Morphometric analyses of brain atrophy in Diabetes type 2: evidence from both T1 and T2 MRI

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Abstract

OBJECTIVE: Type 2 diabetes (DM2) is associated with brain atrophy and microvascular pathology. However, the available literature is poor concerning the distribution of brain atrophy in DM2. We aimed to study the regional distribution of brain atrophy in DM2, with an emphasis on vascular anomalies, analyzing both T1 and T2-weighted magnetic resonance imaging (MRI) scans.

METHODS: This study used MRI scans in 34 participants with DM2 and 42 participants without DM2. Voxel-based morphometry was used to study the regional distribution of atrophy in DM2. T1-weighted scans were analyzed with the usual intent of identifying anatomical abnormalities in brain tissue, whereas T2-weighted scans were used to assess both anatomical and vascular disturbances.

RESULTS: T1-VBM showed a bilateral distribution of atrophy, affecting mainly the sub-lobar and insular areas, but also the occipital and temporal lobes. T2-VBM showed similar patterns, namely atrophy in the limbic lobe, as well as in the sub-lobar, insular and temporal areas, all bilaterally. An ANOVA test allowed to visualize the overlapping areas of both analyses.

CONCLUSIONS: In conclusion, we found that gray-matter atrophy in DM2 patients is bilaterally distributed in the sub-lobar and insular areas, as well as in the temporal and occipital lobes and limbic system.

I. Introduction

Diabetes mellitus type 2 (DM2) is the most prevalent metabolic disorder in the world, affecting 347 million people as of 2013, up from 285 million patients in 2010 (1). A chronic condition, DM2 is associated with the occurrence of both micro and macrovascular complications. As such, a mix of both general metabolic dysfunction and vascular pathologies affect multiple organ systems and are lead to co-morbidities, which include blindness, end-stage renal disease, sexual dysfunction, non-trauma amputation, 2-6 times increased cardiovascular risk, neuropathy and even cognitive dysfunction (2). Relating to this

latter issue, the literature has shown clear links between DM2 and dementia, cognitive impairment, Alzheimer's disease and depression (3) (4) (5). At a brain morphology level, DM2 patients are known to develop brain vascular changes, such as subcortical infarctions, and brain atrophy, as seen in both grey and white matter volume (6) (7).

MRI allows to detect such morphological changes in the brain. It is well established that neurodegenerative diseases, e.g. Alzheimer's disease and other dementias, present specific patterns of atrophy that can be detected by the soft tissue contrast characteristic of MRI scans (8) (9). While these structural changes are usually assessed by trained radiologists on an individual basis, automated techniques are also available for group analyses. Not only are these accurate, they also allow analysis across large numbers of subjects in a time-efficient manner so as to assess the overall (average) imaging profile of any given pathology (10).

One such technique is Voxel-based morphometry (VBM), a structural neuroimaging analysis method that tests hypothesis pertaining to differences of gray matter volume (GMV) between groups or correlated with a given metric (e.g. test score), across a large numbers of subjects (11) (12). It has been successfully used to study GMV differences in e.g. migraine, tension-type headache, chronic back pain, numerous dementias, multiple sclerosis, schizophrenia and others (13) (14) (15) (16). Technically, it consists in computer-aided statistical analysis, using a mass univariate implementation of the general linear model (GLM, the t-test being a particular case) across all voxels, so as to detect GMV correlates of differences across subjects. VBM has proven to be biologically valid by acceptably corresponding with manual and visual techniques of volumetric measurements, notably with region of interest (ROI) analyses (17).

In the interest of assessing the current knowledge in the literature, describing generic brain parenchyma alterations related to DM2, a sistematized review was conducted in the scope of this project (details available at http://goo.gl/2l2leW). It describes the results of 13 included papers from a total of 105 that were the result of the query "diabetes and mri and and (anatomical or vascular) and cognitive" on the PubMed database.

