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RESEARCH ARTICLE

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Brain alterations in regions associated with end-organ diabetic microvascular disease in diabetes mellitus: A UK Biobank study

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Abstract

Background: Diabetes mellitus (DM) is associated with structural grey matter alterations in the brain, including changes in the somatosensory and pain processing regions seen in association with diabetic peripheral neuropathy. In this case-controlled biobank study, we aimed to ascertain differences in grey and white matter anatomy in people with DM compared with non-diabetic controls (NDC).

Methods: This study utilises the UK Biobank prospective, population-based, multi-centre study of UK residents. Participants with diabetes and age/gender-matched controls without diabetes were selected in a three-to-one ratio. We excluded people with underlying neurological/neurodegenerative disease. Whole brain, cortical, and subcortical volumes (188 regions) were compared between participants with diabetes against NDC corrected for age, sex, and intracranial volume using univariate

regression models, with adjustment for multiple comparisons. Diffusion tensor imaging analysis of fractional anisotropy (FA) was performed along the length of 50 white matter tracts.

Results: We included 2404 eligible participants who underwent brain magnetic resonance imaging (NDC, $n = 1803$ and DM, $n = 601$). Participants with DM had a mean (±standard deviation) diagnostic duration of 18 ± 11 years, with adequate glycaemic control ($HbA1_C$ 52 ± 13 mmol/mol), low prevalence of microvascular complications (diabetic retinopathy prevalence, 5.8%), comparable cognitive function to controls but greater self-reported pain. Univariate volumetric analyses revealed significant reductions in grey matter volume (whole brain, total, and subcortical grey matter), with mean percentage differences ranging from 2.2% to 7% in people with DM relative to NDC (all $p < 0.0002$). The subcortical (bilateral cerebellar cortex, brainstem, thalamus, central corpus callosum, putamen, and pallidum) and cortical regions linked to sensorimotor (bilateral superior frontal, middle frontal, precentral, and postcentral gyri) and visual functions (bilateral middle and superior occipital gyri), all had lower grey matter volumes in people with DM relative to NDC. People with DM had significantly reduced FA along the length of the thalamocortical radiations, thalamostriatal projections, and commissural fibres of the corpus callosum (all; $p < 0{\cdot}001$).

Interpretation: This analysis suggests that anatomic differences in brain regions are present in a cohort with adequately controlled glycaemia without prevalent microvascular disease when compared with volunteers without diabetes. We hypothesise that these differences may predate overt end-organ damage and complications such as diabetic neuropathy and retinopathy. Central nervous system alterations/neuroplasticity may occur early in the natural history of microvascular complications; therefore, brain imaging should be considered in future mechanistic and interventional studies of DM.

KEYWORDS
brain volumetry, diabetes, diabetic peripheral neuropathy, magnetic resonance imaging, painful diabetic neuropathy

1 | INTRODUCTION

The global prevalence of diabetes is estimated to increase by 46% from ~537 million people in 2021 to >783 million people by 2045.[1] The economic cost of diabetes increased by 26% from 2012 to 2017, primarily due to the growing prevalence of complications in an ageing population.[2] Long term microvascular complications of diabetes include kidney disease, retinopathy, and peripheral neuropathy.[3] The central nervous system has also demonstrated end-organ damage.[4,5] Recently published longitudinal data have shown accelerated cognitive decline in a large cohort of deeply phenotyped participants with diabetes.[6] Cognitive deficits in psychomotor and mental efficiency domains equivalent to an additional 9·4 years of ageing are present in late-middle age people with diabetes.[6] Indeed, there is strong evidence of the association of cognitive decrements with diabetes-related cerebral small vessel disease and cerebral atrophy.[7] Longitudinal studies have also demonstrated global grey matter reductions accompanied by the expansion of the lateral ventricles synonymous with a neurodegenerative process.[8] In both type 1 (T1D) and type 2 (T2D) diabetes, regional reductions in volume have been identified in cortical brain regions of the frontal, posterior and temporal lobes, and also sub-cortical structures.[9]

The microvascular complications of diabetes are associated with structural alterations in the central nervous system, notably affecting the functional connectivity of key brain networks. These include the default-mode network, a group of brain regions active during self-referential thoughts and internal monologue; the visual network, responsible for processing visual information; and the salience network, which is implicated in the integration of sensory and emotional stimuli as well as internal and externally directed

cognition.[10] The presence and severity of retinopathy in people with T2D is associated with decreased grey matter volume and a higher incidence of white matter abnormalities.[11] Sink and colleagues[12] demonstrated a relationship of T2D with diabetic kidney disease to cerebral atrophic changes and a greater white matter lesion volume. Further, volumetric grey matter reductions occur in regions associated with sensorimotor function in diabetic peripheral neuropathy.[13] Previous data have demonstrated significant anatomic and functional changes in the somatosensory cortex, including reductions in cortical thickness and expansion of the homuncular area of the lower limb to include regions which represent the face and lip.[4] These alterations in regions associated with sensory and motor functions have implications for the understanding of the natural history of microvascular complications.

Over the last decade, studies using diffusion magnetic resonance imaging (MRI) in people with diabetes have shown decreased white matter integrity and network disorganisation in white matter pathways.[14] Alterations in fractional anisotropy (FA), a scalar metric of diffusion tensor imaging (DTI), indicate microstructural abnormalities in people with diabetes, frequently found in the frontal, temporal, and parietal lobes, corpus callosum, cingulum, uncinate fasciculus, corona radiata, and internal and external capsules.[15] These alterations are particularly prominent in white matter tracts associated with sensorimotor functions in people with diabetic peripheral neuropathy.[13] To our knowledge a large community-based cohort of people with diabetes has not yet been analysed for differences in grey matter volume and white matter tracts. This study aims to investigate grey matter volumetric and microstructural white matter alterations in a large prospective community-based cohort of comprehensively phenotyped people with diabetes, in comparison to a control cohort without diabetes.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design

Between 2006 and 2010, 502,490 participants aged between 40 and 69 years, from a variety of settings, attended one of 22 UK assessment centres.[16] The initial visit comprised of self-reported outcomes from touch-screen questionnaires, physical measures, and blood tests. Of the 502,490 participants who attended the baseline visit, 221,320 were invited to take part in a follow-up imaging visit. Excluding those who did not respond to the invitation and those contraindicated for MRI, 48,712 participants attended an imaging visit at the time of data release.[17] The UK Biobank is a national epidemiological resource, with the protocol available here: https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf.

This biobank study obtained data release from all 502,490 UK Biobank participants. Within this dataset, we identified 26,402 participants with ICD-10 codes for Diabetes mellitus (DM) (Figure 1). Participants with ICD-10 codes for DM must also have answered "Yes" to having had diabetes diagnosed by a doctor. Before exclusions, there were 19,227 (15,748 type two and 3479 type one) eligible participants with diabetes. Five participants with diabetes who withdrew their consent were removed before matching. Control participants without diabetes were selected from the study population if they had no ICD-10 codes associated with their unique electronic identifier and had answered "No" to diabetes having been diagnosed by a doctor (n = 89,448). Optmatch[18] was used to identify unique participant identifiers of non-diabetic controls that were most similar (partial matching) using the default parameters of the 'pairmatch' argument to individuals with diabetes matched by age and sex at baseline at a 1:1 ratio, giving a combined total of 38,444 participants.

