

A novel morphometric signature of brain alterations in type 2 diabetes: Patterns of changed cortical gyrification

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Abstract

Type 2 diabetes is a chronic disease that creates atrophic signatures in the brain, including decreases of total and regional volume of grey matter, white matter and cortical thickness. However, there is a lack of studies assessing cortical gyrification in type 2 diabetes. Changes in this emerging feature have been associated mainly with genetic legacy, but environmental factors may also play a role. Here, we investigated alterations of the gyrification index and classical morphometric measures in type 2 diabetes, a late acquired disease with complex aetiology with both underlying genetic and more preponderant environmental factors. In this cross-sectional study, we analysed brain anatomical magnetic resonance images of 86 participants with type 2 diabetes and 40 healthy control participants, to investigate structural alterations in type 2 diabetes, including whole-brain volumetric measures, local alterations of grey matter volume, cortical thickness and the gyrification index. We found concordant significant decrements in total and regional grey matter volume, and cortical thickness. Surprisingly, the cortical gyrification index was found to be mainly increased and mainly located in cortical sensory areas in type 2 diabetes. Moreover, alterations in gyrification correlated with clinical data, suggesting an influence of metabolic profile in alterations of gyrification in type 2 diabetes. Further studies should address causal influences of genetic and/or environmental factors in patterns of cortical gyrification in type 2 diabetes.

KEYWORDS

brain, gyrification, morphometry, sensory cortex, type 2 diabetes

Abbreviations: AC, anterior commissure; AUC, area under the curve; BMI, body mass index; CNT, control group; CSF, cerebrospinal fluid; FWE, family-wise error; FOV, field of view; FWHM, full width at half maximum; GM, grey matter; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MNI, Montreal Neurological Institute; MPRAGE, magnetization-prepared rapid gradient echo; MRI, magnetic resonance imaging; PC, posterior commissure; ROC, receiver operating characteristic; SBM, surface-based morphometry; SEM, standard error of the mean; T2D, type 2 diabetes group; TE, echo time; TI, inversion time; TIV, total intracranial volume; TR, repetition time; VBM, voxel-based morphometry; WM, white matter.

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1 | INTRODUCTION

Type 2 diabetes is a highly prevalent chronic metabolic disease that affects many tissues and organs, and the brain is not an exception. Despite the ongoing controversies on the nature of its impact in the brain, changes in structure and function are well documented in diabetes. This disease is commonly associated with cerebrovascular disease, cognitive decline, Alzheimer's disease and other types of dementias and depression (Bancks et al., 2017; Cheng et al., 2012; Moheet et al., 2015; Verdile et al., 2015). Studies of structural magnetic resonance imaging (MRI) with volumetric analysis at the whole-brain level and voxel-based morphometry (VBM) have shown brain atrophy, including lower total and regional volume of grey matter (GM) and white matter (WM) in type 2 diabetes patients when compared with non-diabetic controls (Moheet et al., 2015; Moran et al., 2013). Decrements in cortical thickness were also already demonstrated with surface-based morphometry (SBM) studies in type 2 diabetes patients (Chen et al., 2017; Moran et al., 2019). Conceptually, the volume of GM and the cortical thickness seem to be influenced by environmental factors related with diabetes progression, such as patients' glycaemic profile, lipid status, vascular complications and insulin taking (Brundel et al., 2010; Bryan et al., 2014; Chen et al., 2015, 2017; Shi et al., 2019). Notably, cortical gyrification, which to the best of our knowledge was never assessed in type 2 diabetes, is an interesting surface feature that was initially suggested to be more specifically influenced by genetic and neurodevelopmental factors (Ronan & Fletcher, 2015).

Gyrification refers to the development of the folding surface patterns on the brain (Welker, 1990; Zilles et al., 1988), being highly heritable, evolutionarily conserved, and similar among closely related animal species (Alexander-Bloch et al., 2020; Zilles et al., 2013). Due to gyrification, the cortical surface area and thus the volume of cortical GM can increase dramatically (White et al., 2010). It is postulated to be dictated by the genetic signature, and the period of greatest development of brain gyrification is during intrauterine development (Papini et al., 2020; White et al., 2010; Zilles et al., 1988, 2013). Genetic control of this process is now starting to be understood both in animal models using genome editing (Johnson et al., 2018) and also in the human brain (Alexander-Bloch et al., 2020).