Through the analysis of the Results section of each of the included articles, it was observed that: 5 of them reported decreased cortical grey matter density in different locations, namely the hippocampus, cingulate gyrus, temporal and parietal lobes; 3 others described changes in white matter tracts, including disturbed overall connectivity. Finally, 2 papers detected increased risk of lacunar or cortical infarctions, as well as other vascular lesions and cerebrovascular disease. All papers, except for one, documented functional disturbances as well, notably decreased cognitive performance.

VBM is typically performed resorting to T1-weighted images (spin-lattice relaxation), better suited to find focal lesions and to segment

the grey matter from the white matter. In turn, T2-weighted images (spin-spin relaxation) are more suitable when assessing vascular and white matter lesions (18). The aformentioned studies resorted either to T1-VBM or to other analytical methods to quantify losses of brain volume. Recent studies, however, have successfully employed T2-weighted images in the joint analysis of GMV and vascular changes/ion deposition, as demonstrated by the validation of T2-VBM (19). In this case, changes were assessed not only pertaining to atrophic processes but also to vascular or physiological factors.

Since there is no consensus between the authors of the included articles of the reviewed literature, as similar approaches yielded different results (distinct affected brain regions), it becomes clear that further studies are in order to better understand the neural impact of DM2. On the other hand, since T2-VBM has not been performed before on MRI results of DM2 patients, the additional information provided by this technique could provide further information related to vascular effects rather than only atrophy.

II. Methods

The study was approved by the ethics committee of the University of Coimbra. Informed consent was obtained from all participants. All investigation was conducted according to the principles of the Declaration of Helsinki.

I. Patient Selection

Thirty-four participants with DM2 and forty-two matched control subjects were recruited. Controls were recruited from the general population of Hospital or University staff, and DM2 patients from the Endocrinology Department, of the University Hospital (Centro Hospitalar e Universitário de Coimbra). DM2 patients presented with the condition for at least one year prior to the commencement of this study, and were diagnosed using standard WHO criteria (20) (21). The demographic details can be found in Table 1, alongside values for glycated hemoglobin (HbA1c). Participants were included between November 2011 and November 2013. Exclusion criteria for both groups were severe cardiovascular disease (AIT or stroke), neurologic diseases unrelated to diabetes likely to affect cognitive functions, known history of psychiatric disease and alchool abuse.

II. Study population

There were 34 patients in the DM2 group (mean age 60,0 [SD 7,4] years) and 42 in the healthy control group (mean age 50,4 [SD 7,9] years). Group characteristics and comparisons are presented in Table 1. DM2 participants had greater fasting blood glucose levels and HbA1c values, higher BMI and were more likely to report a history of hypertension. (Table 1)

	Diabetes (n=34)	Controls (n=42)
Age (years, mean ± SD)	60,0 ± 6,4	50,4 ± 7,9
Gender (male:female)	21:13	21:21
BMI (kg/m2, mean ± SD)	25,9 ± 3,2	19,3 ± 11,5
Blood glucose (mg/dL, mean ± SD)	165,3 ± 58,5	82,1 ± 28,4
HbA1c (%, mean ± SD)	9,4 ± 3,2	4,6 ± 1,9
HTN (yes:no)	28:6	7:32
TIV (l, mean ± SD)	1,5 ± 2,2	1,5 ± 2,3

Table 1: *Description of subjects, from both the DM2 and control groups*

III. Image Acquisition

The MR scans were acquired at the Portuguese Brain Imaging Network facilities in Coimbra, Portugal, on a 3T research scanner (Magnetom TIM Trio, Siemens) using a phased array 12-channel birdcage head coil (Siemens). For each participant, a 3D anatomical MPRAGE (magnetization-prepared rapid gradient echo) scan was acquired using a standard T1-weighted gradient echo pulse sequence with TR = 2530 ms, TE = 3.42 ms, TI = 1100 ms, flip angle 7○, 176 single shot slices with voxel size 1x1x1 mm, and FOV 256 mm. True 3D, high-resolution, T2-weighted images were also acquired. The turbo spin echo with variable flip-angle distribution (sampling perfection with application optimized contrasts using different flip angle evolution; SPACE) pulse sequence was used with the following scan parameters: TR/TE/NEX = 3200ms/450ms/2; matrix, 192x192x144 slices; voxel resolution 1.25x1.25x1.25mm3. Parallel acquisition of independently-reconstructed images was allowed, using generalized, auto calibrating, partially-parallel acquisitions to reduce SAR and scanning time.