Unique participant identifiers were tracked against ICD-10 codes, and participants with ineligible diagnoses were excluded (Table S1). The ICD-10 codes for participants with T1D and T2D, which encode diabetes associated microvascular complications (e.g., "E102", "E103", "E112"), were tabulated for all participants at baseline and at follow-up. The ICD-10 codes pertaining to diabetes-associated retinopathy, nephropathy, and hypoglycaemia were consolidated to calculate the overall frequency and percentage of each condition. There were subsequently 601 participants with diabetes with MRI-derived grey matter volume data. Control participants without diabetes with complete MRI-derived grey matter data were matched using Optmatch by age and sex at a ratio of three-to-one (n = 1803). The ICD-10 codes of the included participants were listed by frequency at the imaging visit (Table S2). Participants provided full informed consent to participate in the UK Biobank. The UK Biobank received a favourable ethical opinion 17 June 2011 from the National Health Service Research Ethics Service (Ref 11/NW/0382).

2.2 | Cognitive tests

Data from the following cognitive tests were extracted: Trail-Making, Symbol Digit Substitution Pair Matching, Fluid Intelligence and Numeric Memory. A summary of each test is detailed in the supplementary appendix. The baseline cognitive data were collected using an unsupervised touchscreen interface.

2.3 | Pain measures

Participants remotely completed a questionnaire on the location, nature and impact of their pain. We utilised replies to questions about 'General pain in the last 3 months' and 'Pain types experienced in the last month'. The pain questionnaire is available here: https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/pain_questionnaire.pdf.

2.4 | Brain imaging and analysis

All brain MRI data from 2015 onwards were acquired using a Siemens Skyra 3 T scanner with a Siemens 32-channel head coil.

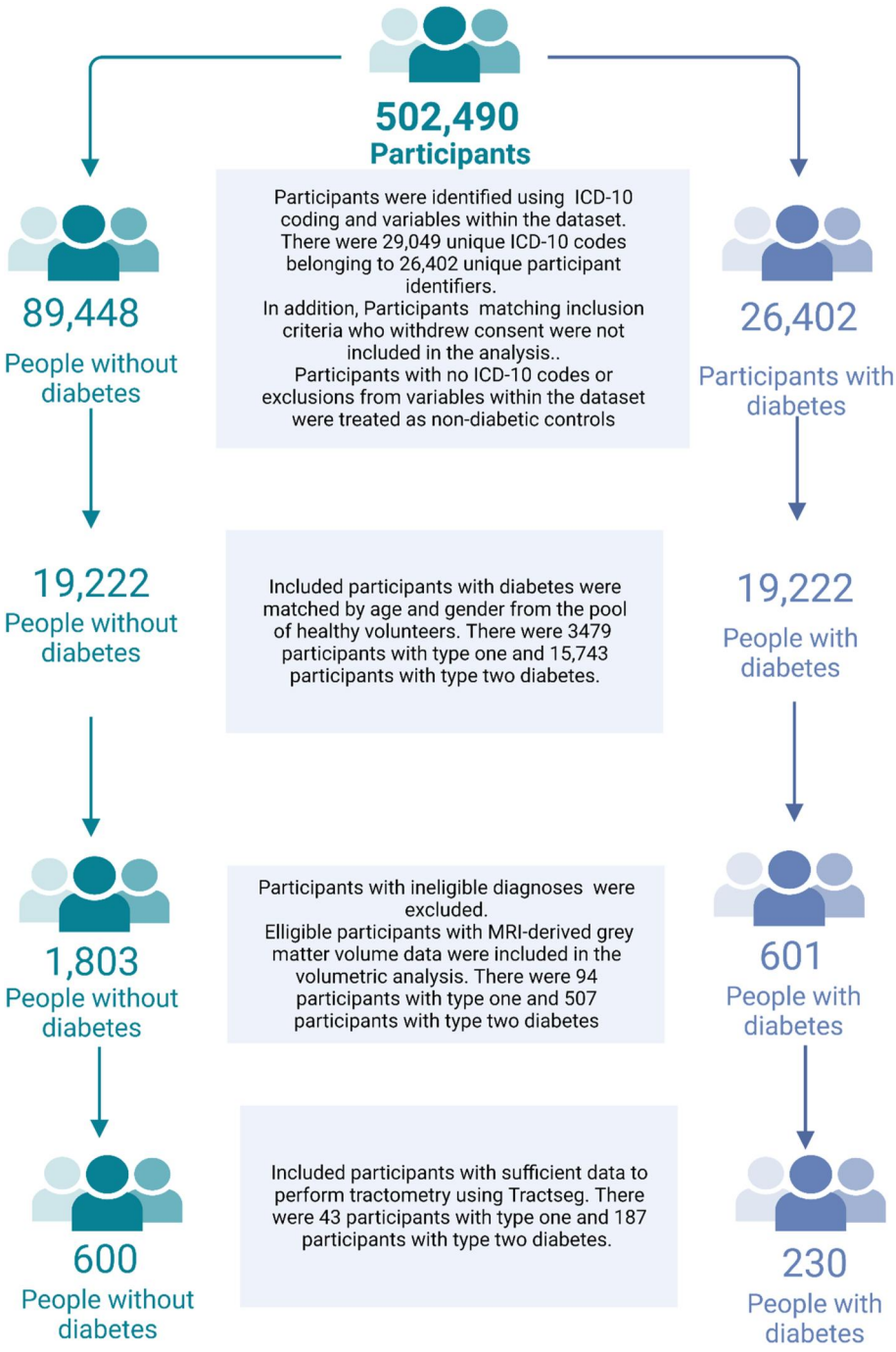

FIGURE 1 Flow chart showing the process of participant selection and inclusion for each step of participant selection, matching by age and sex, and participant numbers within each analysis. Created with BioRender.com.

Volumetric whole brain and regional MRI data were generated by the UK Biobank Oxford Biomedical Research Computing team. For cortical and subcortical grey matter volume analysis, Freesurfer software (version 6.0; https://surfer.nmr.mgh.harvard.edu/) was used, utilising both the ASEG Atlas and a2009s Destrieux Atlas for detailed brain parcellations. Automated white matter tract segmentation was performed using TractSeg[19] (https://github.com/MIC-DKFZ/TractSeg), which segments the original fibre orientation distribution function peaks into tract orientation maps.[20] These maps allow for 'along-tract' comparisons, assessing FA at 100 equidistant points within each segmented white matter tract. This enabled a detailed analysis of FA variations along each tract, which contrasts with other methods such as tract-based spatial statistics (TBSS), as it facilitates the localised examination of FA along tracts. Visual representations of diffusion models for each tract were generated to highlight significant group differences. Further details on brain imaging acquisition and analysis are available in the supplementary appendix.

