GLP-1 and the neuroendocrine control of feeding in obesity and type 2 diabetes: food for thought

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CHAPTER 7

Alterations in white matter volume and integrity in obesity and type 2 diabetes

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is characterised by obesity, hyperglycaemia and insulin resistance. Both T2DM and obesity are associated with cerebral complications, including an increased risk of cognitive impairment and dementia, however the underlying mechanisms are largely unknown. In the current study, we aimed to determine the relative contributions of obesity and the presence of T2DM to altered white matter structure.

We used diffusion tensor imaging (DTI) and voxel-based morphometry (VBM) to measure white matter integrity and volume in obese T2DM patients without micro- or macrovascular complications, age- gender- and BMI-matched normoglycaemic obese subjects and age- and gender-matched normoglycaemic lean subjects.

We found that obese T2DM patients compared with lean subjects had lower axial diffusivity (in the right corticospinal tract, right inferior fronto-occipital tract, right superior longitudinal fasciculus and right forceps major) and reduced white matter volume (in the right inferior parietal lobe and the left external capsule region). In normoglycaemic obese compared with lean subjects axial diffusivity as well as white matter volume tended to be reduced, whereas there were no significant differences between normoglycaemic obese subjects and T2DM patients. Decreased white matter integrity and volume were univariately related to higher age, being male, higher BMI, HbA1C and fasting glucose and insulin levels. However, multivariate analyses demonstrated that only BMI was independently related to white matter integrity, and age, gender and BMI to white matter volume loss.

Our data indicate that obese T2DM patients have reduced white matter integrity and volume, but that this is largely explained by BMI, rather than T2DM *per se*.

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are major public health problems, not only due to their pandemic occurrence, but also due to their association with adverse consequences, such as cardiovascular disease, cancer and cerebral complications (1;2). T2DM is characterised by hyperglycaemia and obesity-related insulin resistance (3;4). Patients with T2DM are at an increased risk of (vascular) dementia (5), stroke (6), white matter lesions (7) and cognitive impairment (8;9). Furthermore, T2DM is related to loss of grey and white matter volume (10) and to loss of white matter integrity (9). Although less well established, obesity is also associated with brain disease, including an increased risk of dementia and accelerated cognitive decline at older age, with complementary structural brain changes (1;11;12). Both obesity-related insulin resistance and hyperglycaemia seem strong risk factors for cerebral pathology (13).

Studies assessing brain alterations in T2DM usually include a heterogeneous sample of patients in early and more advanced stages of the disease, i.e. with clinically manifest microvascular and cardiovascular complications. It is therefore not yet clear to what extent structural brain changes are present in early stages of T2DM. Imaging studies in obese subjects have likewise included heterogeneous or inadequately characterised samples with regard to glucose tolerance, insulin resistance, and sometimes cardiovascular disease (13).

In the current study, we aimed to determine the relative contributions of obesity and the presence of non-complicated T2DM to altered white matter volume and integrity. We therefore performed voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) in obese T2DM patients, BMI-matched normoglycaemic obese subjects and normoglycaemic lean subjects. We hypothesised that white matter integrity and volume are altered in obese T2DM patients compared with BMI-matched normoglycaemic obese subjects and lean subjects.

METHODS

Participants

This study, part of a larger study (NCT01281228), was approved by the Medical Ethics Committee of the VU University Medical Center and was performed in accordance with the Helsinki Declaration. All participants provided written informed consent before participation. We included 16 obese T2DM patients, 16 obese normoglycaemic and 16 healthy lean individuals. Inclusion and exclusion criteria have been reported previously (14). Briefly, inclusion criteria included right-handedness, BMI >30kg/m^2 for obese individuals and T2DM patients, BMI <25 kg/m^2 for lean controls,

normoglycaemia for obese individuals and lean controls as defined by fasting plasma glucose <5.6mmol/l and 2-hour glucose <7.8mmol/l following a 75g oral glucose tolerance test (OGTT). For T2DM patients, HbA1c had to be 6.0-8.5%. Exclusion criteria included cardiovascular diseases, micro-albuminuria, neurological or psychiatric disorders including depression (assessed by Center for Epidemiologic Studies Depression scale) (15), substance abuse or use of any centrally acting agent. Microalbuminuria was tested by calculating the albumin:creatinine ratio in urine, and was defined as an albumin:creatinine ratio >2.5 for men or >3.5 for women.

