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Research article

Brain structural alterations detected by an automatic quantified tool as an indicator for MCI diagnosing in type 2 diabetes mellitus patients: A magnetic resonance imaging study

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ABSTRACT

Background and objectives: Type 2 diabetes mellitus (T2DM) is an important risk factors for mild cognitive impairment (MCI). Structural magnetic resonance imaging (sMRI) is an effective and widely used method to investigate brain pathomorphological injury in neural diseases. In present study, we aimed to determine the brain regional alterations that correlated to the incidence of MCI in T2DM patients.

Materials and methods: Eighteen T2DM patients with and without MCI (DMCI/T2DM) respectively, and eighteen age/gender-matched healthy controls (HC) were recruited. Brain MRI imagines of all the individuals were subjected to automatic quantified brain sub-structure volume segmentation and measurement by Dr. brain ™ software. The relative volume of total gray matter (TGM), total white matter (TWM), and 68 pairs (left and right) of brain sub-structures were compared between the three groups. Cognitive function correlation analysis and receiver operating characteristic (ROC) curve analysis were conducted in the MCI-related brain regions in T2DM patients, and we utilized a machine learning method to classify the three group of subjects.

Results: 10 and 27 brain sub-structures with significant relative volumetric alterations were observed in T2DM patients without MCI and T2DM patients with MCI, respectively ($p < 0.05$). Compared with T2DM patients without MCI, eight critical regions include right anterior orbital gyrus, right calcarine and cerebrum, left cuneus, left entorhinal area, left frontal operculum, right medial orbital gyrus, right occipital pole, left temporal pole had significant lower volumetric ratio in T2DM patients with MCI ($p < 0.05$). Among them, the decrease of volumetric ratio in several regions had a positive correlation with Montreal Cognitive Assessment (MoCA) scores and Mini-Mental State Examination (MMSE) scores. The classification results conducted based on these regions as features by random forest algorithm yielded good accuracies of T2DM/HC 69.4%, DMCI/HC 72.2% and T2DM/DMCI 69.4%.

Conclusions: Certain brain regional structural lesions occurred in patients with T2DM, and this condition was more serious in T2DM patients combined with MCI. A systematic way of segmenting and measuring the whole brain has a potential clinical value for predicting the presence of MCI for T2DM patients.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance or deficiency of insulin function, which commonly cause microvascular and macrovascular complications [1]. Compared with healthy people, T2DM patients have an approximate 47% increased incidence of dementia - [2, 3]. Mild cognitive impairment (MCI) is an intermediate stage between normal cognitive function and

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dementia, and the prevalence of MCI is estimated 4 times that of dementia [4]. MCI is usually characterized by impaired or declined cognition, minimal impairment of complex activities, essentially normal daily functional activities, and absence of dementia [5]. It has been demonstrated that T2DM mainly impair the cognitive function by affecting cerebral blood flow, glucose metabolism and brain structure in MCI patients [6, 7].

Several studies have illustrated brain structural alterations as the imaging correlation between T2DM and MCI, which is independent of cardiovascular risk factors. For instance, Groeneveld O. et al. have reported that in T2DM patients, gray matter atrophy instead of vascular brain injury related to the incidence of MCI and early dementia [8]. Li Chang et al. have concluded that T2DM accelerated gray matter atrophy, subcortical and cortical atrophy could be the primary events associated with MCI [9, 10]. Therefore, it is necessary to further investigate the brain structural alterations in T2DM patients to clarify the association between T2DM and cognitive impairment.

Structural magnetic resonance imaging (sMRI) is an effective and widely used technology to study brain pathomorphological injury in neural diseases [11]. Moreover, plenty of studies have used voxel-based morphometry (VBM) method to evaluate alterations of gray matter volumes in T2DM and MCI patients [12, 13, 14, 15]. In [12] a quantitative meta-analysis of volumetric and whole-brain VBM data was conducted on 5 VBM and 15 volume related studies and revealed that the GM reduction in patients with T2DM. In [13] the relationships between GM status of cognitive and mood control sites and these scores in T2DM were investigated through a VBM analysis. In [14] VBM methods have also been used to examine gray matter changes in vascular MCI patients. In [15] a voxel level analysis was performed to explore critical brain regions that predict the presence of MCI or AD over a decade prior to the onset of clinical symptoms. However, as far as we known, very few studies have reported the measurement and location of the structural changes through a whole brain segmentation method in T2DM patients combined with MCI.