A quantitative approach to measure local gyrification is known as the gyrification index, which is a ratio between the length of the outer folded surface of the brain, including sulci, and the length of the outer surface excluding sulci (Schaer et al., 2008; Yotter et al., 2011;

Zilles et al., 1988). The development of this quantification concept has allowed to identify altered gyrification in several diseases. The literature has consistently reported altered gyrification index in diseases with genetic or neurodevelopmental basis (Bearden et al., 2009; Casanova et al., 2004; Gaser et al., 2006; Jou et al., 2010; Palaniyappan & Liddle, 2012; Zhang et al., 2010). Nonetheless, the idea of unchanged gyrification during the whole life seems to be reductive and outdated. The brain nearly triples its size from birth to adulthood and alterations in brain morphology, including in gyrification index, also occur in healthy aging (Hogstrom et al., 2013; Lamballais et al., 2020) and due to environmental life style factors (Amunts et al., 1997; Luders et al., 2012). Changes have also been observed in late acquired diseases with complex aetiology (Lebed et al., 2013; Lin et al., 2007).

Regarding the complex and multifactorial aetiology of type 2 diabetes with underlying genetic and environmental factors, as well as subsequent pathological disease environment, we hypothesized that alterations in the brain surface morphology, namely, in gyrification, may also occur.

In this cross-sectional study, we aimed at investigating this novel feature of cortical gyrification in type 2 diabetes, as well as more classical structural measures, including whole-brain volumetric tissue volumes — total intracranial volume (TIV), GM, WM, and cerebrospinal fluid (CSF), local GM volume and cortical thickness.

2 | MATERIALS AND METHODS

2.1 | Participants

After signing the informed consent, 190 participants were enrolled in a cross-sectional study, between 2012 and 2014, and divided in two experimental groups: a type 2 diabetes group (T2D) and a control group (CNT). Type 2 diabetes patients were recruited at the Endocrinology Department of the University of Coimbra Hospital, diagnosed using standard WHO criteria at the moment of recruitment, based on glucose levels, oral glucose tolerance test and glycated haemoglobin (HbA1c) (World Health Organization, 1999; World Health Organization, 2011). Inclusion criteria for T2D were as follows: (i) age between 40 and 75 years and (ii) type 2 diabetes for at least 1 year before the enrolment in the study. Control individuals were recruited from the general population of the hospital or university staff and their relatives. Inclusion criteria for CNT group were as follows: (i) age between 40 and 75 years and (ii) type 2 diabetes diagnosis excluded based on levels of HbA1c and fasting glucose.

General exclusion criteria were as follows: (i) history of neurological or psychiatric disorders, (ii) substance abuse/dependence and (iii) contraindication for MR imaging.

Demographic and clinical data were collected for all participants by research physicians, and fasting blood samples were collected by venous puncture by research nurses for posterior biochemical analysis, according to the hospital standard procedures.

All experimental procedures were in accordance with the Declaration of Helsinki and were approved by competent Ethics' Committees.

2.2 | MRI data acquisition

Data were collected at the Institute of Nuclear Sciences Applied to Health, University of Coimbra, using a Siemens Magnetom TIM Trio 3 Tesla MRI scanner with a phased array 12-channel birdcage head coil (Siemens, Munich, Germany). For each participant, a 3D anatomical T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence was acquired with the following parameters: repetition time (TR) = 2530 ms; echo time (TE) = 3.42 ms; inversion time (TI) = 1100 milliseconds; flip angle 7°; 176 single-shot interleaved slices with no gap with isotropic voxel size 1 × 1 × 1 mm; field of view (FOV) = 256 mm.

During the MRI session, participants performed a visual motion discrimination task, aimed to determine a speed discrimination threshold. This psychophysics threshold is described in detail in a previous study (Duarte et al., 2015) and was used in this study to correlate with the local gyrification index.

2.3 | Data analysis

Out of 190 participants recruited, 17 dropped out before MRI scanning. Additionally, 3 participants were excluded after a quality assessment by visual inspection of acquired structural data, because of severe movement artefacts and anatomical anomalies. Then, aiming to do between-groups analysis balanced for age, 86 type 2 diabetes participants and 40 CNT participants were selected, which is well above recommended sizes for neuroimaging studies (Friston, 2012).

Images were processed and analysed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) and CAT12 toolbox (Structural Brain Mapping Group, Jena University Hospital, Jena, Germany; <http://dbm.neuro.uni-jena.de/cat/>), as it offers processing and analysis

pipelines for both VBM as well as SBM (including cortical thickness and gyrification index). This toolbox has been previously used and validated in morphometric studies in clinical populations, including by our own group (Madeira et al., 2020).

2.3.1 | Voxel-based morphometry

After quality assessment of original images, the images were centred in the anterior commissure and oriented in AC-PC (anterior commissure–posterior commissure) plane. Subsequently, images were spatially normalized into Montreal Neurological Institute (MNI) standard space and segmented into three tissue classes—GM, WM and CSF—using partial volume segmentation with adaptive maximum a posteriori approach. TIV was also determined for all scans. The extracted modulated normalized GM maps were smoothed using a 12-mm full width at half maximum (FWHM) kernel and used for further analysis. An absolute masking threshold of 0.1 was applied to the VBM data. The Automated Anatomical Labelling and Yale BioImage Suite (v1.3) brain atlases were used to label the regions with differences between groups, according to their MNI coordinates.

