001                  |
| P value (two-sided)                                    |         |         |         |                        |
| Cingulum (hippocampus), left                          | 0.005   | -0.153  | -0.050  | 0.024                  |
| Correlation coefficient                                | 0.955   | 0.102   | 0.598   | 0.803                  |
| P value (two-sided)                                    |         |         |         |                        |
| Fornix (cres)/Stria terminalis, right                  | 0.210   | 0.288   | 0.176   | 0.211                  |
| Correlation coefficient                                | 0.024   | 0.002   | 0.060   | 0.025                  |
| P value (two-sided)                                    |         |         |         |                        |
Discussion

Obesity and its associated comorbidities, such as insulin resistance and dyslipidaemia, are known to individually associate with changes in brain structure and function, although the underlying cause of the observed effects remains inconclusive. In the present study, we used whole-brain proton density imaging to quantify brain water content in 115 normal weight, overweight and obese individuals. We found obesity-associated measures to positively correlate with brain water content, mainly in the subcortical and cerebellar regions and the white matter tracts connecting these regions. Individuals with obesity, particularly those with visceral obesity and altered lipid profiles, showed an enhanced water content in spatially discrete brain regions and white matter tracts, including the cerebellum, hypothalamus, striatum, thalamus, fornix, anterior limb of internal capsule and posterior thalamic radiation. In accordance with our hypothesis, the hypothalamus and white matter tracts surrounding the hypothalamus displayed the most prominent alterations in water content. However, our results additionally show that brain inflammation is not restricted to the hypothalamic area and also affects the surrounding brain regions. This coincides with structural MRI studies showing that individuals with obesity and metabolic syndrome exemplify grey matter atrophy primarily in the cerebellum and subcortical regions and show reduced white matter integrity in fibres connecting these regions.

Although the underlying cause still remains elusive, genetic factors, as well as cellular and cerebrovascular mechanisms, contribute to this deteriorating brain health seen in obesity. In this context, inflammation has gained particular notoriety as a potential cellular mechanism leading to neuronal atrophy and compromised white matter integrity. However, inflammation in the brain does not replicate the usual process seen in the periphery with the recruitment of peripheral immune cells. This is largely a result of the presence of

| Anatomical regions                                      | BMI | Age   | Sex | BMIadj for age and sex |
|--------------------------------------------------------|-----|-------|-----|------------------------|
| Fornix (cres)/Stria terminalis, left                   | 0.138 | 0.157 | 0.044 | 0.124                 |
| Correlation coefficient                                | 0.143 | 0.094 | 0.638 | 0.189                 |
| Superior longitudinal fasciculus, right                | 0.214 | 0.100 | −0.064 | 0.195                 |
| Correlation coefficient                                | 0.021 | 0.287 | 0.499 | 0.038                 |
| Superior longitudinal fasciculus, left                 | −0.025 | 0.171 | −0.162 | −0.081                |
| Superior fronto-occipital fasciculus, right            | 0.789 | 0.067 | 0.084 | 0.392                 |
| Superior fronto-occipital fasciculus, left             | 0.177 | 0.650 | −0.091 | 0.080                 |
| Correlation coefficient                                | 0.058 | < 0.0007 | 0.331 | 0.401                 |
| Superior fronto-occipital fasciculus, left             | 0.220 | 0.531 | −0.019 | 0.161                 |
| Correlation coefficient                                | 0.018 | < 0.0007 | 0.838 | 0.089                 |
| Uncinate fasciculus, right                             | −0.262 | −0.413 | 0.249 | −0.182                |
| Correlation coefficient                                | 0.005 | < 0.0007 | 0.007 | 0.054                 |
| Uncinate fasciculus, left                              | −0.112 | −0.307 | 0.198 | −0.036                |
| Correlation coefficient                                | 0.232 | 0.001 | 0.034 | 0.703                 |
| Tapetum, right                                         | 0.169 | 0.429 | 0.228 | 0.164                 |
| Correlation coefficient                                | 0.070 | < 0.0007 | 0.014 | 0.083                 |
| Tapetum, left                                          | 0.075 | 0.381 | 0.163 | 0.044                 |
| Correlation coefficient                                | 0.423 | < 0.0007 | 0.082 | 0.641                 |