Based on previous studies, we aimed to investigate cerebral volumetric changes in T2DM patients with or without MCI by a systematic way of segmenting the whole brain. We supposed that atrophy of brain parenchyma (gray matter and white matter), and certain cerebral region volumetric alterations should be related to the presence of T2DM, and these structural lesions could be useful to explain the later cognitive impairment of the patients. Moreover, volumetric changes of certain brain sub-structures should have a potential predication benefit for MCI diagnosing in T2DM patients.

2. Materials and methods

2.1. Study individuals

Eighteen T2DM patients, eighteen T2DM patients combined with MCI, and eighteen age-matched healthy controls were enrolled from the outpatient clinic of the Second People's Hospital of Wuxi of Nanjing Medical University from April 2020 to October 2020. The diagnose criteria of T2DM was referred to the 1999 criteria provided by the World Health Organization [16]. MCI was diagnosed in patients with complains of memory loss, Montreal Cognitive Assessment (MoCA) score <26, Mini-Mental State Examination (MMSE) score >24, normal Activities of Daily Living (ADL) score [17]. Patients with previous dementia diagnosis, stroke history, epilepsy, or depression (24-item Hamilton Depression Scale [HAMD] score >20) were excluded. Age, education level, duration of T2DM, smoking and drinking history were collected from the research population. The age distribution of all enrolled individuals was from 43 to 51 years old (average age $\pm$SD $= 52.4 \pm 5.3$ years). All the recruited patients were orally informed, and a written contract was collected before the research. The study was approved by the Ethics Committee of the Second People's Hospital of Wuxi of Nanjing Medical University.

2.2. Physical, biochemical, and neurophysiology examination

Blood pressure, weight, height, and body mass index (BMI) of each individual were measured by standard survey method. Regular lab examinations were carried out to evaluate fasting plasma glucose (FPG), fasting C-peptide (FCP), glycosylated hemoglobin (HBA1C), total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), cystatin C, thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), uric acid (UA), homocys-teine, creatinine, glomerular filtration rate (GFR), alanine transaminase (ALT), and aspartate transaminase (AST). All enrolled individuals received MoCA, MMSE, ADL, and HAMD test independently.

2.3. MRI data collection

A Siemens 3.0 T MRI scanner were utilized to acquire T1- weighted images from each subject. The parameters of 3-dimensional magnetization prepared rapid gradient echo (3D MP-RAGE) were as following: sagittal view; repetition time (TR) $= 8.0$ ms; echo time (TE) $= 3.7$ ms; number of slices $= 250$; slice thickness $= 1.2$ mm; flip angle $= 9^{\circ}$; field of view (FOV) $= 256 \times 256$ mm^2; acquisition matrix $= 252 \times 227 \times 250$; voxel size $= 0.98 \times 0.98 \times 1.20$ mm^3.

2.4. Brain sub-structure volume segmentation and measurement

The segmentation and measurement of brain region volume were conducted by the Dr. Brain ™ software (version 3.3.6, Shenzhen Yiwei Medical Technology Co. LTD, Guangdong, China; http://www.drbrain.net), an automatic MRI quantification tool based on VBM method. Every MRI image was segmented into 68 ROIs (left and right) of brain sub-structures (including amygdala, hippocampus, entorhinal area etc.) according to the neuromorphometrics template. The total intracranial volume (TIV) was calculated as the sum of total gray matter (TGM) volume, total white matter (TWM) volume, and cerebrospinal fluid (CSF) volume. Intracranial volume ratio of sub-structure ROI = volume of brain region/TIV (%).