2.3.2 | Cortical thickness

Cortical thickness was extracted based on the absolute mean curvature approach (Luders et al., 2006). Extraction of the cortical surface (using CAT12 standard procedure) resulted in the construction of a mesh of the central surface, that is, the surface between the GM/CSF border and the GM/WM boundary. The central surface as well as cortical thickness are estimated in one step using a projection-based distance measure (Dahnke et al., 2013). The vertex-wise cortical thickness measures were resampled and smoothed using a 15-mm FWHM Gaussian kernel.

2.3.3 | Gyrification index

Local (vertex-wise) gyrification index maps were calculated based on the same algorithm for extraction of the cortical surface implemented in CAT12, as given above for cortical thickness analysis (Luders et al., 2006; Yotter et al., 2011). The local absolute mean curvature of this central surface was then calculated by averaging the mean curvature values from each vertex point within 3 mm from a given point. In a second step, we applied 15-mm FWHM smoothing to the gyrification index maps.

2.4 | Statistical analysis

The analysis of demographic, clinical data and total brain volumes (TIV, GM, WM and CSF) was performed with GraphPad Prism 6. Normality of the data was tested using D'Agostino–Pearson test. Parametric and non-parametric tests were used when data were normally distributed or when assumption of normality was not met, respectively. Parametric *t* test and non-parametric Mann–Whitney test were used to assess between-group's differences. Parametric Pearson test and non-parametric Spearman test were used to calculate correlations of the gyrification index with clinical data [age at diagnosis; disease duration; glucose; HbA1c; total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol; triglycerides; body weight; and body mass index (BMI)] and with behaviour (psychophysics threshold). Chi-square test was used to assess the difference in gender distribution between groups.

The statistical analyses of imaging data were performed in the CAT12/SPM12 statistical module applying *t* test to each of the three morphometric measures: GM volume with VBM, and cortical thickness and gyrification index with SBM. Using age and gender as covariates (and for VBM analyses, additionally, TIV), group differences applying thresholds of $p < 0.05$ with family-wise error (FWE) rate correction for multiple comparisons were

tested. When the correction was too stringent, and not to miss an exploratory interesting effect, the statistical maps were thresholded at voxel level with $p < 0.001$ and then corrected at the cluster level with cluster extent correction. The potential of the gyrification index to be discriminative of type 2 diabetes was investigated with receiver operating characteristic (ROC) analysis, by computing the area under the curve (AUC) for each significant cluster.

3 | RESULTS

3.1 | Demographic and clinical data

Demographic and clinical data are depicted in Table 1. The mean age of T2D was 60.67 years and of CNT was 57.73 years, and no statistically significant difference between groups was found. Gender distribution between groups was also not different. The mean age at diagnosis of diabetes was 47.73 years, and mean disease duration was 12 years. As expected, T2D showed significantly higher levels of fasting glucose and HbA1c, when compared with controls. Regarding lipid profile, patients showed significantly lower cholesterol and higher triglycerides levels. This group had significantly higher weight and BMI, although both groups had the same obesity

TABLE 1 Demographic and clinical data

Group Number	T2D 86	CNT 40	Test	<i>p</i> value
Age (years)	60.67 ± 7.89	57.73 ± 8.06	<i>t</i> = 1.94	0.06
Gender (%)	Male	59.3	$\chi^2 = 0.96$	0.33
	Female	40.7		
Age at diagnosis (years)	47.73 ± 10.26	—	—	—
Disease duration (years)	12.05 ± 8.88	—	—	—
Fasting glucose (mg/dl)	166.5 ± 62.56	95.05 ± 10.89	<i>U</i> = 295.5	<0.0001
HbA1c	(mmol/mol)	79.53 ± 25.72	<i>t</i> = 10.21	<0.0001
	(%)	9.43 ± 2.37		
Total cholesterol (mg/dl)	174.0 ± 59.98	204.2 ± 31.65	<i>U</i> = 822.0	<0.0001
HDL cholesterol (mg/dl)	41.07 ± 11.14	57.68 ± 12.35	<i>t</i> = 7.34	<0.0001
LDL cholesterol (mg/dl)	115.0 ± 35.02	137.1 ± 25.7	<i>t</i> = 3.48	0.0007
Triglycerides (mg/dl)	160.3 ± 84.97	108.3 ± 54.18	<i>U</i> = 847.0	<0.0001
Body weight (kg)	79.25 ± 12.81	71.27 ± 11.88	<i>t</i> = 3.33	0.0012
BMI	29.66 ± 4.96	25.73 ± 3.17	<i>t</i> = 4.59	<0.0001

Note: Data are presented as mean ± SD for continuous data or % for categorical data.