Data acquisition

MRI scanning was performed on a 3.0 Tesla GE Signa HDxt scanner (General Electric, Milwaukee, Wisconsin, USA) using an 8-channel phased-array head coil. For this study we used an echo planar imaging based DTI acquisition consisting of 5 volumes without directional weighting and 30 volumes with 30 non-collinear diffusion gradient directions (b-value 1000 s/mm^2, repetition time (TR) 6200 ms, echo time (TE) 81 ms, 45 contiguous axial slices of 2.4mm). Participants furthermore had a T2-based Fluid Attenuating Inverse Recovery (3D-FLAIR; TR 8000 ms, TE 126 ms, slice thickness 1.2mm) and a T1-weighted fast spoiled gradient-echo (TR 8.2 ms, TE 3.2 ms, 1 mm slice thickness) sequence.

DTI tract-based analysis

Processing of DTI-scans was performed using the FMRIB's Diffusion Toolbox of FMRI's Software Library (FSL) version 5.04 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki)(16). First, DTI scans and gradient-vectors were corrected for motion and eddy-current induced distortions (17). Next, the diffusion tensor was calculated for each voxel, providing fractional anisotropy (FA), axial (λ1), radial (mean of λ2 and λ3) and mean diffusivity (mean of λ1, λ2 and λ3) (18;19). Tract-based spatial statistics (TBSS) was used for voxelwise statistical analysis (20). All individual FA images were non-linearly registered to FMRIB58FA standard space, to allow group averaging and comparison. These registered images were then averaged and the mean image was skeletonised, and thresholded at 0.2 to include only white matter. Individual non-linear warps and skeleton projection of FA-images were used to project axial, radial and mean diffusivity to the skeleton and to allow voxelwise statistics. All steps were manually checked, no errors occurred.

VBM analysis

T1-weighted images were visually inspected for motion artefacts. Data preprocessing was performed with Statistical Parametric Mapping 8 software (SPM8; Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). First, structural images were oriented along the anterior/posterior commissure axis and segmented into grey matter, white matter and cerebrospinal fluid with a bias-field correction cut-off of 60 mm full width at half maximum (FWHM). In the next step, DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) was used to create a group-specific grey and white matter template and the individual flow fields. These flow fields contain

the non-linear deformations between each individual's MRI-scan and the DARTEL template. The individual grey and white matter segmentations were registered to MNI standard space using linear affine registration and non-linear deformation using the flow fields. The images were modulated to preserve relative volume and corrected for brain size, in order to allow group comparisons. Lastly, the segmented, modulated and normalised images were smoothed using an 8mm FWHM Gaussian kernel. Both segmentation and normalization results were manually checked, no errors occurred.

White matter lesions

White matter lesions were scored visually by an experienced neuro-radiologist (FB) based on 3D-FLAIR sequence using Fazekas criteria (21).

Statistical analyses

Clinical group data are expressed as mean ± SEM (unless otherwise stated) and were analysed with the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS, Chicago, IL, USA). Between group differences in clinical data, including white matter lesions, were analysed using a one-way ANOVA with Bonferroni post-hoc correction or χ^2-test whether appropriate.

Differences in DTI parameters between groups were analysed with the FSL function "randomise", using threshold-free cluster enhancement non-parametric permutation testing (5000 permutations). Family Wise Error (FWE) was applied as multiple comparisons correction. For the VBM analysis of white matter volume, clusters were considered relevant if at least 150 voxels at $P_{uncorrected} < 0.002$. For these clusters FWE-correction for multiple comparisons was applied. Both the DTI and VBM analyses were corrected for age, gender and systolic blood pressure. A *P*-value <0.05 after FWE-correction was considered statistically significant.