2.5. Statistical analysis

All data analyses were performed by the MedCalc Statistical Software version 15.2.2 (MedCalc Software bvba, Ostend, Belgium). Comparisons of demographic and clinical features of patients among the three groups were conducted by Chi-squared test, independent samples t-test, and one-way analysis of variance (ANOVA) followed by Turkey-Kramer test. D'Agostino-Pearson test was used to assess the normality of data. If the data follow normality, the statistic difference in intracranial volume ratio of brain sub-structures between each 2 groups were calculated by independent samples t-test, or otherwise, by Mann-Whitney test. Partial correlations between the relative volume of brain sub-structures and the rating scale (MoCA and MMSE) scoring were performed adjusted for age, gender and education level. A significant statistic difference was presented as $p < 0.05$. At last, a random forest classification using normalized ROI volume ratio as features was performed to demonstrate the predicting power of the critical brain regions deduced from the above tests.

3. Results

3.1. Characteristics of study population

Demographic and clinical features of healthy control, T2DM without and with MCI groups were presented in Table 1. No significant difference was observed in age, gender, BMI, DBP, TC, TG, HDL-C, or LDL-C among the three groups ($p > 0.05$). There was significant difference between education level, duration of T2DM, SBP, FPG, FCP, HbA1c, MoCA and MMSE score ($p < 0.05$). Compared with healthy control, patients with T2DM had higher levels of FPG, HbA1c, and SBP. Compared with T2DM

Table 1. Demographic and clinical features of healthy control, T2DM without MCI and T2DM with MCI groups.

Characteristics	Healthy control (n = 18)	T2DM without MCI (n = 18)	T2DM with MCI (n = 18)
Age, years	54 ± 5.25	55.61 ± 5.74	57.05 ± 5.24
Gender, female/male	9/9	9/9	8/10
Education level, years	12.75 ± 2.48	11.5 ± 1.54	10.33 ± 4.1*
Duration of T2DM, years		4.17 ± 4.1	8.68 ± 5.22#
BMI, kg/m^2	22.79 ± 3.36	23.85 ± 3.01	23.84 ± 3.77
SBP, mm Hg	122.06 ± 17.18	133.38 ± 13.24*	129.55 ± 15.45
DBP, mm Hg	80.43 ± 8.28	83.88 ± 9.94	79.38 ± 7.34
FPG, mmol/L	5.06 ± 0.33	10.15 ± 2.47*	10.53 ± 2.94*
FCP, nmol/L	0.92 ± 0.2	0.74 ± 0.39	0.56 ± 0.34*
HbA1c, %	5.3 ± 0.36	6.98 ± 1.16*	8.66 ± 2.22 *#
Total cholesterol, mmol/L	4.81 ± 1.16	4.65 ± 1.62	4.91 ± 1.18
TG, mmol/L	1.63 ± 1.16	1.84 ± 1.47	1.55 ± 0.81
HDL-C, mmol/L	1.62 ± 0.63	1.42 ± 0.33	1.36 ± 0.26
LDL-C, mmol/L	2.83 ± 0.9	2.8 ± 1.16	3.06 ± 0.81
MoCA score	27.05 ± 0.99	26.88 ± 1.07	20.77 ± 2.04*#
MMSE score	29.33 ± 0.59	29.16 ± 0.78	26.55 ± 1.46*#

Notes: T2DM = type II diabetes mellitus; MCI = mild cognitive impairment; BMI = body mass index, SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; FCP = fasting C-peptide; HbA1c = hemoglobin alpha 1; TG = triglyceride; HDL = high density lipoprotein; LDL = low density lipoprotein; MoCA = Montreal cognitive assessment; MMSE = mini mental state exam. * indicates significant statistical difference compared with control group, # indicates significant statistical difference compared with T2DM without MCI.

patients without MCI, T2DM patients with MCI had longer duration of T2DM, and higher HbA1c levels. T2DM patients with MCI had lower MMSE and MoCA scores than patients with T2DM patients and healthy control. Moreover, T2DM patients with MCI had lower education level compared with healthy control.