Abbreviations: BMI, body mass index; CNT, control group; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoproteins; T2D, type 2 diabetes group.

classification on average - overweight. All patients were taking oral antidiabetic drugs, 81.3% of which in combination with insulin (data not shown).

3.2 | Volumetric analysis

Volumetric measures for the participants' brain are in Figure 1. T2D had significantly lower TIV ($p < 0.05$), and total GM and WM volumes ($p < 0.0001$, for both) in comparison with the CNT. In contrast, the total CSF volume was significantly higher ($p < 0.05$) in participants with type 2 diabetes than in control participants.

3.3 | VBM analysis

VBM analysis of GM showed 18 clusters with significantly decreased GM volume in participants with type 2 diabetes (Figure 2), whereas 5 clusters were located in frontal lobe (D, E, G, L and N), 3 clusters in limbic lobe (B, C and R), 2 clusters in occipital lobe (K and M), 2 clusters in posterior lobe (F and H), 1 cluster in temporal lobe (Q) and 5 clusters were found in sub-lobar regions of insula (A, I, J and P) and of lentiform nucleus (O).

3.4 | Cortical thickness analysis

SBM analysis of cortical thickness revealed 3 clusters with significantly decreased cortical thickness in participants with type 2 diabetes (Figure 3). Clusters were found in temporal lobe (A and C) and in the limbic lobe (B).

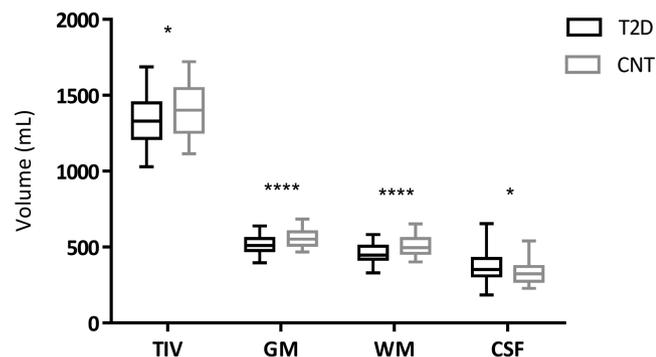


FIGURE 1 Boxplots of the distribution of total intracranial volume (TIV), total grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) volumes in each group. A significant difference between groups is indicated by * $p < 0.05$ and **** $p < 0.0001$, assessed with t (TIV, GM and WM) and Mann-Whitney (CSF) tests. CNT, control group; T2D, type 2 diabetes group

3.5 | Cortical gyrification analysis

SBM analysis of cortical gyrification index showed a distinctive pattern in particular in sensory regions, revealing 5 clusters with a significant increase in cortical gyrification index in participants with type 2 diabetes and only 1 with lower gyrification index in type 2 diabetes patients (Figure 4). Clusters with increased gyrification index were found in temporal lobes (C and F), posterior lobe (B), parietal lobe (D) and occipital lobe (E). The cluster with decreased gyrification index was in the temporal lobe (A). Sensitivity and specificity analysis of gyrification in patients versus controls, performed by computation of the ROC curves, showed significant discriminative values in all clusters (Figure 4c). The AUC ranged from 0.662 (SEM = 0.052, $p = 0.004$) to 0.755 (SEM = 0.046, $p < 0.001$).

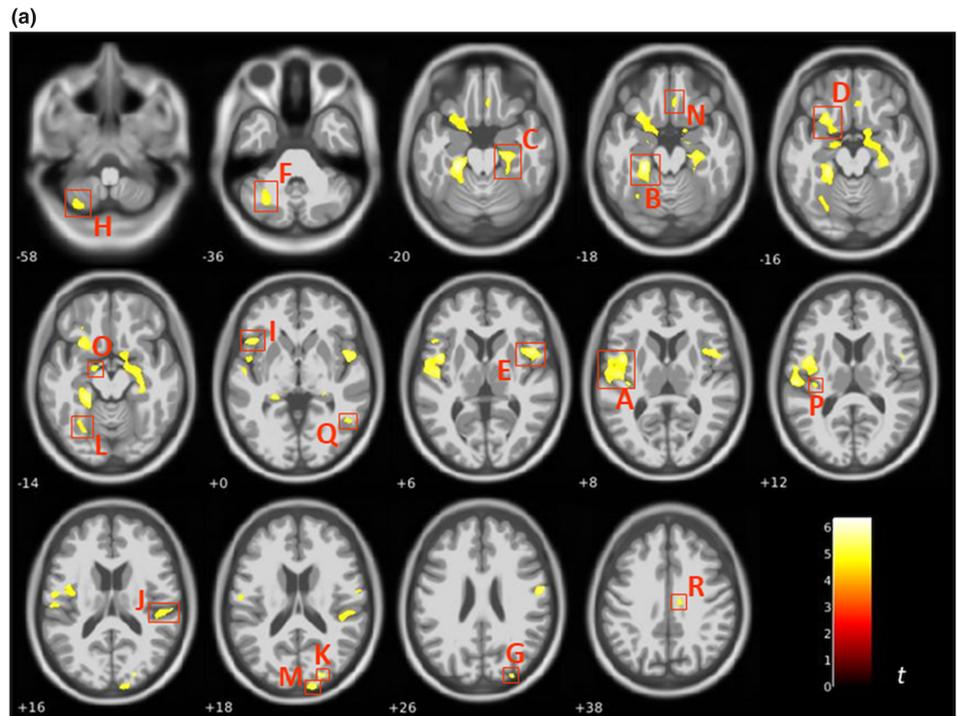
The correlation between clinical data and altered local gyrification index in type 2 diabetes patients, presented in Table 2, was significant mostly for measures of glycaemic profile. HbA1c was positively correlated with decreased gyrification in right primary auditory cortex (Cluster A) and with increased gyrification in right primary sensory cortex (Cluster D). Fasting glucose was positively correlated with increased gyrification in left inferior occipital cortex (Cluster F). In the right primary auditory cortex (Cluster A), decreased gyrification was moderately negatively correlated with disease duration and positively correlated with LDL cholesterol. Regarding the thresholds of the sensory task, they were positively correlated with increased gyrification in right primary sensory cortex (Cluster D).