Note: Table shows non-parametric correlations using Spearman rho; §partial correlations significant after correcting for number of regions investigated (critical P value of 0.0007).
with local swelling. This can damage the cell by compressing distinct microenvironments.\textsuperscript{18} Quantitative MRI techniques are sensitive with respect to detecting local changes in brain water content,\textsuperscript{18,40} located in multiple tissues, including neurones, axons, myelin sheaths, extracellular space, blood vessels and glial cells. Most abundantly, water diffusion, as assessed by diffusion tensor imaging (DTI) measurements, has been used to evaluate obesity-associated changes in white matter structures. These studies reveal a negative impact of obesity on white matter microstructure regardless of age, particularly in tracts of the limbic system and those connecting temporal and frontal lobes.\textsuperscript{33} However, it is difficult to disentangle the contribution of changes in water and myelin content in DTI metrics. To explore specific brain tissue properties, quantitative MRI techniques are implemented to specifically investigate the contribution of water content to the MRI signal.\textsuperscript{11} Within the white matter, the initial evidence points to an increase in water rather than a decrease myelin in young adults with obesity.\textsuperscript{11} However, very little is known about changes in water content within the grey matter. Thaler et al\textsuperscript{10} were the first to investigate potential hypothalamic inflammation, by means of a measure often implemented in standard diagnostics (ie, $T_2$-relaxation time over a limited field of view). Obese volunteers revealed a hyperintensity (longer $T_2$-relaxation time) in the hypothalamus compared to a control region. The hypothalamic signal significantly correlated positively with BMI, the magnitude of peripheral insulin resistance\textsuperscript{41,42} and systemic low-grade inflammation.\textsuperscript{43} Importantly, MRI postmortem scans and histological staining confirmed that the signal detected by in vivo MRI is a valid surrogate measure for hypothalamic inflammation.\textsuperscript{44} The findings of the present study are in agreement with these previous findings, revealing an increased hypothalamic free water content (higher proton density values compared to the control region) in individuals with obesity independent of age and sex. Moreover, our results show that water content is elevated in subcortical regions and white matter tracts connecting homeostatic and limbic system. Whether brain inflammation is reversible is currently not known. The initial evidence suggests that some aspects of neuroinflammation can be rescued in both humans and rodents.\textsuperscript{35,42} However, it is not known whether this is the result of direct central effects or is caused by decreased peripheral inflammation. Moreover, Kreutzer et al\textsuperscript{45} did not identify this beneficial effect because the hypothalamic signal remained increased after bariatric surgery. It is currently not known which factors contribute to improved gliosis in response to an intervention. It is postulated that metabolic health prior to the intervention plays a critical role, particularly components of the metabolically unhealthy phenotype such as insulin resistance and abdominal obesity.\textsuperscript{42} In the present study, especially metabolically unhealthy individuals show the greatest increase in brain water content, particularly in the hypothalamus and surrounding white matter tracts. Insulin signalling in the brain is blunted in individuals with obesity in similar regions as identified in the present study. Particularly, individuals with central obesity show brain insulin resistance in subcortical regions,\textsuperscript{23,44,45} with negative consequences on peripheral metabolism.\textsuperscript{46-49} Whether brain inflammation contributes to insulin resistance in the brain or vice versa currently remains unknown.

![Figure 3](image-url)
Other proposed mechanisms to explain structural and function changes in obesity include cerebrovascular mechanisms. Core features of the metabolic syndrome, such as insulin resistance and dyslipidaemia, can lead to endothelial dysfunction, along with vascular reactivity and cerebral blood flow. In our present sample, however, we did not observe any changes in regional or global cerebral blood flow in individuals with obesity. This emphasises that it is most likely inflammation, rather than cerebrovascular mechanisms, that led to our current findings.

A limitation of the method used in our cohort was the presence of motion artefacts in MR images, especially in obese patients, as a result of breathing. However, the MR images were visually inspected and the datasets with no visible motion artifacts were selected for the analysis. Because of the cross-sectional design of the study, no cause-effect relationship can be established between obesity and brain inflammation, such that we cannot distinguish between brain inflammation induced by dietary excess or chronic low-grade inflammation; a sequel of obesity and excess adipose tissue. Further longitudinal studies are required to investigate whether this inflammatory process can be manipulated acutely through diet, weight loss and pharmaceutical interventions, with potential benefits for further health.

In conclusion, we postulate that chronic low-grade inflammation, as observed in obesity, metabolic syndrome and diabetes, also affects the brain, which may facilitate further weight gain and brain insulin resistance. In 115 volunteers, we observed an increase in local water content in individuals with obesity. Remarkably, this local increase is specifically found in subcortical regions; further supporting the idea that inflammation in the brain may be a cause of altered brain function and structure.

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**CONFLICT OF INTERESTS**

The authors declare that they have no conflicts of interest.

**PEER REVIEW**

The peer review history for this article is available at https://publon.com/publon/10.1111/jne.12907.

**DATA AVAILABILITY**

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available as a result of privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.