3.2. Relative volume changes of the major brain tissues

The relative volume of brain tissue (total gray matter [TGM], total white matter [TWM], and cerebrospinal fluid [CSF]) and total intracranial volume (TIV) were measured and presented in Table 2. There was significant difference in volume proportion of TGM, TWM and CSF between the three groups. Patients with T2DM had lower proportion of TWM than healthy control. The proportion of CSF in patients with or without MCI were greater than that in healthy control. T2DM patients with MCI had lower proportion of TWM and TGM than healthy control. There was no significant difference in the TIV among the three groups.

3.3. Relative volume changes of 68 pairs of brain sub-structures

The relative volume of 68 pairs (left and right) of brain sub-structures of the three groups were shown in Supplementary Table 1. The brain sub-structures which had significant relative volume changes were presented in Table 3. Compared with healthy control, T2DM patients without MCI had lower relative volumes in the bilateral exterior cerebellum, bilateral cerebral white matter, left lingual gyrus, left middle occipital gyrus, right temporal lobe, left cerebrum and motor, and greater relative volumes in the bilateral ventral ventricle ($p < 0.05$). T2DM patients with MCI had lower relative volumes in the bilateral exterior cerebellum, right cerebral white matter, left anterior cingulate gyrus, left anterior orbital gyrus, left calcarine and cerebrum, left central operculum, bilateral entorhinal area, bilateral frontal operculum, right rectus gyrus, left lingual gyrus, left middle occipital gyrus, bilateral medial precentral gyrus, right superior medial frontal gyrus, right temporal lobe, left cerebrum and motor, left inferior frontal angular gyrus, and right temporal transverse gyrus, and had higher relative volumes in the bilateral ventral ventricle ($p < 0.05$). Meanwhile, compared with T2DM patients without MCI, T2DM patients with MCI had lower relative volumes in the right anterior orbital gyrus, right calcarine and cerebrum, left cuneus, left entorhinal area, left frontal operculum, right medial orbital gyrus, right occipital pole, left temporal pole ($p < 0.05$).

Table 2. MRI features of brain tissues (mean ± standard deviation).

Characteristics	Healthy control (n = 18)	T2DM without MCI (n = 18)	T2DM with MCI (n = 18)
TGM, %[a]	41.83 ± 2.88	40.87 ± 2.63	39.85 ± 2.76*
TWM, %[a]	35.79 ± 2.14	33.87 ± 1.8*	34.07 ± 2.7*
CSF, %[a]	22.49 ± 3.4	25.25 ± 3.91*	26.06 ± 4.97*
TIV, mL	1426.92 ± 141.14	1436.24 ± 149.74	1433.16 ± 121.91

Notes: T2DM = type II diabetes mellitus; MCI = mild cognitive impairment; TGM = total gray matter; TWM = total white matter; CSF = cerebrospinal fluid; TIV = total intracranial volume. [a] Proportion in TIV. * indicates significant difference compared with healthy control.

3.4. Correlation analysis between brain structural changes and scale scoring

For further investigating the association between brain structural atrophy and cognitive impairment in T2DM, a partial correlation analysis was performed on the 8 sub-structures with the most significant difference in relative volume between T2DM patients with and without MCI (shown in Figure 1), is. The results were shown in Figure 2. After adjusting for age, gender, and education level, relative volume in the right calcarine and cerebrum, left cuneus, left entorhinal area, left frontal operculum showed significant positive correlations with MoCA scores ($p < 0.05$). Besides, relative volume in the left cuneus, left frontal operculum and right occipital pole had significant positive correlations with MMSE scores ($p < 0.05$).

3.5. Diagnostic accuracy of the critical regions for MCI diagnosing in T2DM patients

To evaluate the diagnostic accuracy of *the critical regions* for MCI diagnosing, all T2DM patients were selected for the receiver operating characteristic (ROC) curve analysis, and the results were presented in Table 4. The results indicated that the right anterior orbital gyrus (sensitivity = 94.12%, specificity = 55.56%, AUC = 0.725), right calcarine and cerebrum (sensitivity = 82.35%, specificity = 66.67%, AUC =

Table 3. Intracranial proportion of brain sub-structures in healthy control, T2DM without MCI, and T2DM with MCI groups (mean ± standard deviation, percentage).