Using FSL the mean value of white matter integrity of voxels differing between groups was extracted. For each subject the mean white matter volume of significant clusters was extracted using MarsBar 0.41 (http://marsbar.sourceforge.net). Using Spearman's ρ the demographical and clinical correlates of altered volume/integrity were determined. These correlations were calculated in all participants. To determine the strongest predictors, variables significantly correlating with volume/integrity, were entered in a forward regression model.

RESULTS

Group demographics

Due to technical problems, DTI scans were not available for 1 lean control and 1 obese subject. All subjects were matched for age and gender, while T2DM patients and normoglycaemic obese subjects were also BMI matched (Table 1). Patients with T2DM had higher systolic blood pressure,

HbA1c, fasting plasma glucose and insulin levels compared with normoglycaemic obese and lean subjects. Total cholesterol and LDL cholesterol levels were lower in T2DM patients compared with obese and lean subjects, whereas HDL cholesterol levels were higher in lean compared with T2DM and obese subjects. Eight T2DM patients were treated with metformin monotherapy and 8 used metformin in combination with a sulphonylurea. Twelve T2DM patients and 3 obese subjects used antihypertensive medication, 13 T2DM patients and 1 obese subject used statins. There were no significant differences in Fazekas score (white matter lesions) between the groups (P = 0.8) (Table 1).

Table 1 | Subject characteristics

	Lean (n=15)	**Obese (n=15)**	**T2DM (n=16)**	**ANOVA P-value**
Age (years)	57.3 ± 1.9	57.7 ± 2.2	61.4 ± 1.5	0.2
Gender, male/female (n)	8/7	8/7	8/8	-
Weight (kg)	71.5 ± 2.9	100.7 ± 3.0*	97.9 ± 3.0*	<0.001
Body mass index (kg/m^2)	23.4 ± 0.4	32.6 ± 0.8*	34.0 ± 0.9*	<0.001
Waist circumference (cm)	85.7 ± 2.1	112.3 ± 2.2*	115.7 ± 1.8*	<0.001
Systolic blood pressure (mmHg)	119 ± 4	127 ± 3	141± 3†	<0.001
Diastolic blood pressure (mmHg)	76 ± 2	79 ± 2	83 ± 2	0.057
Fasting plasma glucose (mmol/l)	5.2 ± 0.1	5.3 ± 0.1	8.4 ± 0.5†	<0.001
Glucose 2h after OGTT (mmol/l)	5.1 ± 0.3	5.4 ± 0.2	-	0.4
HbA1c (%)	5.5 ± 0.03	5.5 ± 0.06	6.9 ± 0.22†	<0.001
HbA1c (mmol/mol)	37 ± 0.3	37 ± 0.7	52 ± 2.4†	<0.001
Total cholesterol (mmol/l)	5.6 ± 0.2	5.6 ± 0.2	4.5 ± 0.3†	0.002
LDL-cholesterol (mmol/l)	3.3 ± 0.2	3.4 ± 0.2	2.3 ± 0.2†	<0.001
HDL-cholesterol (mmol/l)	1.9 ± 0.1	1.4 ± 0.1*	1.3 ± 0.1*	<0.001
Triglycerids (mmol/l)	0.9 ± 0.1	1.7 ± 0.3	1.8 ± 0.3	0.046
Fasting NEFA (mmol/l)	0.46 ± 0.04	0.45 ± 0.03	0.64 ± 0.04†	0.001
Fasting insulin (pmol/l)	36 ± 2.8	81 ± 14	117 ± 17†	<0.001
Diabetes duration (years)	-	-	7.0 [4.25, 10.75]	-
Fazekas score (0; 1; 2; 3)	6; 7; 2; 0	8; 5; 2; 0	5; 9; 2; 0	0.8