3 | STATISTICAL ANALYSIS

All data analyses were conducted by *R* software (*R* Foundation, *R* version 4·0·2). Descriptive analysis is provided for the baseline and imaging visit demographic, clinical, cognitive and pain variables. Continuous variables within the dataset are summarised as group mean and standard deviation. Categorical variables are presented as frequencies and percentage. Prior to statistical analysis, continuous volumetric variables were assessed for normality by relevant plots and statistical tests. For the volumetric analysis, separate individual multiple linear regression models were fitted for each brain region with age, sex, and intra-cranial volume as co-variates to identify regions of interest which were significantly different between participants with diabetes and non-diabetic controls. In this study, we opted for multiple linear regression over the more typical analysis of covariance to directly discern the direction and magnitude of volumetric changes in specific brain regions. The threshold of significance for each individual test was calculated as 0·05 divided by the number of included brain regions (n = 188). Therefore, a threshold of significance was applied of <0·00026 after Bonferroni correction. A less conservative approach was also applied using a threshold of significance of <0·05 after false discovery rate correction (equivalent to the Benjamini–Hochberg procedure[21]) to mitigate the likelihood of type one error. The mean percentage difference was calculated, for every region, by subtracting the uncorrected mean brain volume between the two groups and dividing by the first group's mean value (people with diabetes) and expressing this value as a percentage. Tractseg[19] was used for tractometry analysis of DTI data. The alpha family wise error measurement represents the p-threshold after accounting for multiple along-tract comparisons with age and sex as covariates.

4 | RESULTS

4.1 | Baseline characteristics: Descriptive analysis

4.1.1 | Baseline demographic, anthropometric and clinical measures

Of the 502,490 participants who took part in the UK Biobank project, 38,444 participants were included in the group summary of cognitive function and pain measures as detailed in Figure 1. The total number of complete data entries for each demographic and metabolic variable at baseline is shown in table S3. The demographic and metabolic measures are summarised in Table 1. Similar summary values in age, sex, or blood pressure were observed between the two groups. Participants with diabetes had a greater waist circumference and increased body mass index (BMI), triglycerides, glucose, and glycated haemoglobin (HbA1c) but lower high-density lipoprotein (HDL) and low-density lipoprotein (LDL). In the diabetic group, the mean (± standard deviation) duration of known diabetes was 11 ± 14 years at baseline. Participants with DM at baseline were associated with ICD-10 codes for renal and ophthalmic complications in 2.6% and 13.2% of cases, respectively, and episodes of hypoglycaemia were recorded in 6%. The demographic composition differed between the groups; there were fewer White individuals in the DM group compared to the non-diabetic controls (NDC) group, and higher proportions of Asian

TABLE 1 Baseline anthropometric, clinical and demographic measures of non-diabetic control participants with people with diabetes.

Characteristic	Controls N = 19,222[a]	Diabetes N = 19,222[a]
Age	60 (7)	60 (6.9)
Sex (Male)	11,904 (61.9)	11,979 (62.3)
Systolic blood pressure (mmHg)	144.5 (20.2)	143.5 (18.8)
Diastolic blood pressure (mmHg)	83.5 (10.6)	80.8 (10.5)
Body mass index (kg/m^2)	26.7 (4)	31.7 (6)
Waist circumference (cm)	90.5 (12.2)	103.8 (14.5)
Diabetes duration (Years)	0 (0)	11 (13.8)
Triglycerides (mmol/L)	1.7 (1)	2.1 (1.2)
Cholesterol (mmol/L)	5.8 (1.1)	4.4 (1)
HDL cholesterol (mmol/L)	1.5 (0.4)	1.2 (0.3)
LDL cholesterol (mmol/L)	3.7 (0.8)	2.6 (0.7)
Glucose (mmol/L)	5 (0.8)	7.7 (3.5)
Hb_{A1C} (mmol/L)	35.4 (4.4)	54.1 (14.1)
C-reactive protein (mg/L)	2.2 (3.6)	3.7 (5.5)

[a]Mean (SD); *n* (%).

Abbreviations: HbA1C, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

TABLE 2 Baseline cognitive function and pain outcomes comparing non-diabetic control participants with people with diabetes.

Characteristic	Controls *N* = 19,222[a]	Diabetes *N* = 19,222[a]
Cognitive measures		
Pairs matching —Time to complete round (dS)	14,257.1 (12,190)	14,358.6 (11,717.2)
Pairs matching—Number of incorrect matches (*n*)	0.8 (1.6)	0.9 (1.5)
Trail making—Time to complete numeric path (*S*)	39.8 (14.6)	42.9 (16.6)
Trail making—Total errors during numeric path (*n*)	3.6 (7)	3.8 (8.4)
Trail making—Time to complete alpha numeric path (*S*)	68.4 (25.9)	76.6 (30.2)
Trail making—Total errors during alpha numeric path (*n*)	3.3 (4.9)	3.5 (6.1)
Numeric memory—Number of symbol digit matches made correctly (*n*)	19.1 (5)	17.4 (5.2)
Numeric memory—Maximum digits remembered correctly	7 (1.5)	6.6 (1.6)
Fluid intelligence score	6.6 (2.1)	5.9 (2.1)
Pain measures		
General pain in the last 3 Months		
Yes	55 (54)	790 (87)
No	46 (45)	115 (12)
Pain types experienced in the last month		
None	10,086 (52.6)	5663 (29.5)
Headache	2592 (13.5)	3390 (17.7)
Facial pain	82 (0.4)	152 (0.8)
Neck or shoulder pain	2339 (12.2)	3891 (20.3)
Back pain	2129 (11.1)	2613 (13.6)
Stomach or abdominal pain	232 (1.2)	483 (2.5)
Hip pain	390 (2)	714 (3.7)
Knee pain	1236 (6.4)	1342 (7)
Pain all over the body	103 (0.5)	918 (4.8)

[a]Mean (SD); *n* (%).

Abbreviations: dS, decisecond; n, number; S, second.

or Asian British, Black, Black British, Caribbean, or African, Mixed or Multiple Ethnic Groups, and Other Ethnic Groups in the DM group.

4.1.2 | Baseline visit cognitive measures

There were differences between the cognitive scores of participants with diabetes and controls without diabetes, as seen in Table 2. Participants with diabetes took relatively longer on both the numeric and alphanumeric trail exercises, although there were no differences seen in the number of errors made. Furthermore, the symbol digit, numeric memory and fluid intelligence scores were marginally lower in participants with diabetes relative to controls. No differences were likely in the pairs matching exercise in either time to complete the round or the number of incorrect matches. The total number of complete data entries for each of the cognitive measure is shown table S4.

4.1.3 | Baseline visit pain measures

There was a greater proportion of participants with diabetes who reported general pain in the last 3 months, as shown in Table 2. There tended to be a greater proportion of participants with diabetes who reported pain in the last month, particularly due to headache, and locations such as the neck, stomach, and hip compared to controls without diabetes. A greater proportion of participants with diabetes reported pain all over the body in the last month relative to non-diabetic controls. The total number of complete data entries of the pain questionnaire is shown in table S5.

TABLE 3 Anthropometric, clinical and demographic measures comparing non-diabetic control participants with people with diabetes who attended the imaging visit.

Characteristic	Controls *N* = 1,803[a]	Diabetes *N* = 601[a]
Age (Years)	67.5 (6.8)	67 (6.8)
Sex (Male)	1242 (67%)	415 (66%)
Systolic blood pressure(mmHg)	144.7 (19.8)	144.2 (18.2)
Diastolic blood pressure(mmHg)	79.1 (10.7)	76.5 (10.1)
Body mass index (kg/m^2)	26 (3.8)	29.6 (5.1)
Waist circumference (cm)	89.1 (11.4)	99.2 (13.6)
Right handed	1636 (88%)	555 (89%)
Diabetes duration (Years)	0 (0)	17.6 (10.6)
Triglycerides (mmol/L)	1.7 (0.9)	2 (1.2)
Cholesterol (mmol/L)	5.8 (1)	4.4 (1)
HDL cholesterol (mmol/L)	1.5 (0.4)	1.2 (0.3)
LDL cholesterol (mmol/L)	3.7 (0.8)	2.6 (0.7)
Glucose (mmol/L)	5 (0.6)	7.6 (3.4)
Hb_{A1C} (mmol/L)	34.9 (3.7)	51.9 (12.6)
C-reactive protein (mg/L)	1.8 (2.6)	2.8 (4.2)

[a]Mean (SD); *n* (%).