Brain sub-structures (%)	Healthy control (n = 18)		T2DM without MCI (n = 18)		T2DM with MCI (n = 18)	
	Left	Right	Left	Right	Left	Right
Exterior Cerebellum	2.573 ± 0.251	2.609 ± 0.249	**2.415 ± 0.15**	**2.429 ± 0.157**	**2.419 ± 0.264**	**2.434 ± 0.276**
Cerebral White Matter	2.461 ± 0.116	2.364 ± 0.114	**2.326 ± 0.182**	**2.236 ± 0.167**	2.353 ± 0.196	**2.252 ± 0.192**
Ventral Ventricle	0.072 ± 0.013	0.065 ± 0.009	**0.083 ± 0.01**	**0.074 ± 0.009**	**0.083 ± 0.013**	**0.075 ± 0.01**
Anterior Cingulate Gyrus	0.314 ± 0.038	0.219 ± 0.04	0.297 ± 0.04	0.221 ± 0.034	**0.287 ± 0.03**	0.209 ± 0.024
Anterior Orbital Gyrus	0.112 ± 0.016	0.119 ± 0.014	0.114 ± 0.016	0.121 ± 0.017	0.105 ± 0.009	**0.108 ± 0.01**
Calcarine and Cerebrum	0.227 ± 0.037	0.24 ± 0.039	0.218 ± 0.025	0.237 ± 0.026	0.206 ± 0.03	**0.212 ± 0.03**
Cuneus	0.287 ± 0.031	0.3 ± 0.037	0.28 ± 0.025	0.306 ± 0.023	**0.253 ± 0.035**	0.29 ± 0.039
Entorhinal Area	0.149 ± 0.014	0.154 ± 0.013	0.149 ± 0.016	0.149 ± 0.018	**0.136 ± 0.013**	**0.141 ± 0.018**
Frontal Operculum	0.138 ± 0.016	0.143 ± 0.017	0.132 ± 0.015	0.137 ± 0.015	**0.123 ± 0.011**	**0.128 ± 0.011**
Rectus Gyrus	0.121 ± 0.013	0.127 ± 0.015	0.117 ± 0.015	0.12 ± 0.008	0.113 ± 0.014	**0.112 ± 0.013**
Lingual Gyrus	0.496 ± 0.046	0.524 ± 0.04	**0.465 ± 0.044**	0.511 ± 0.045	**0.455 ± 0.058**	0.486 ± 0.048
Medial Frontal Cerebrum	0.106 ± 0.015	0.115 ± 0.015	0.101 ± 0.017	0.107 ± 0.013	0.097 ± 0.012	**0.103 ± 0.011**
Middle Occipital Gyrus	0.396 ± 0.03	0.316 ± 0.031	**0.371 ± 0.038**	0.321 ± 0.032	**0.374 ± 0.034**	0.311 ± 0.035
Medial Orbital Gyrus	0.245 ± 0.023	0.255 ± 0.03	0.241 ± 0.026	0.251 ± 0.024	0.241 ± 0.023	**0.236 ± 0.017**
Medial Precentral Gyrus	0.15 ± 0.023	0.159 ± 0.019	0.143 ± 0.016	0.146 ± 0.017	**0.134 ± 0.021**	**0.139 ± 0.016**
Superior Medial Frontal Gyrus	0.36 ± 0.046	0.443 ± 0.066	0.358 ± 0.043	0.421 ± 0.055	0.35 ± 0.026	**0.404 ± 0.042**
Occipital Pole	0.234 ± 0.032	0.21 ± 0.024	0.229 ± 0.027	0.213 ± 0.027	0.226 ± 0.027	0.194 ± 0.027
Temporal lobe	0.144 ± 0.021	0.15 ± 0.019	0.137 ± 0.02	**0.133 ± 0.014**	0.135 ± 0.019	**0.134 ± 0.022**
Cerebrum and Motor	0.357 ± 0.032	0.331 ± 0.047	**0.333 ± 0.036**	0.317 ± 0.04	**0.332 ± 0.033**	0.303 ± 0.034
Temporal Pole	0.507 ± 0.061	0.518 ± 0.056	0.507 ± 0.049	0.513 ± 0.064	0.468 ± 0.059	0.487 ± 0.051
Inferior Frontal Angular Gyrus	0.204 ± 0.022	0.211 ± 0.016	0.19 ± 0.022	0.209 ± 0.027	**0.178 ± 0.022**	0.199 ± 0.02
Temporal Transverse Gyrus	0.088 ± 0.014	0.081 ± 0.013	0.085 ± 0.009	0.074 ± 0.008	0.086 ± 0.016	0.072 ± 0.011