Data are means ± SEM or median [interquartile range].
*Statistically significant different from lean (post-hoc Bonferroni corrected P < 0.05)
†Statistically significant different from lean and obese (post-hoc Bonferroni corrected P < 0.05)
OGTT, oral glucose tolerance test; NEFA, non-esterified fatty acids; T2DM, type 2 diabetes patients
Fazekas score for white matter lesions: 0 indicates no lesions; 1 indicates punctate foci; 2 indicates beginning confluence of foci; 3 indicates large confluent areas

White matter integrity

DTI tract-based analyses showed significantly lower axial diffusivity (λ_1) in T2DM patients compared with lean subjects. Tracts most affected were the right corticospinal tract, right inferior fronto-occipital tract, right superior longitudinal fasciculus and right forceps major (Figure 1a). On the left side of the forceps major there was a cluster of voxels where axial diffusivity tended to be lower in subjects with obesity compared with lean controls ($P_{FWE} = 0.1$; Figure 1b). There were no significant differences in FA, mean diffusivity and radial diffusivity between T2DM patients, normoglycaemic obese and lean subjects.

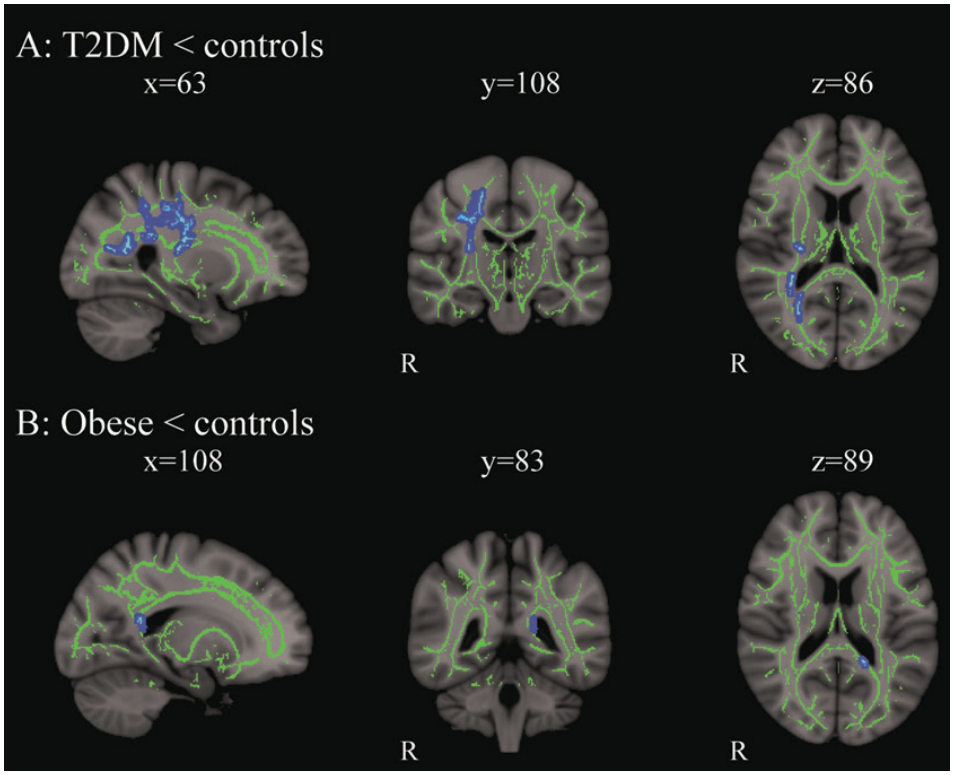

Figure 1 | Changes in axial diffusivity in T2DM patients and obese compared with lean subjects.

A | Brain slices showing decreased axial diffusivity (λ_1) in T2DM patients compared with lean subjects in right corticospinal tract, right inferior fronto-occipital tract, right superior longitudinal fasciculus and right forceps major;

B | Brain slices showing a cluster of voxels on the left side of the forceps major where axial diffusivity tended to be lower in subjects with obesity compared with controls ($P_{FWE} = 0.11$).