4 | DISCUSSION

Diabetes is known to impair brain structure and function. In this study, we focused in structural analysis, and we targeted morphometric properties that are not captured by VBM or cortical thickness analyses, by evaluating for the first time cortical gyrification in type 2 diabetes.

We found changes in local gyrification index in type 2 diabetes and ROC analysis showed a powerful discriminative ability of this feature between patients and controls. These alterations were mainly located in sensory areas. These results are in agreement with studies suggesting that the sensory cortex is more prone to suffer alterations of gyrification (Alexander-Bloch et al., 2020; Ronan & Fletcher, 2015). Furthermore, the topology of sensory areas, including cortical folding, is suggested to be more genetically constrained (Alexander-Bloch et al., 2020). Although sulcal length seems to have a moderate degree of genetic control, different characteristics of

FIGURE 2 Voxel-based morphometry (VBM) analysis of grey matter (GM). (a) Statistical map presenting the clusters with significantly decreased GM volume in type 2 diabetes participants, thresholded at $p < 0.05$ with family-wise error (FWE) correction for multiple comparisons at voxel level, and with minimum extent cluster size correction ($K = 114$) at cluster level. (b) Labelling of the regions containing clusters with differences, according to their MNI coordinates, based in the Automated Anatomical Labelling and Yale BioImage Suite brain atlases. MNI, Montreal Neurological Institute