IV. Image Analysis

Images were processed with SPM8 (http://www.fil.ion.ucl.ac.uk/), running on MATLAB 8.01 (The Math-Works, Inc., Natick, MA), in order to perform the VBM analyses. This included spatial normalization and grey matter segmentation using the unified segmentation algorithm (22). Modulated grey matter segments, registered to the ICBM152 template, were then smoothed with an 8mm full width at half maximum (FWHM) three-dimensional gaussian kernel to ensure normality of the data. Statistical analyses were then performed us-

ing the standard implementation of the GLM, adapted for independent group t-test comparisons (12), using the total intracranial volume data as a confounding covariate. Results were presented with a threshold of 0.05, corrected for family-wise error (FWE). The extent threshold used was k = 50.

III. Results

I. Standard VBM

VBM from T1 scans showed a widespread pattern of bilateral atrophy, not only restricted to mesial area, demonstrating high sensibility to detect GM atrophy (Figure 1). Among the structures identified, sub-lobar, insular and basal ganglia atrophy was detected. Volumetric decreases were also detected in the frontal, temporal and occipital lobes in both hemispheres. Besides these encephalic structures, atrophic patterns were also found in the left hemisphere of the cerebellum (Table 2).

II. T2 VBM

VBM from T2-weighted images also showed a bilateral pattern of atrophy (Figure 2). The areas of atrophy found mostly coincide with the T1-weighted analysis. Amongst the areas identified, the insula, the sub-lobar area and the temporal lobe were notably affected, bilaterally (Table 3).

III. ANOVA VBM

The execution of an ANOVA test allowed to assess the joint information as extracted from the T1 and T2 analyses (Figure 3). A considerable area of superposition was found, confirming the previous results. These areas were bilateral and mostly present in both individual methods (Table 4).

IV. Discussion

This study aimed to determine which areas of the brain were affected by the adverse physiological effects of chronic hyperglycemia. Indeed, the results show patterns of atrophy in both T1 and T2 weighted analysis. Furthermore, comparison between the two further confirmed the pathological patterns.

Until now, the available literature is relatively poor in the study of either the distribution of brain atrophy or tissue pathology in DM2. Some previous studies demonstrated the association of DM2 with the decrease of grey matter (7) (23) (24) and even hippocampal losses (25). To our knowledge, only one study to date sampled a relatively large population (350 patients and 364 controls) and employed VBM in their analysis (26). This study suggested a pattern of gray matter loss mainly in the medial temporal, anterior cingulate and medial frontal lobes. These structural changes were correlated with functional disturbances, such as poorer visuospatial construction, planning and overall cognitive performance. Another study used

Number voxels	T	P(unc)	x, y, z (mm)	Areas
2174	7,041 6,634 6,508	<0,00001	-42, -16, 8 2, -6, -14 -8, 10, 10	Left Cerebrum, Sub-lobar, Left Insula, Caudate
1166	7,229 5,65 5,934	< 0,00001	42, 12, -14 46, -90, 0 50, 42, 18	Right Cerebrum, Right Insula, Sub-lobar, Temporal Lobe, Frontal Lobe
383	6,294	< 0,00001	-40, -68, -56	Left Cerebellum
100	5,959	< 0,00001	-44, -92, -10	Left Occipital Lobe
75	6,1342	< 0,00001	24, -102, 18	Right Occipital Lobe
54	5,793	< 0,00001	-48, -82, 24	Left Middle Temporal Gyrus

Table 2: *Areas with gray matter atrophy in patients with DM2, in T1-weighted analysis*