Abbreviations: HbA1C, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

4.1.4 | Demographic, anthropometric and clinical measures in the magnetic resonance imaging subgroup

Of the included 19,222 participants with DM, 601 (T1D = 94; T2D = 507) had complete volumetric data from structural MRI scans, with Freesurfer segmentations as shown in Figure 1. Volumetric data from non-diabetic controls were matched at a ratio of 3:1 to participants with DM and complete volumetric data ($n = 1803$). The total number of complete data entries for each demographic and metabolic variable at the imaging visit is shown in Table S6. The cumulative demographic and metabolic measures of the participants who completed the MRI visit are summarised in Table 3. As expected by design, there was no difference in age or sex between the two groups. The mean ($\pm$ standard deviation) duration of known diabetes was 18 $\pm$ 11 years at the imaging visit. Compared to the control group, participants with diabetes had differences in BMI, waist circumference, triglycerides, cholesterol, HDL, LDL, glucose, C-reactive protein, and HbA1c. As expected, there was a longer mean $\pm$ SD duration of DM in participants with T1D compared with T2D (T1D 28 $\pm$ 14 vs. T2D 16 $\pm$ 9 years), as shown in Table S7. A frequency table of common medications prescribed to participants with diabetes is shown in Table S8. Participants with DM at the imaging visit were associated with ICD-10 codes for renal and ophthalmic complications in 0.2% and 5.8% of cases, respectively, and episodes of hypoglycaemia were recorded in 2.3%. The demographic compositions differed; the NDC group had a higher proportion of White individuals compared with the DM group. The DM group had higher proportions of Asian or Asian British, Black, Black British, Caribbean or African, and Other Ethnic Groups, with both groups having an equal representation of Mixed or Multiple Ethnic Groups.

4.1.5 | Imaging visit cognitive measures and pain measures

No differences were seen in any of the cognitive measures, as shown in Table 4. There tended to be a greater proportion of participants with diabetes who reported pain in the last month since attending the research visit, particularly due to headache, and locations such as the back, stomach, hip, and knee in the last month. Furthermore, a greater proportion of participants with diabetes reported pain all over the body in the last month relative to non-diabetic controls. There were no differences found in either cognitive or pain measures between T1D and T2D, as shown in Tables S9 and S10.

4.2 | Grey matter volumetric analysis

There was a reduction in the whole brain, subcortical grey matter, and total grey matter volume in people with diabetes (all $p < 0{\cdot}0002$) relative to controls, as seen in Table 5. Figure 2 illustrates an increase in the volume of the third, fourth and lateral ventricles bilaterally using the subcortical segmentation analysis (all $p < 0{\cdot}0002$). Decreased volume was observed bilaterally in the basal ganglia, thalami, cerebellum (both grey and white matter), central and mid-anterior corpus callosum in the diabetic group relative to non-

TABLE 4 Cognitive function and pain outcomes comparing non-diabetic control participants with people with diabetes who attended the imaging visit.

Characteristic	Controls $N = 1,803$[a]	Diabetes $N = 601$[a]
Cognitive measures		
Pairs matching—Time to complete round (dS)	13,030.1 (11,163.3)	12,033.9 (9198.5)
Pairs matching—Number of incorrect matches (*n*)	0.7 (1.2)	0.7 (1.4)
Trail making—Time to complete numeric path (*S*)	38.5 (13.5)	38.9 (12.9)
Trail making—Total errors during numeric path (*n*)	3.8 (8)	2.8 (3)
Trail making – Time to complete alpha numeric path (*S*)	65.5 (22.9)	68.2 (25.1)
Trail making—Total errors during alpha numeric path (*n*)	3.2 (4.1)	2.9 (3.2)
Numeric memory—Number of symbol digit matches made correctly (*n*)	19.7 (4.7)	18.6 (5.1)
Numeric memory—Maximum digits remembered correctly	7.1 (1.5)	6.7 (1.6)
Fluid intelligence score	6.8 (2.1)	6.5 (2)
Pain measures		
Pain types experienced in the last month		
None	1116 (60.1)	241 (38.6)
Headache	134 (7.2)	63 (10.1)
Neck or shoulder pain	5 (0.3)	3 (0.5)
Back pain	176 (9.5)	102 (16.3)
Stomach or abdominal pain	169 (9.1)	90 (14.4)
Hip pain	22 (1.2)	11 (1.8)
Knee pain	72 (3.9)	35 (5.6)
Pain all over the body	140 (7.5)	59 (9.5)

[a]Mean (SD); *n* (%).

Abbreviations: dS, decisecond; n, number; S, second.

diabetic controls (all $p < 0{\cdot}0002$). Decreased volume was found in regions associated with the visual, sensorimotor and default mode networks (all $p < 0{\cdot}0002$) (Figure 2, Figure 3 (left)). When *p*-value correction was adjusted using false discovery rate correction, additional cortical and sub-regions were identified as statistically different between participants with diabetes relative to non-diabetic controls (Table S11). There were no significant differences in grey matter volume between participants with T1D and T2D.

4.3 | Mean percentage difference

There was a negative mean volume percentage difference in the whole brain (−3·7%), grey matter (−3·8%), and subcortical grey matter volume (−2·9%) in people with diabetes relative to controls as shown in Table 5. Positive differences in mean volume percentage were found in the right lateral ventricle (8·4%), left lateral ventricle (9%), third ventricle (8·4%), and fourth ventricle (6%) in people with diabetes relative to controls. Negative changes in mean volume percentage difference were found in regions associated with the sensorimotor network such as the bilateral front superior (right −4·9% and left −4·6%), precentral (right: −4·8% and left: −5·3%), and postcentral (right: −4·9% and left −5%) gyri. Similar changes are seen in the short insular gyrus (4.3%), right central insular gyrus and sulcus (−4%) and right anterior cingulate gyrus and sulcus (−3·4%). Negative mean volume percentage differences were found in subcortical structures such as the brain stem (−4·5%), bilateral cerebellar white matter (right −5·4% and left −5·9%), cerebellar cortex (right: −4·5% and left −3·8%), left amygdala (−3·3%), bilateral putamen (right −3% and left −2·9%), pallidum (both −3·4%), thalami (right −2·9% and left −3·5%), and corpus callosum (central −4·5% and mid-anterior −4·8%).

4.4 | Tractometry using fractional anisotropy

There were significant reductions in FA along the length of the thalamocortical radiations, thalamostriatal projections and sensory ascending tracts including the corticospinal tract and commissural somatosensory associated tracts of the corpus callosum in participants with diabetes relative to non-diabetic controls (Figure 4; all $p < 0{\cdot}001$). The tracts with reduced FA and typical connections to areas with decreased grey matter regions associated with

TABLE 5 People with diabetes versus non-diabetic controls: Significant global, cortical and sub-cortical regions after bonferroni correction for multiple comparisons.