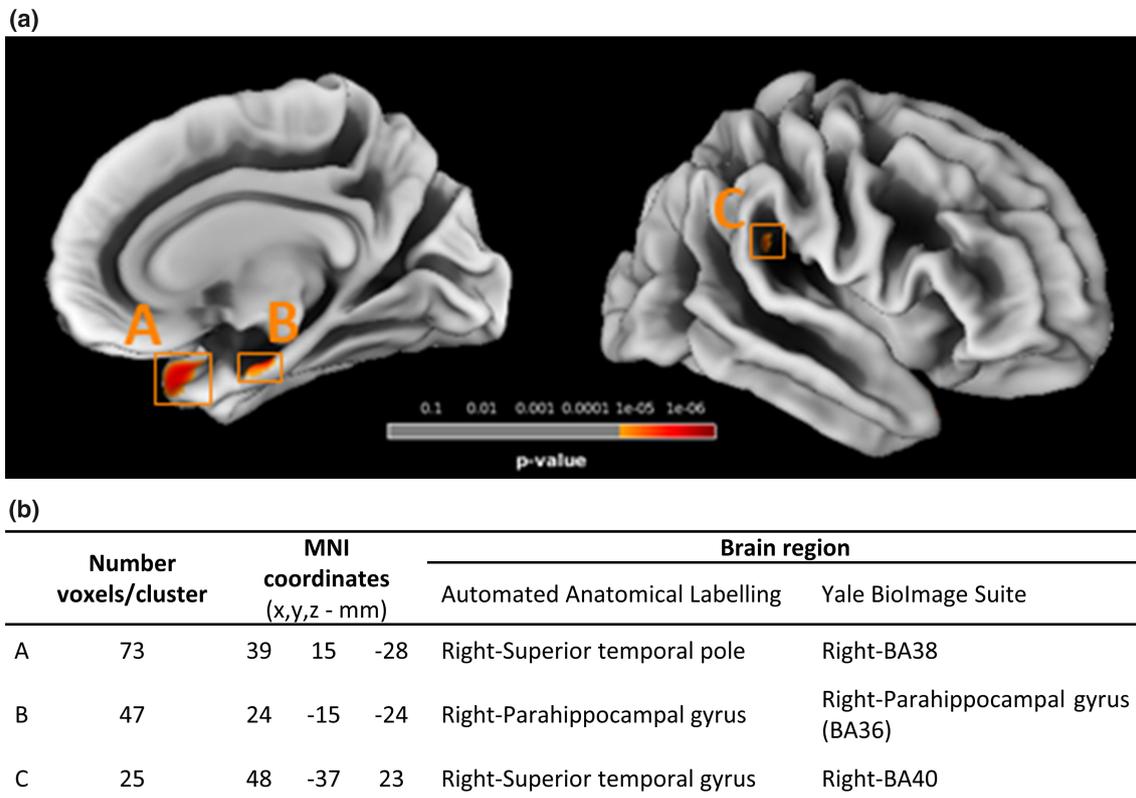
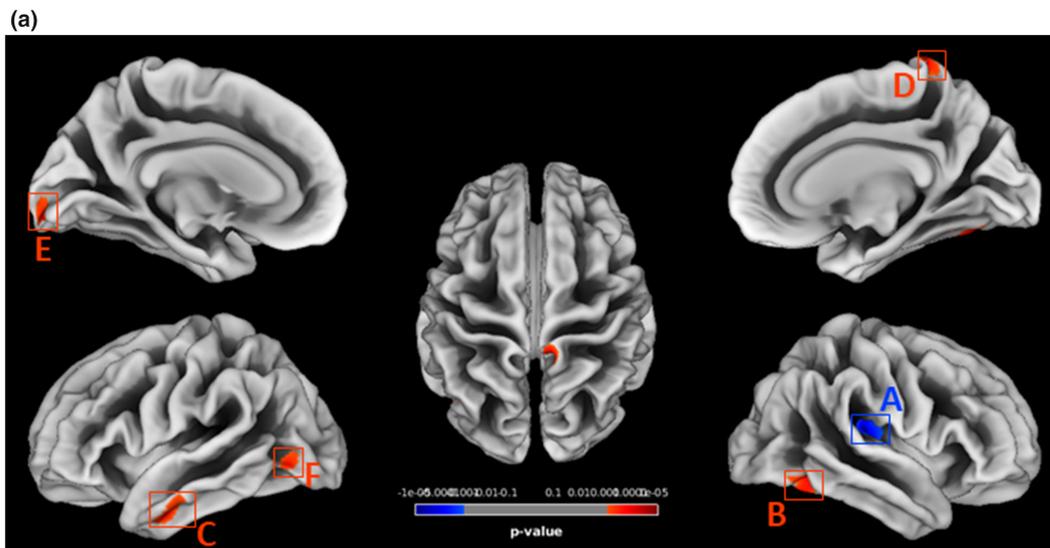


FIGURE 3 Surface-based morphometry (SBM) analysis of cortical thickness. (a) Statistical map presenting the clusters with significantly decreased cortical thickness in type 2 diabetes participants, thresholded at $p < 0.05$ with family-wise error (FWE) correction for multiple comparisons at vertex level, and with minimum extent cluster size correction ($K = 25$) at cluster level. (b) Labelling of the regions containing clusters with differences, according to their MNI coordinates, based in the Automated Anatomical Labelling and Yale BioImage Suite brain atlases. MNI, Montreal Neurological Institute

gyrification, such as the shape of sulci and gyri, might be more susceptible to environmental effects (Atkinson et al., 2015). Therefore, different external factors, both related with diabetes aetiology and the pathological environment caused by the disease, might have an effect in gyrification. Our correlation analysis indeed suggests a role of glycaemic profile in local gyrification alterations. As the clusters found to be different between groups were mainly in sensory cortex, we further investigated the correlation of gyrification with performance of a sensorial task, which we have previously reported to be impaired in diabetic patients in the same cohort (Duarte et al., 2015). We found a positive correlation between increased local gyrification in right primary sensory cortex, suggesting a relation between altered cortical gyrification and behavioural anomalies observed in such patients. A study with an animal model of diabetes also supports the idea of environmental influence in gyrification. This study showed a severe reduction in cortical convolution in streptozotocin-induced diabetic rats, which showed improvements in this morphologic measure after an antioxidant treatment (Nurdiana et al., 2018).