The mean skeleton is shown in green, and significant differences are displayed as thickened tracts in blue for visualization purposes. Left side of the axial slices is the right side of the brain. X, y, z are the Montreal Neurological Institute (MNI) coordinates of the brain in standard space.

White matter volume

VBM analyses demonstrated significantly lower white matter volume in T2DM patients relative to lean control subjects in a left hemisphere cluster comprising predominantly the external capsule region. Another cluster of lower white matter volume in T2DM patients versus lean control subjects was found in the right inferior parietal lobe (Figure 2a; Table 2).

In normoglycaemic obese compared with lean subjects, lower white matter volume was found in the left external capsule region as well (Figure 2b; Table 2), although this cluster was smaller than the cluster found in T2DM patients. In addition, this cluster was not statistically significant after FWE-correction for multiple comparisons (P_{FWE}=0.380). No differences were identified in the comparison between normoglycaemic obese subjects and T2DM patients.

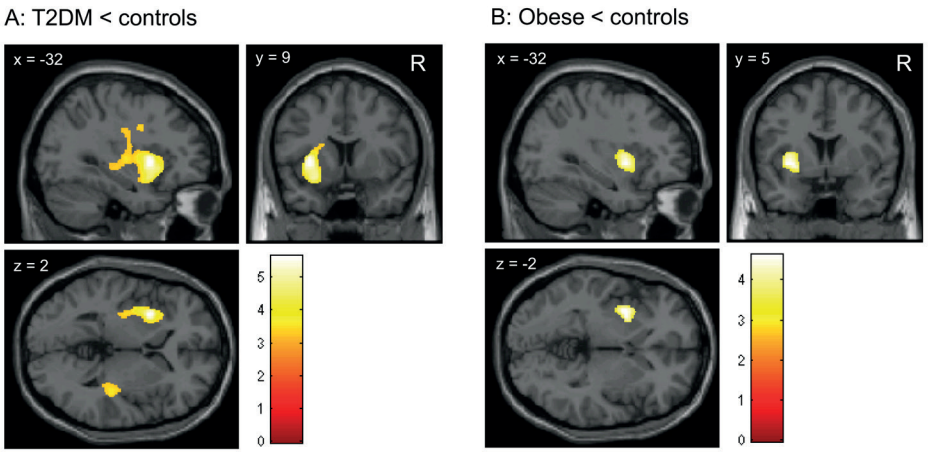

Figure 2 | Reduced white matter volume in T2DM patients compared with lean subjects.

A | Brain slices showing clusters of reduced white matter volume in the external capsule region in obese T2DM patients compared with lean subjects, as determined with VBM;

B | Brain slices showing a cluster of reduced white matter volume in the external capsule region in obese compared with lean subjects. This cluster, however, was not statistically significant after FWE-correction for multiple comparisons (P_{FWE}=0.380).

The colour scale reflects the T-value. Right side of the axial slices is the right side of the brain. X, y, z are the Montreal Neurological Institute (MNI) coordinates of the brain in standard space.

Associations between white matter parameters and biomedical variables

For each subject the mean axial diffusivity value was extracted for the significant voxels in the comparison between T2DM patients and lean controls. The same was done for white matter volume of the two VBM clusters that reached statistical significance when comparing T2DM patients with lean control subjects. With these values correlations with demographic and clinical characteristics were calculated in the overall group. As can be found in Table 3, univariate correlations of lower axial diffusivity with higher BMI, fasting plasma glucose, fasting insulin levels and HbA1c were