Number voxels	T	P(unc)	x, y, z (mm)	Areas
954	5,586 6,226 6,908	< 0,00001	-64 -60 -8 -56, 22, 12 -12, 16, 2	Left Cerebrum, Left Insula, Sub-lobar, Left Inferior Temporal Gyrus
390	5,859 6,191	< 0,00001	46, 6, 2 10, 16, 4	Right Cerebrum, Right Insula, Sub-lobar, Temporal Lobe

Table 3: *Areas with gray-matter atrophy in patients with DM2, in T2-weighted analysis*

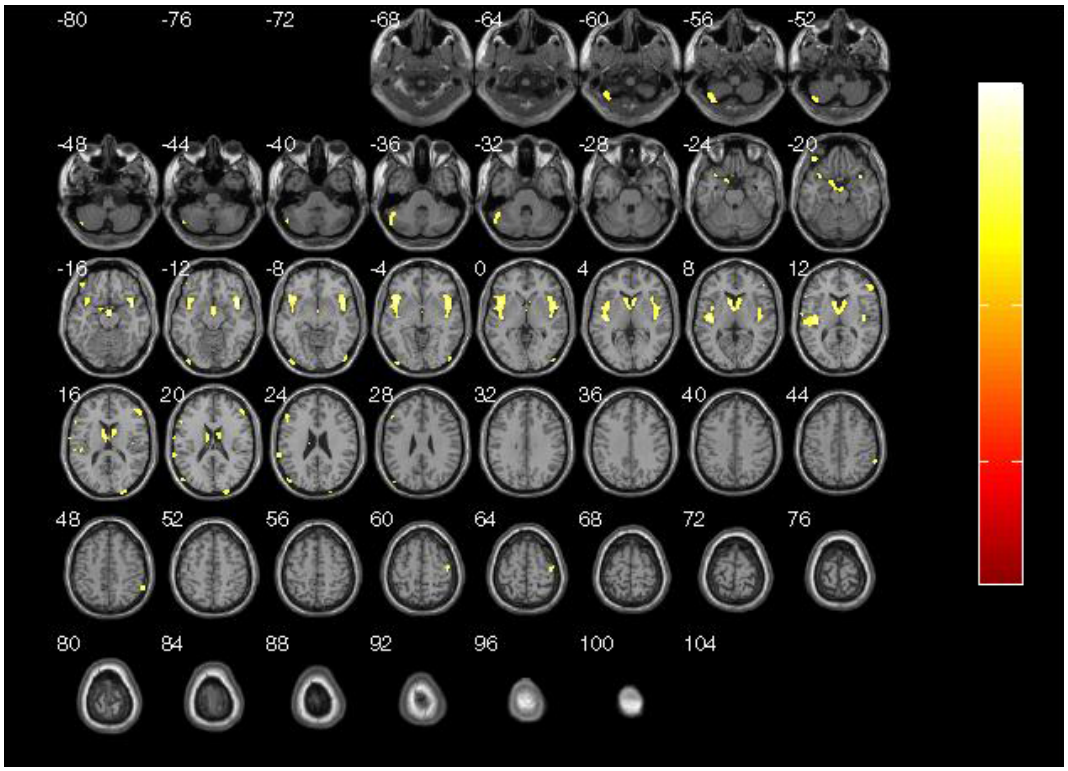

Figure 1: *Parametric mapping of grey-matter loss in DM2 compared to control (T1-weighted scans).*