Region	*p*-value	Adjusted *p*-value	t-value	Mean volume difference (%)
Whole brain volume	<0.000000001	<0.000000001	−11.577	−3.71%
Total sub-cortical grey matter volume	<0.000000001	<0.000000001	−7.019	−2.88%
Whole brain grey matter volume	<0.000000001	<0.000000001	−11.722	−3.82%
Whole brain ventricle choroid	<0.000000001	<0.000000001	8.237	9.20%
3rd ventricle	<0.000000001	<0.000000001	9.236	8.41%
4th ventricle	0.0000000001	<0.000000001	6.517	6.02%
Brain stem	<0.000000001	<0.000000001	−7.711	−4.48%
Central corpus callosum	0.0000196878	0.0036230000	−4.277	−4.48%
Mid-anterior corpus callosum	0.0000859628	0.0158170000	−3.934	−4.84%
Left hemisphere cerebral white matter volume	<0.000000001	<0.000000001	−9.196	−4.72%
Left lateral ventricle	<0.000000001	<0.000000001	7.76	8.99%
Left cerebellum white matter	<0.000000001	<0.000000001	−8.167	−5.86%
Left cerebellum cortex	<0.000000001	<0.000000001	−6.785	−3.80%
Left thalamus proper	<0.000000001	<0.000000001	−7.086	−3.52%
Left putamen	0.0000444411	0.0081770000	−4.091	−2.94%
Left pallidum	0.0000008586	0.0001580000	−4.935	−3.37%
Left hippocampus	0.0000005470	0.0001010000	−5.023	−2.66%
Left amygdala	0.0000111081	0.0020440000	−4.404	−3.29%
Left accumbens area	0.0000000066	0.0000010000	−5.822	−6.17%
Left ventral DC	<0.0000000001	<0.0000000001	−9.947	−4.70%
Right hemisphere cerebral white matter	<0.0000000001	<0.0000000001	−8.694	−4.54%
Right lateral ventricle	<0.0000000001	<0.0000000001	7.426	8.39%
Right cerebellum white matter	0.0000000001	<0.0000000001	−6.472	−5.38%
Right cerebellum cortex	0.0000000007	<0.0000000001	−6.185	−3.62%
Right thalamus proper	0.0000001143	0.0000210000	−5.319	−2.91%
Right putamen	0.0000160991	0.0029620000	−4.322	−3.05%
Right pallidum	0.0000066966	0.0012320000	−4.513	−3.43%
Right hippocampus	0.0001603613	0.0295060000	−3.78	−2.18%
Right accumbens area	0.0000000041	0.0000010000	−5.901	−5.23%
Right ventral DC	<0.0000000001	<0.0000000001	−9.915	−4.57%
Right choroid plexus	<0.0000000001	<0.0000000001	9.348	7.78%
Left gyrus and sulcus frontomargin	0.0000177244	0.0032610000	−4.301	−3.70%
Left gyrus and sulcus occipital inferior	0.0000089531	0.0016470000	−4.451	−4.83%
Left gyrus and sulcus paracentral	0.0000255043	0.0046930000	−4.219	−3.59%
Left gyrus and sulcus subcentral	0.0000964261	0.0177420000	−3.906	−3.78%
Left gyrus and sulcus transv frontopol	0.0000266696	0.0049070000	−4.208	−3.99%
Left gyrus front middle	0.0000258905	0.0047640000	−4.215	−4.15%
Left gyrus front superior	<0.0000000001	<0.0000000001	−7.07	−4.58%
Left gyrus insular short	0.0000000385	0.0000070000	−5.515	−4.34%
Left gyrus occipital middle	0.0000005543	0.0001020000	−5.02	−5.09%

(Continues)

TABLE 5 (Continued)

Region	*p*-value	Adjusted *p*-value	t-value	Mean volume difference (%)
Left gyrus occipital superior	0.0000006882	0.0001270000	−4.978	−4.74%
Left temporal lateral fusiform gyrus	0.0001407262	0.0258940000	−3.813	−3.90%
Left gyrus orbital	0.0000680247	0.0125170000	−3.99	−3.19%
Left gyrus pariet inferior angular	0.0000000525	0.0000100000	−5.46	−5.22%
Left gyrus pariet inferior supramargin	0.0001276804	0.0234930000	−3.837	−4.36%
Left gyrus postcentral	0.0000017615	0.0003240000	−4.791	−4.97%
Left gyrus precentral	<0.0000000001	<0.0000000001	−6.849	−5.31%
Left gyrus precuneus	0.0000001657	0.0000300000	−5.25	−4.69%
Left gyrus rectus	0.0000063994	0.0011770000	−4.523	−3.66%
Left subcallosal gyrus	0.0001308673	0.0240800000	−3.831	−6.99%
Left gyrus temp superior lateral	0.0000395745	0.0072820000	−4.118	−3.54%
Left gyrus temp superior plan polar	0.0000108648	0.0019990000	−4.409	−4.61%
Left gyrus temp superior plan tempo	0.0001280836	0.0235670000	−3.836	−5.40%
Left gyrus temporal inferior	0.0001193167	0.0219540000	−3.854	−3.91%
Left gyrus temporal middle	0.0000000018	<0.0000000001	−6.038	−5.10%
Left central sulcus	0.0000000017	<0.0000000001	−6.049	−4.63%
Left posterior transverse collateral sulcus	0.0000124419	0.0022890000	−4.379	−6.02%
Left intraparietal sulcus	0.0000030048	0.0005530000	−4.682	−4.62%
Left superior occipital transverse sulcus	0.0000000998	0.0000180000	−5.343	−5.98%
Left lateral occipitotemporal sulcus	0.0000038996	0.0007180000	−4.627	−5.78%
Left medial occipitotemporal gyrus	0.0000001043	0.0000190000	−5.335	−4.45%
Left postcentral sulcus	0.0000030914	0.0005690000	−4.676	−5.04%
Left superior temporal sulcus	0.0000000006	<0.0000000001	−6.228	−4.95%
Right frontomargin gyrus and sulcus	0.0000000438	0.0000080000	−5.493	−4.59%
Right inferior occipital gyrus and sulcus	0.0000002919	0.0000540000	−5.143	−5.65%
Right subcentral gyrus and sulcus	0.0000064502	0.0011870000	−4.521	−4.52%
Right transverse frontopolar gyrus and sulcus	0.0000195676	0.0036000000	−4.278	−3.82%
Right anterior cingulate gyrus and sulcus	0.0000756673	0.0139230000	−3.965	−3.39%
Right inferior frontal opercular gyrus (pars opercularis)	0.0000004010	0.0000740000	−5.083	−4.73%
Right front middle gyrus	0.0000004023	0.0000740000	−5.082	−4.94%
Right front superior gyrus	<0.0000000001	<0.0000000001	−7.564	−4.92%
Right central insular gyrus and sulcus	0.0001916080	0.0352560000	−3.736	−4.02%
Right occipital middle gyrus	0.0000093421	0.0017190000	−4.441	−4.64%
Right superior occipital gyrus	0.0000000782	0.0000140000	−5.388	−5.33%
Right fusiform gyrus	0.0001872526	0.0344540000	−3.741	−4.06%
Right orbital gyrus	0.0000787563	0.0144910000	−3.955	−3.02%
Right parietal inferior angular gyrus	0.0000176833	0.0032540000	−4.301	−4.43%
Right inferior parietal inferior supramarginal gyrus	0.0000003938	0.0000720000	−5.086	−5.31%
Right parietal superior gyrus	0.0000999076	0.0183830000	−3.897	−3.98%
Right postcentral gyrus	0.0000035617	0.0006550000	−4.646	−4.92%
Right precentral gyrus	0.0000000164	0.0000030000	−5.666	−4.79%
Right gyrus rectus	0.0000070930	0.0013050000	−4.501	−3.68%