Table 2 | Between-group differences in white matter volume

	Region	Side	Cluster	T	$P-_{uncorr}$	$P-_{FWE}$	MNI coordinates (x, y, z)
T2DM < Lean	External capsule	L	5735	5.64	<0.001	<0.001	-32,9,2
				4.99	<0.001	<0.001	-27,8,-13
				4.03	<0.001	<0.001	17,-16,33
	Inferior Parietal Lobe	R	3276	4.69	<0.001	<0.001	45,-42,54
				4.49	<0.001	<0.001	47,-31,30
				4.48	<0.001	<0.001	39,-12,36
Obese < Lean	External capsule	L	903	4.62	<0.001	0.380	-32,5,-1

T, t-statistic; $P-_{FWE}$, p-value Family-Wise Error corrected for multiple comparisons; R, right; L, left; MNI, Montreal Neurological Institute coordinates in mm

significant. Of these variables, higher BMI was the only independent predictor of lower axial diffusivity (β=-0.48; P=0.001), which explained 21% of the variance. Lower white matter volume in the left external capsule cluster was univariately related to higher age, BMI, fasting plasma glucose and insulin levels, HbA1c, and being male. Being male (β=0.432; P<0.001), higher BMI (β=-0.353; P=0.002) and higher age (β=-0.342; P=0.003) were independently related with lower white matter volume in this cluster. This model explained 47% of the variance of white matter volume differences in this cluster. Similar univariate correlations were found for the cluster of lower white matter volume in the right inferior parietal lobe, with the exception of fasting plasma glucose (Table 2). Independent predictors were gender (being male; β=0.449; P<0.001), higher age (β=-0.345; P=0.004), and higher BMI (β=-0.284; P=0.016), together explaining 44% of the variance.

Table 3 | Associations between white matter parameters and demographic and clinical characteristics

	Axial diffusivity *		White matter volume cluster L**		White matter volume cluster R**	
	Spearman's rho	P-value	Spearman's rho	P-value	Spearman's rho	P-value
Age	-0.09	0.573	-0.34	0.021	-0.30	0.041
Gender	0.27	0.069	0.52	<0.001	0.54	<0.001
BMI	-0.47	0.001	-0.55	<0.001	-0.43	0.003
Fasting glucose	-0.45	0.002	-0.31	0.035	-0.24	0.10
Fasting insulin	-0.44	0.002	-0.40	0.006	-0.30	0.040
HbA1c	-0.38	0.008	-0.42	0.004	-0.38	0.010

* Mean axial diffusivity value for the significant voxels in the comparison between T2DM patients and lean controls. **Mean white matter volume of the two significant VBM clusters in the comparison between T2DM patients and lean controls. With these values correlations with biomedical variables were calculated in all subjects (lean, obese and T2DM).

DISCUSSION

In the current study we showed that both white matter integrity, as measured by axial diffusivity, and white matter volume are decreased in obese T2DM patients compared with lean subjects. In normoglycaemic obese compared with lean subjects axial diffusivity as well as white matter volume tended to be reduced, whereas there were no significant differences between normoglycaemic obese subjects and T2DM patients. Higher BMI independently predicted decreased white matter integrity, and, together with higher age and being male, it predicted lower white matter volume as well. Higher HbA1C, fasting plasma glucose and insulin levels were no independent predictors of decreased white matter volume and integrity.

Using DTI, we found that obese T2DM patients compared with lean subjects have lower axial diffusivity in the right corticospinal tract, right inferior fronto-occipital tract, right superior longitudinal fasciculus and right forceps major. Our findings are in line with previous studies showing lower axial diffusivity in type 1 diabetes patients with and without microvascular complications in comparable tracts (22) and in T2DM patients (23), although the latter study only observed a trendwise reduced axial diffusivity in the cingulum bundle. In the current study, we combined DTI with VBM of white matter and found that T2DM patients have reduced white matter volume in the right inferior parietal lobe and the left external capsule region. A previous study in a large cohort of T2DM patients (of which 24% had known cardiovascular and 11% cerebrovascular complications), also demonstrated white matter loss in T2DM, but mainly in frontal and temporal regions (10). In addition, in obese adolescents with T2DM versus BMI-matched non-diabetic subjects, reduced frontal and whole brain white matter volume has been demonstrated, paralleled by reductions in cognitive performance (24).