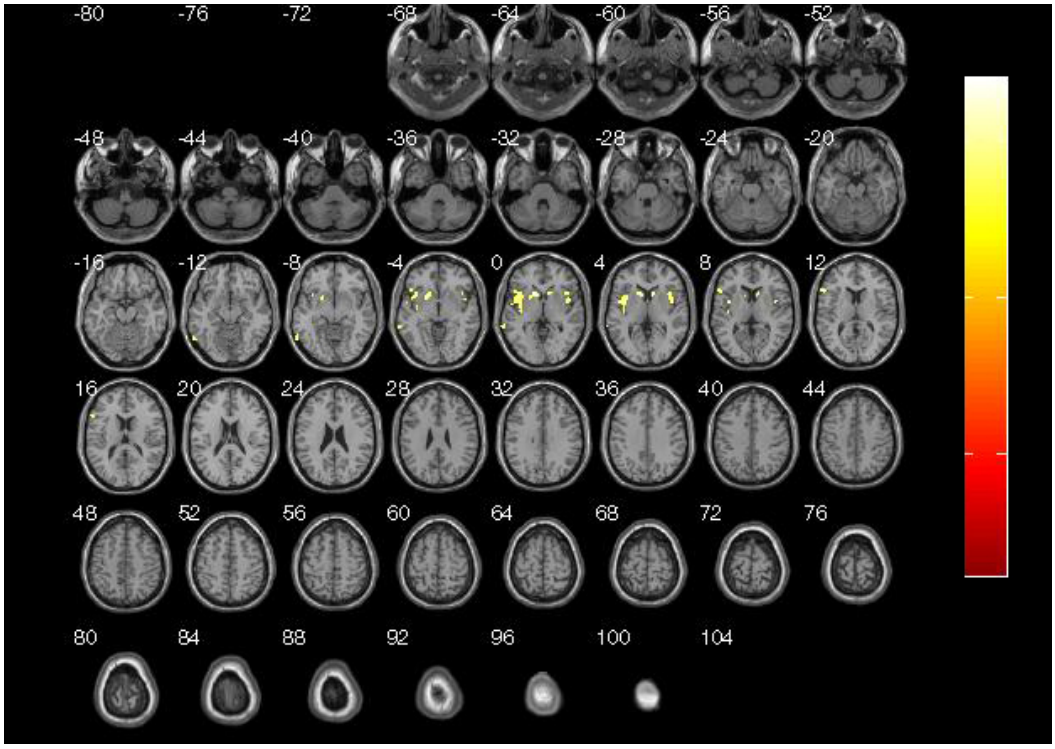

Figure 2: *Parametric mapping of grey-matter loss in DM2 compared to control (T2-weighted scans).*

Number voxels	F	P(unc)	x, y, z (mm)	Areas
14899	44,227	<0,00001	-10, 16, 2	Left Cerebrum, Gray Matter, Left Cerebellum, Temporal Lobe, Frontal Lobe
5736	37,808	<0,00001	10, 16, 4	Right Cerebrum, Gray Matter, Frontal Lobe, Right Inferior Frontal Gyrus
2242	29,087	<0,00001	36, -30, -30	Right Cerebellum, Right Cerebrum, Limbic Lobe
1917	27,571	<0,00001	30, 58, 16	Right Frontal Lobe, Right Superior Frontal Gyrus
253	23,675	<0,00001	-46 -92 -10	Left Occipital Lobe
171	22,958	<0,00001	-10 -14 -2	Left thalamus

Table 4: *Areas with grey-matter atrophy in patients with DM2 in both T1 and T2 contrasts*