TABLE 5 (Continued)

Region	*p*-value	Adjusted *p*-value	t-value	Mean volume difference (%)
Right superior temporal gyrus	0.0000012953	0.0002380000	−4.853	−3.90%
Right temporal plan polar gyrus	0.0000006088	0.0001120000	−5.002	−5.60%
Right inferior temporal gyrus	0.0000271424	0.0049940000	−4.204	−4.30%
Right temporal middle gyrus	0.0000010090	0.0001860000	−4.903	−4.16%
Right lateral posterior fissure	0.0001383588	0.0254580000	−3.817	−2.96%
Right central sulcus	0.0000003632	0.0000670000	−5.102	−4.23%
Right marginal sulcus	0.0000121076	0.0022280000	−4.385	−4.21%
Right front middle sulcus	0.0000517696	0.0095260000	−4.055	−5.53%
Right front superior sulcus	0.0000465638	0.0085680000	−4.08	−4.86%
Right superior occipital transverse sulcus	0.0000231266	0.0042550000	−4.241	−5.22%
Right medial lingual occipital temporal sulcus	0.0000112509	0.0020700000	−4.401	−3.74%
Right orbital H-shaped sulcus	0.0000003651	0.0000670000	−5.101	−4.15%
Right inferior temporal sulcus	0.0001072844	0.0197400000	−3.88	−4.40%
Right temporal superior sulcus	0.0000000934	0.0000170000	−5.356	−4.22%

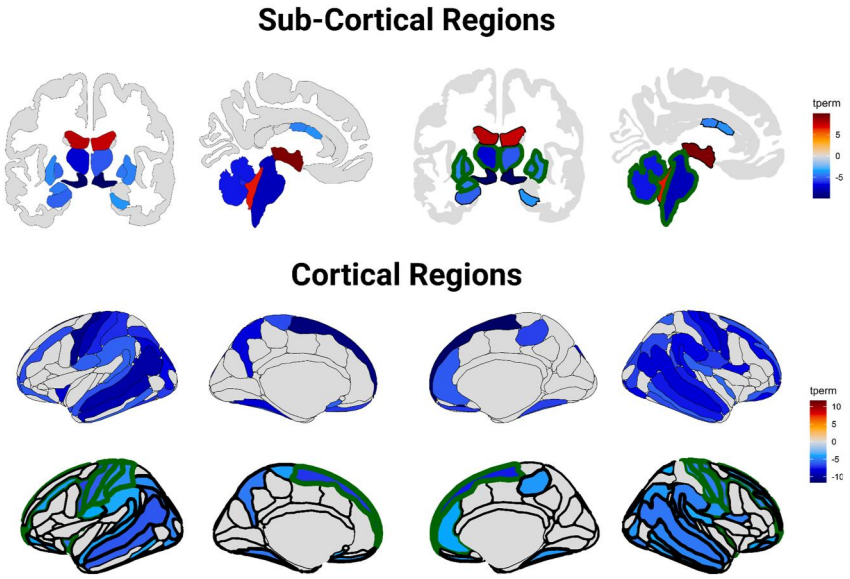

FIGURE 2 Cortical and subcortical regions. The t value statistic indicates either an increase or decrease in volume compared to healthy volunteers, where **red** indicates an increase in volume, whilst **blue** indicates a decrease. **Sub-cortical regions:** An increase in volume is shown in the ventricles. A decrease in volume is seen bilaterally in the ventral diencephalon, basal ganglia, brain stem, cerebellar cortex and central corpus callosum. **Cortical Regions**: A decrease in volume is shown in regions associated with the visual, sensorimotor and default mode networks. The areas highlighted in **green** are implicated in sensorimotor function and pain processing. Created with BioRender.com.

sensorimotor functions in people with diabetes are shown in Figure 3 (right). In addition, reduced FA was observed in white matter tracts associated with co-ordinating movements and visual information synthesis, such as the middle cerebellar peduncle, right superior cerebellar peduncle, parieto-occipital pontine, right fronto-pontine tract and bilateral inferior occipitofrontal fascicle.

5 | DISCUSSION

This is the largest volumetric and tractometric study to examine structural grey and white matter changes in a prospective cohort of people with diabetes. Volumetric analysis showed lower grey matter volume in participants with adequately controlled glycaemia and a

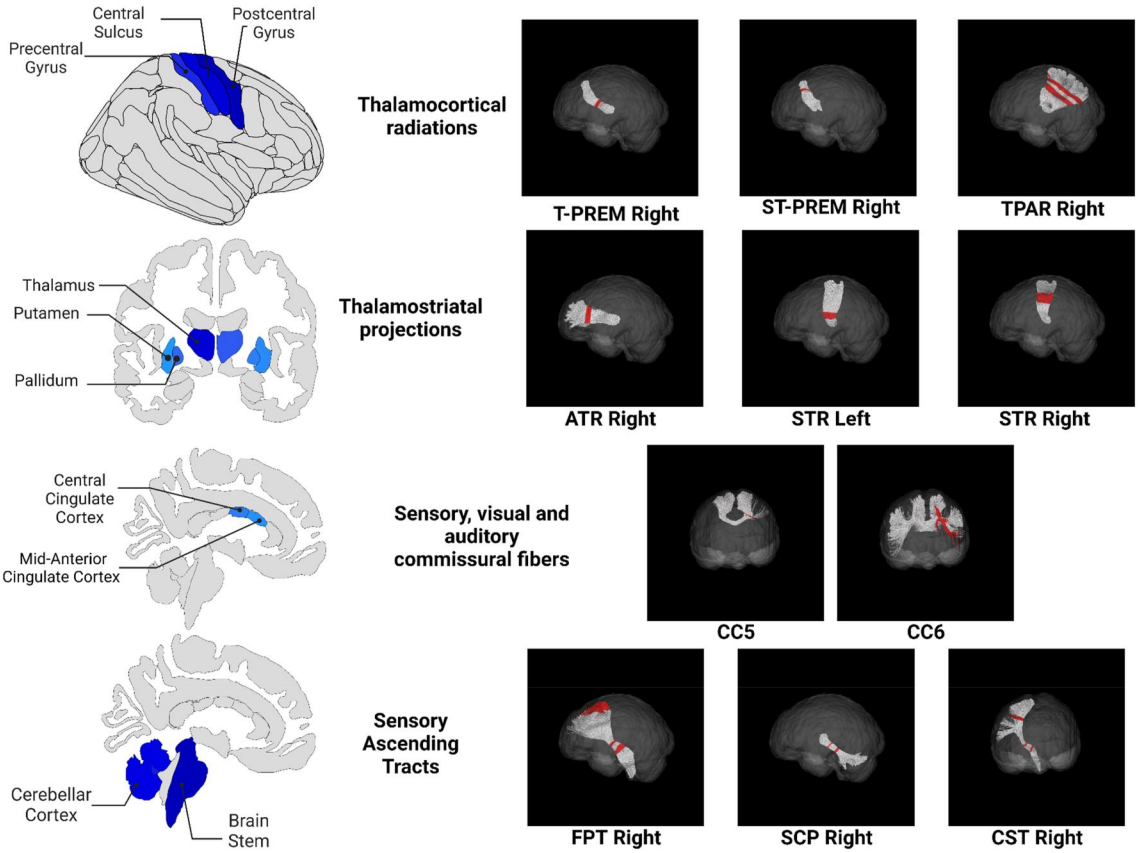

FIGURE 3 The cortical and sub-cortical regions of grey matter with decreased volume (shown in **blue**) associated with sensorimotor functions and the white matter streamlines with reduced fractional anisotropy (FA) (shown in **red**) which typically connect them. ATR-Left, Left anterior thalamic radiation; CC5, Corpus callosum (Primary Somatosensory); CC6, Corpus callosum (isthmus); CST-Right, Right corticospinal tract; STR-Left, Left superior thalamic radiation; STR-Right, Right superior thalamic radiation; TPAR-Right, Right thalamo-parietal tract; TPREM-Right, Right thalamo-premotor tract. Created with BioRender.com.