Using more conventional measures, we could observe highly significant differences in the total volumes of brain tissues, namely, the global reduction of GM and WM in type 2 diabetes patients, which is in line with an even larger cohort study (Moran et al., 2013). This reduction was accompanied by a difference also in TIV, though less pronounced, likely due to increased CSF values in the T2D, which is also observed in aging and dementia (Tanna et al., 1991; White et al., 2010). VBM analysis also supported what we found at the global whole-brain level, showing only clusters with lower GM volume in T2D. Consistently, we only observed regional cortical thinning in T2D. These results are in accordance with previous studies of brain atrophy using VBM (Moran et al., 2013; Moulton et al., 2015; Wang et al., 2014) and cortical thickness (Brundel et al., 2010; Chen et al., 2015, 2017; Li et al., 2018; Shi et al., 2019) analysis in diabetic populations. In our study, decreased regional GM volumes appeared in several regions in type 2 diabetes patients, mainly in the frontal lobe, as in Moran et al. (2013), Moulton et al. (2015) and Roy et al. (2020), and sub-lobar cortex. Specifically, we observed decreased GM volume in different clusters of the insula, which has



(b)

	Number voxels/cluster	MNI coordinates (x,y,z - mm)	Brain region	
			Automated Anatomical Labelling	Yale BioImage Suite
A*	188	34 -27 11		Right-Primary auditory (BA41)
B#	127	37 -63 -18	Right-Fusiform gyrus	Right-Fusiform gyrus (BA37)
C#	82	-50 -6 -32	Left-Inferior temporal gyrus	Left-BA20
D#	80	9 -40 76	Right-Paracentral lobule	Right-Primary sensory (BA1)
E#	60	-9 -96 -10	Left-Calcarine	Left-Visual associative (BA18)
F#	57	-44 -71 -4	Left-Inferior occipital gyrus	Left-BA19

*T2D<CNT; #T2D>CNT

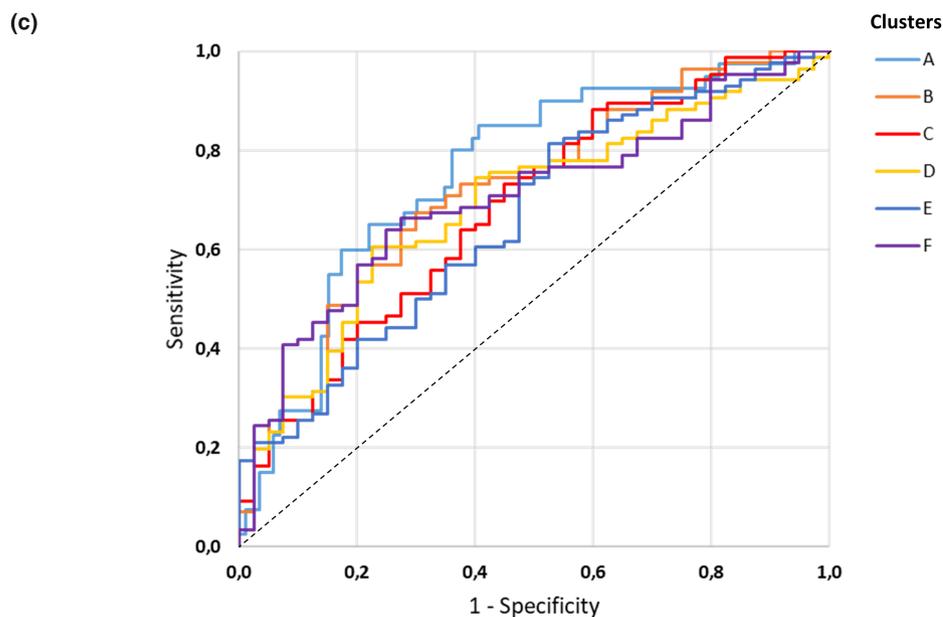


FIGURE 4 Surface-based morphometry (SBM) analysis of cortical gyricity. (a) Statistical map presenting the clusters with significantly decreased (*) or increased (#) cortical gyricity index in type 2 diabetes participants, thresholded at $p < 0.001$ at vertex level, and with minimum extent cluster size correction ($K = 47$) at cluster level. (b) Labelling of the regions containing clusters with differences, according to their MNI coordinates, based in the Automated Anatomical Labelling and Yale BioImage Suite brain atlases. (c) Receiver operating characteristic (ROC) curves for significant clusters in differentiation between groups. MNI, Montreal Neurological Institute