To determine the relative contributions of obesity and T2DM to structural brain changes, we also studied normoglycaemic obese subjects (BMI-matched with the T2DM patients). We found in normoglycaemic obese compared with lean subjects reduced axial diffusivity, as well as reduced white matter volume, but these differences in white matter integrity and volume were only trendwise significant after strict FWE-correction for multiple comparisons. It could be speculated that obesity is associated with early white matter alterations and that hyperglycaemia may further impact brain white matter structure. However, in the current study we found no significant differences between obese T2DM patients and obese normoglycaemic subjects in white matter structure.

Relating our findings of localised lower white matter volume and integrity to specific functions is not straightforward given the complexity of brain networks. However, it is well known that the corticospinal tracts have a major role in motor coordination, whereas the forceps major and

parietal cortices have been related to the transfer and processing of somatosensory information. In a previous study in T2DM patients white matter integrity of the inferior longitudinal fasciculus has been related to cognitive functioning, mainly information processing speed (25). Similar correlations between the inferior fronto-occipital tract and cognition were found in type 1 diabetes patients (22). Our finding of reduced white matter volume in the external capsule region in obese T2DM patients furthermore corroborates previous findings of white matter alterations in the external capsule in obese versus lean women (26). The external capsule connects medial and ventral prefrontal cortices with limbic regions, contains fibres from both the inferior fronto-occipital fasciculus and uncinate fasciculus, and connects the hippocampus and amygdala with prefrontal and OFC regions (26;27). Future studies are needed to better understand the consequences of the observed changes in white matter volume and integrity in our study.

We did not observe any differences in FA or any of the other diffusion tensor parameters. Previous studies have shown alterations in FA or mean and radial diffusivity in T2DM (23;25;28). In the current study we only observed reduced axial diffusivity in T2DM patients. The biological substrate of axial diffusivity has mainly been derived from animal studies, and therefore careful interpretation is required. These animal studies, however, suggest that changes in axial diffusivity may represent changes in integrity of axons (29;30). This could result from a less favorable alignment of fibres within the bundle, but it could also represent damage to the axons themselves. In a mouse model of multiple sclerosis it was demonstrated that greater decreases in axial diffusivity were associated with greater amounts of axonal damage and with more neurological disability (31). Further studies are needed to determine the clinical relevance of loss of axial diffusivity in T2DM patients.

In the overall group we found univariate correlations between altered white matter integrity and volume, age, being male, BMI, and fasting glucose and insulin levels. These correlations suggest that hyperglycaemia and insulin-resistance partly relate to obesity/T2DM related cerebral alterations. However, in a multivariate model only BMI was related to white matter integrity, and age, gender and BMI to white matter volume loss. The association between higher BMI and lower white matter volume is in line with a previous study in elderly subjects (32).

A strength of this study is that groups were well-phenotyped as we only included patients with non-complicated T2DM, BMI-matched normoglycaemic subjects and healthy lean subjects. A limitation of our study is the relatively small sample size, limiting the power to detect significant differences between the groups. However, despite the small sample size we observed significant differences between T2DM patients and lean subjects in measures of white matter tract integrity and white matter volume. Another limitation of the current study is that measurements of cognitive functions were not performed. Previous studies have demonstrated associations between reduced white matter volume/integrity and cognitive functions in T2DM as well as

in obesity (1;10;23;25;33). Reduced white matter integrity and volume may play a key role in obesity- and T2DM-related cognitive impairment (1).

In conclusion, we found that both white matter integrity and white matter volume are focally decreased in obese patients with non-complicated T2DM compared with lean subjects. In normoglycaemic obese compared with lean subjects axial diffusivity as well as white matter volume only tended to be reduced. Higher BMI was an independent predictor of decreased white matter integrity as well as white matter volume. Our data indicate that obese T2DM patients have reduced white matter integrity and volume, but that this is largely explained by BMI, rather than the presence of T2DM *per se*.

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