low prevalence of microvascular complications compared to non-diabetic controls. Moreover, both volumetric grey matter and microstructural white matter changes were found in regions associated with the visual and sensorimotor networks. A pathophysiological relationship appears to exist between regions involved in sensory processing and diabetic peripheral neuropathy severity,[22] neuropathic pain[4] and worsening visual impairment in diabetic retinopathy.[23]

Previous studies reported structural alterations in the central nervous system in T1D[24] and T2D.[25] Structural changes in regions associated with cognitive and sensorimotor function have been demonstrated in participants with microvascular alterations. In the present study, we show lowered brain volumes which occur in these same regions in people with diabetes without prevalent microvascular disease. Our analysis found decreased global grey matter volume and increased ventricular volume synonymous with neurodegenerative processes, and labile cognitive function test scores in people with diabetes. A recent longitudinal study in older people with T2D suggests that cerebral atrophic changes begin in middle age, resulting in cognitive decline, which accelerates in later life.[26] This was demonstrated in a large cohort of deeply phenotyped participants with diabetes, where mild cognitive impairment prevalence was comparable to age-adjusted rates of the general population despite accelerated incipient cognitive decline.[6]

In the current study, participants with diabetes reported more general and widespread pain, although the neuropathic pain subtype which occurs in diabetic peripheral neuropathy is not routinely captured in the self-reported outcomes. Interestingly, regional reductions in brain volume associated with chronic pain are seen in diabetes, such as the insula, sensorimotor areas, the cerebellum and deep basal nuclei.[13] Our analysis found reduced brain volume in regions associated with sensorimotor processing. However, these observations (despite exhibiting excess pain) occurred despite a lack of a formal diagnosis of diabetic peripheral neuropathy or any detailed pain phenotyping. Indeed, if we were to advance the hypothesis of a neurodegenerative process perhaps driven by diabetes-related end-organ damage, the symptom burden of diabetic peripheral neuropathy could be potentiated by these early changes in the central nervous system.

In diabetic peripheral neuropathy, significant peripheral grey matter decrements are reported, affecting the sensorimotor cortex, somatosensory area, and supplementary sensorimotor area.[4,13,22,27]

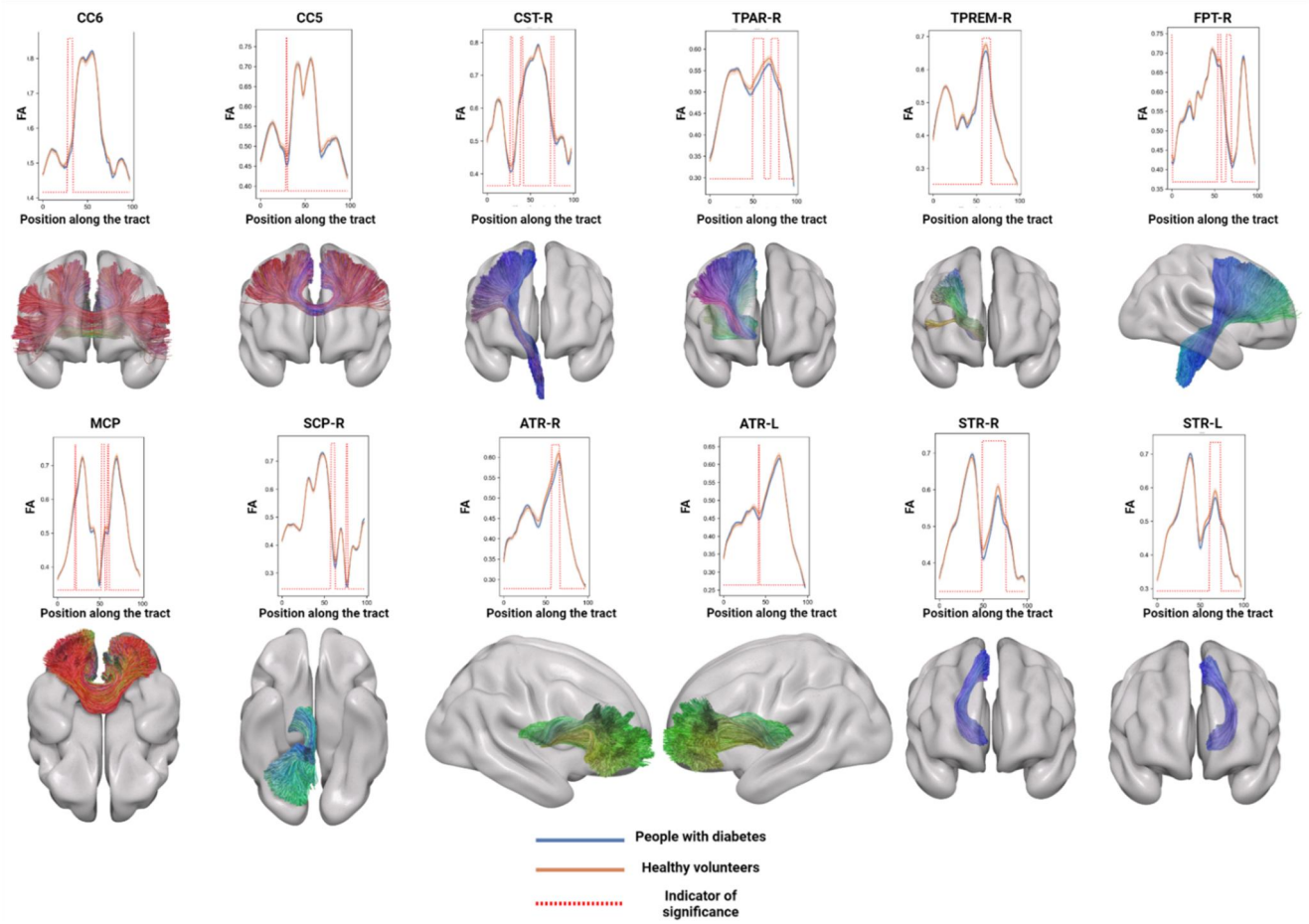

FIGURE 4 Differences in fractional anisotropy (FA) along all white matter tracts between people with diabetes and non-diabetic controls corrected for age, sex and multiple tract comparisons with an alpha family wise error significance threshold of $p < 0.001$. ATR-R, Right anterior thalamic radiation; ATR-L, Left anterior thalamic radiation; CC5, Corpus callosum (primary somatosensory); CC6, Corpus callosum (isthmus); CST-R, Right corticospinal tract; FA, Fractional anisotropy; FPT-R, Fronto-pontine tract; MCP, Middle cerebellar peduncle; SCP-R, Right superior cerebellar peduncle; STR-R, Right superior thalamic radiation; STR-L, Left superior thalamic radiation; TPAR-R, Right thalamo-parietal tract; TPREM-R, Right thalamo-premotor tract. Created with BioRender.com.