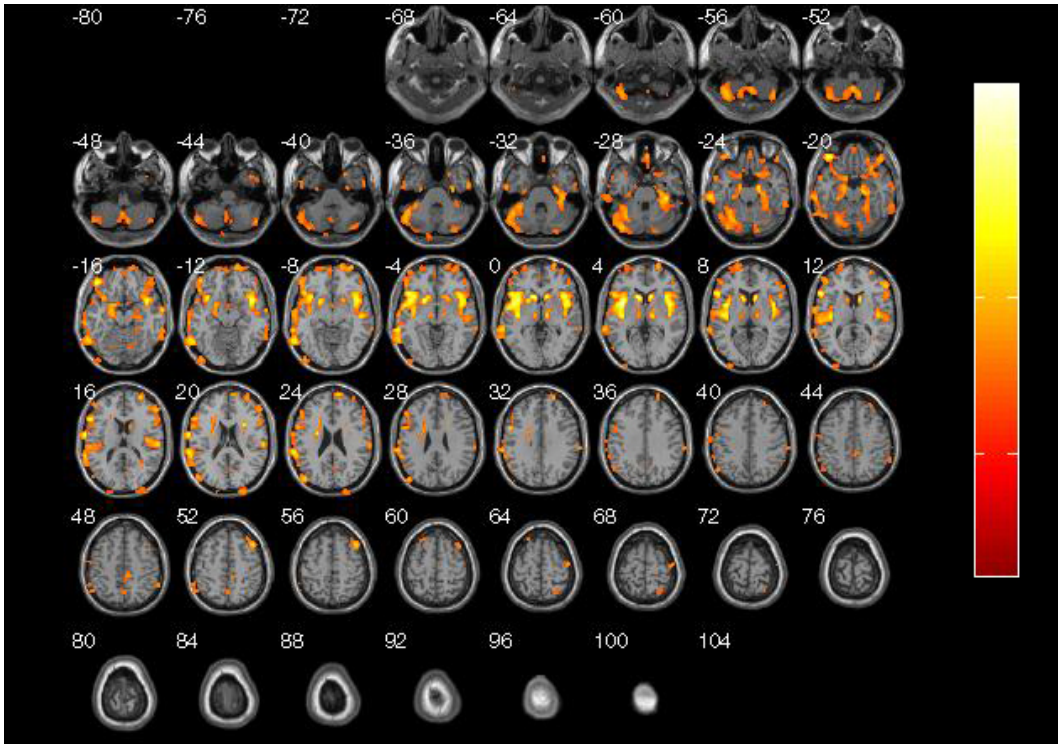

Figure 3: *Visual representation of the result of an ANOVA test to confront the results of both contrasts.*

the VBM technique to investigate the severity of gray matter loss in the hippocampal region. The results indicated a significant loss in hippocampal volume and overall grey matter volume as well (25).

Our results have shown a somewhat similar distribution of atrophic tissue, yet with some particularities. T1-VBM yielded a clear bilateral distribution, affecting mainly the sub-lobar and insular areas, but also the occipital and temporal lobes. The left hemisphere of the cerebellum was also affected. T2-VBM showed similar patterns, namely atrophy in the limbic lobe, as well as in the sub-lobar, insular and temporal areas, bilaterally. The ANOVA allowed to visualize the overlapping areas of both analyses and confirm that both reported similar atrophic regions. This has been seen in the literature, particularly an affection of the limbic system and of the temporo-parietal lobes (cingulum, insular area, and hippocampus) (7).

The novelty of our approach resides in the innovative use of T2-VBM, which, to our knowledge, has not been used before in the context of DM2. While, in general, T1-weighted images are more appropriate for an anatomical analysis of the brain, T2-weighted scans allow for a better visualization of fluids and myelinated tissue, as well as of vasopathies (27). Our analysis showed that T2-weighted scans revealed atrophic tissue in the sub-lobar region, which comprises highly vascularized grey matter and is thus better visualized in T2-weighted scans.

This study had several strengths, mainly concerning the definition of DM2 according to well defined criteria, comprehensive MRI methodology, automated brain segmentation and a voxel-based whole-brain approach to the analysis of atrophic tissue. As far as weaker points are concerned, it would have been advantageous to increase the study's population size. Moreover, a functional assessment of the patients would provide us with a better understanding of how these structural changes affect their overall cognitive performance. The molecular mechanism that causes atrophy in the brains of DM2 patients is still not fully understood. Some authors hypothesized metabolic, vascular and endocrine pathways (28). Vascular disease, in particular microvascular disturbances, are likely to play a role, because of blood flow impairment to the affected tissues (29).

In conclusion, we found that gray-matter atrophy in DM2 patients is bilaterally distributed in the sub-lobar and insular areas, as well as in the temporal and occipital lobes and limbic system.

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V. Acknowledgements

This work would have never been possible if it was not for my mentors, Prof. Doutor João Pereira and Prof. Doutor Miguel Castelo-Branco. I also thank LBIM, IBILI and ICNAS.