TABLE 2 Correlations of gyrification index with clinical and behaviour data

Clusters		A ^a	B ^b	C ^b	D ^b	E ^b	F ^b
		BA41	BA37	BA20	BA1	BA18	BA19
Age at diagnosis	Pearson <i>r</i>	0.012	0.189	0.138	0.095	-0.027	-0.042
	<i>p</i>	0.931	0.153	0.297	0.476	0.837	0.749
Disease duration	Pearson <i>r</i>	-0.357	0.008	0.042	-0.051	0.096	0.216
	<i>p</i>	0.006	0.951	0.752	0.702	0.472	0.100
Fasting glucose	Spearman rho	-0.013	0.0002	-0.028	0.119	-0.198	0.219
	<i>p</i>	0.908	0.999	0.799	0.275	0.07	0.044
HbA1c	Pearson <i>r</i>	0.266	0.051	0.059	0.232	-0.06	0.103
	<i>p</i>	0.015	0.647	0.596	0.035	0.588	0.355
Total cholesterol	Spearman rho	0.168	-0.018	-0.088	0.117	0.099	-0.119
	<i>p</i>	0.124	0.870	0.422	0.287	0.368	0.277
HDL cholesterol	Pearson <i>r</i>	-0.082	-0.065	0.017	0.202	0.076	-0.106
	<i>p</i>	0.455	0.552	0.880	0.064	0.489	0.333
LDL cholesterol	Pearson <i>r</i>	0.259	0.008	-0.109	0.191	0.077	-0.058
	<i>p</i>	0.019	0.946	0.329	0.085	0.493	0.605
Triglycerides	Spearman rho	0.086	0.032	-0.049	-0.068	-0.022	0.097
	<i>p</i>	0.440	0.776	0.659	0.543	0.847	0.384
Body weight	Pearson <i>r</i>	0.087	0.047	0.098	-0.317	-0.043	-0.028
	<i>p</i>	0.427	0.672	0.373	0.773	0.696	0.799
BMI	Pearson <i>r</i>	0.078	-0.018	0.171	0.141	0.148	-0.036
	<i>p</i>	0.477	0.873	0.118	0.197	0.176	0.743
Psychophysics threshold	Spearman rho	-0.015	-0.028	0.031	0.334	0.054	-0.096
	<i>p</i>	0.904	0.818	0.797	0.005	0.659	0.427

Abbreviations: BMI, body mass index; CNT, control group; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoproteins; T2D, type 2 diabetes group.

^aT2D < CNT.

^bT2D > CNT.

been implicated in an overwhelming variety of functions ranging from sensory processing to representation of feelings and emotions (Roy et al., 2020). This structure was already reported to present impaired neurovascular coupling in an fMRI study with the same cohort (Duarte et al., 2015). As previously highlighted (Moran et al., 2013; Roy et al., 2020), lower regional GM volume in type 2 diabetes was also observed in our study in the limbic lobe, namely, in the cingulate cortex and bilateral parahippocampal gyrus. Furthermore, there was a concomitant GM volume reduction and cortical thinning of the parahippocampal gyrus. A region in the temporal lobe also showed a decrease in cortical thickness (Chen et al., 2017; Li et al., 2018).

In contrast to our results showing decreased GM volume and thickness, we mainly observed increased gyrification in type 2 diabetes. The fact that type 2 diabetes brains showed mainly higher gyrification index was

surprising for us, as we expected it would follow the tendency of other morphometric measures. This suggests a more complex underlying mechanism possibly involved. The diabetic brain is susceptible to a pathological environment including inflammation, oxidative stress, and hypoxia, leading ultimately to axonal damage and cellular death. Brain atrophy is related with neurological insult and gyrification may also be affected by other factors such as connectivity changes (Ronan & Fletcher, 2015). Interestingly, previous studies showed the same pattern of cortical morphology change, a thinning of the cortex accompanied by an increase in gyrification, in diseases with more genetic or neurodevelopmental basis, such as 22q11.2 deletion (Bearden et al., 2009), Williams syndrome (Gaser et al., 2006), autism (Jou et al., 2010) and schizophrenia (Palaniyappan & Liddle, 2012).

As a limitation of this study, its cross-sectional nature hinders the investigation of specific disease trajectories,

which only longitudinal data might clarify. Moreover, although the sample size is quite reasonable, this novel finding yields replication in future studies.

5 | CONCLUSION

We found a novel signature of changed brain structure in type 2 diabetes, the gyrification index, in addition to the expected whole-brain cortical atrophy. Our results regarding local gyrification are surprising and cannot be simply explained by local neural loss mechanisms. Notably, we found mainly increased gyrification in sensory areas in type 2 diabetes. Although a genetic influence should be considered, our correlation results concurrently suggest an influence of metabolic control in alterations of gyrification in type 2 diabetes. This is an important issue to consider in further studies of gyrification in diabetes, addressing the complex aetiology of the disease and assessing different underlying factors, including both genetic and environmental determinants. Furthermore, a longitudinal approach will be crucial to investigate in more detail the mechanisms underlying these alterations, ultimately as a potential new biomarker in diabetes management.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JC, JVD, CM, LG and MCB contributed to conception and design of the study. JVD performed acquisition of data. JC, JVD, and MCB performed data analysis and interpretation. JC, JVD and MCB wrote the paper. JC, JVD, CM, LG and MCB contributed to the discussion and revised the manuscript.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ejn.15424>.

DATA AVAILABILITY STATEMENT

The data sets analysed in the current work are not public available to protect the patients. However, the pre-processed anonymized data can be shared on a reasonable request to the corresponding author.

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