The degree of grey matter volume loss is associated with the severity of neuropathy, suggesting a progressive neurodegeneration driven by diabetic peripheral neuropathy. Moreover, in T1D with diabetic peripheral neuropathy, people with either a painless or painful sensory phenotype exhibit greater volume loss in the primary somatosensory cortex, supramarginal gyrus and cingulate cortex.[28] Recent data published by Hansen and colleagues[29] report greater grey matter volume reductions in the thalamus, inferior and superior occipital gyrus, and precentral gyrus in T1D patients with microvascular complications (retinopathy/diabetic peripheral neuropathy) compared with healthy volunteers. In the present analysis, these same areas demonstrate reductions in grey matter volume in people with adequate glycaemia in the absence of significant microvascular complications. It is plausible that sub-clinical vascular pathology in diabetes promotes a neurodegenerative state in vulnerable regions of the central nervous system, which is then catalysed by incipient diabetic peripheral neuropathy. Indeed, a recent UK Biobank study dataset and meta-analysis using functional MRI identified significant reductions in brain activity areas associated with sensorimotor and visual functions in people with T2D.[30] Furthermore, differences are reported in both volume and vascularity of the thalamus in people with painless compared to painful diabetic peripheral neuropathy.[31] MRI has potential as a clinical biomarker in diabetes and diabetic peripheral neuropathy. Furthermore, multimodal MRI studies have suggested the potential underlying pathogenic mechanisms of diabetic peripheral neuropathy and neuropathic pain.[4]

Multiplexed MRI studies, which include DTI measures such as FA, predict white matter hyper-intensities in cerebral small vessel disease prior to their occurrence.[32] Indeed, white matter microstructural alterations in sensorimotor tracts are associated with worsening motor performance.[33] DTI measures such as FA are a measure of the integrity of white matter tracts; a reduction in FA can broadly indicate microstructural disruption, but they have also been used to infer neuronal loss and/or tract demyelination.[34]

Recently published data from Muthulingam and colleagues[35] report reduced FA of the thalamic radiations, longitudinal fasciculi,

internal capsule and corticospinal tract in participants with T1D with diabetic peripheral neuropathy and a high prevalence of retinopathy. The aforementioned microstructural alterations are positively associated with peripheral nerve function (sensory nerve conduction amplitude) and diabetes duration. Indeed, widespread microstructural alterations in white matter tracts that occur in the absence of clinically defined microvascular complications are markedly worse in the presence of diabetic angiopathy.[35,36] Similarly, we have identified significant differences in FA in tracts with associated visual and sensorimotor functions, including the corticospinal tract, corpus callosum, thalamo-premotor tract and thalamic radiations. These white matter tract alterations shown in the present study are in agreement with a recently published systematic review, albeit with the majority of included studies representing cohorts with microvascular complications.[34]

The presence of microvascular complications are associated with microstructural abnormalities in white matter tracts with associated sensorimotor, visual and cognitive functions.[34] Indeed, significant global alterations in subcortical white matter are demonstrated in diabetic peripheral neuropathy, with alterations in sensory ascending tracts such as the corticospinal and spinothalamic tract, and thalamocortical projecting fibres.[13] Motor impairment has been associated with regional reductions in primary motor areas in diabetic peripheral neuropathy.[37] Additionally, recently published data indicate marked disruptions of functional connectivity of the thalamus, and increased connectivity of the default mode network in T1D with painful diabetic peripheral neuropathy.[38]

In the present study, univariate analyses were employed to identify group differences; however, this method does not consider the possible multicollinearity of adjacent brain regions. Furthermore, it is possible that intra-cranial volume may have served better as part of the matching process as opposed to being used as an adjustment within our univariate regression models. The volumetric analysis had many comparisons; however, efforts were made to mitigate false positives using co-variates for adjustment, strict significance thresholds and *p*-value corrections. Moreover, "healthy volunteer" selection bias is evidenced within the UK Biobank dataset[39] and should be considered when interpreting these data. A key strength of this analysis is that it is based on a large prospective population-based study with well phenotyped participants, with many participants also undergoing with brain MRI. Furthermore, the use of the novel TractSeg tool for tractometry may provide a more sensitive means of identifying microstructural group differences in white matter compared to TBSS methodology. We acknowledge that the UK Biobank is not a dedicated resource for diabetes research and diabetic complications, and as such ICD-10 coding was used as a proxy for concomitant complications. Indeed, further comprehensive observational longitudinal studies are required in people with new or early onset diabetes with microvascular risk factor phenotyping. The primary objective of these studies should be to characterise the contribution of changes in the central and peripheral nervous systems in the presence of microvascular complications and cardiovascular risk factors towards the development of cognitive dysfunction or sensory deficits.

6 | CONCLUSION

This analysis demonstrates volumetric and microstructural white matter differences between participants with DM and individuals without diabetes in the central nervous system. Differences are present in areas associated with sensorimotor and visual functions in a cohort with DM, good metabolic control, and minimal microvascular complications. Structural alterations and neural remodelling of the central nervous system are likely to be involved early in the development and maintenance of incipient diabetes-related microvascular complications.

AUTHOR CONTRIBUTIONS

All persons who meet the authorship criteria are listed as authors. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Conceptualisation, Uazman Alam, Simon S. Keller and Jamie Burgess; writing—original draft preparation, Jamie Burgess and Uazman Alam; writing—review and editing, Jamie Burgess, Simon S. Keller, Christophe de Bezenac, Timothy L. Jackson, Bernhard Frank, Varo Kirthi, Ioannis N. Petropoulos, Daniel J. Cuthbertson, Dinesh Selvarajah, Marta Garcia-Finana, Solomon Tesfaye, and Uazman Alam; visualisation, Jamie Burgess, Simon S. Keller, Christophe de Bezenac, and Uazman Alam; supervision, Simon S. Keller, Uazman Alam. All authors have read and agreed to the submitted version of the manuscript. All authors have read and agreed to the submitted version of the manuscript.

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J.B. received a PhD studentship from the Pain Relief Foundation. Linked health data used with the permission of NHS England and the UK Biobank. All rights reserved, © 2024, NHS England. This work uses data provided by patients and collected by the NHS as part of their care and support. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. Our study made use of pre-processed image data generated by an image-processing pipeline developed and run on behalf of UK Biobank.[40]

CONFLICT OF INTEREST STATEMENT

No conflicts of interest are declared by the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the publicly accessible UK Biobank dataset at https://www.ukbiobank.ac.uk/enable-your-research/register.

ETHICS STATEMENT

The UK Biobank was granted approval by the North West Multi-Centre Research Ethics Committee (MREC) in 2011 (approval number 11/NW/0382), with subsequent renewals every five years in 2016 (16/NW/0274) and 2021 (21/NW/0157). Informed consent was obtained from all participants. This research utilised the UK Biobank Resource, under Application Number 45184.

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3772.

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SUPPORTING INFORMATION

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

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