Notes: The area marked with bold indicates significant difference compared with healthy control group. The underlined area indicates significant difference compared with T2DM without MCI group. T2DM = type II diabetes mellitus; MCI = mild cognitive impairment; CLCVLs = cerebellar lobule cerebellar vermal lobules.

0.742), left cuneus (sensitivity = 88.89%, specificity = 58.82%, AUC = 0.745), left entorhinal area (sensitivity = 70.59%, specificity = 72.22%, AUC = 0.752), right medial orbital gyrus (sensitivity = 70.59%, specificity = 77.78%, AUC = 0.719), right occipital pole (sensitivity = 76.47%, specificity = 66.67%, AUC = 0.696) can significantly distinguish T2DM patients with MCI from T2DM patients without MCI. The classification results by random forest based on the above brain regions using relative volume as features yielded accuracy of T2DM/DMCI 69.4% (sensitivity = 61.1%, specificity = 77.7%, AUC = 70.2%) through 6-fold cross-validation (Figure 3).

4. Discussion

It has been known that T2DM is one of the critical risk factors for MCI and subsequent Alzheimer's disease [18, 19]. By using an automatic segmentation method, the present study found that volume change of certain brain regions was observed in T2DM patients with or without MCI. Especially, shrinkage of 8 brain sub-structures (right anterior orbital gyrus, right calcarine and cerebrum, left cuneus, left entorhinal area, left frontal operculum, right medial orbital gyrus, right occipital pole, left temporal pole) was found in T2DM patients with MCI, but not in T2DM patients without MCI. Plenty of previous studies have reported the significant association between the regional atrophy of frontal lobe, temporal lobe, occipital lobe, entorhinal cortex and MCI [14, 20, 21, 22, 23].

In present study, decreased brain parenchyma (both gray matter and white matter) volume and expanded ventricle volume were observed in T2DM patients with or without MCI. It has been reported in a large amount of studies that global brain volume (including gray matter and white matter) shows a decline in patients with T2DM [24, 25, 26, 27, 28, 29, 30, 31] except one [32]. The structural changes in T2DM patients were associated with several critical regions include amygdala atrophy [33, 34, 35], hippocampus atrophy [3, 27, 28, 33, 34, 35, 36, 37, 38, 39, 40], left parahippocampal gyrus atrophy, increased lateral ventricle volume [24, 41], etc. Meanwhile, a longitudinal study of familial Alzheimer's disease showed that obvious ventricle enlarge can be observed 5 years before MCI diagnosis [42]. Furthermore, compared with T2DM patients without MCI, T2DM patients with MCI had more serious brain sub-structural lesions, and long duration of T2DM was associated with a poor cognitive function [43] especially on attention, working memory, and execution function [44]. All these factors indicate that certain brain sub-structural alterations occur at an early stage of T2DM, and gets worse as the disease progresses. From our results, relative volume of several brain regions (including right calcarine and cerebrum, left cuneus, left entorhinal area, left frontal operculum, right occipital pole) have a significant positive correlation with MoCA or MMSE scores, which further indicates that the progression of brain regional lesion in T2DM patients contributes to the decline of cognitive function. In this study, the relationship between the level of glycated hemoglobin and the cognitive tests indicates that an increase of glycated hemoglobin is associated with a significant reduction in the cognitive scores, and that the duration of T2D is associated with worse attention functions and visual-spatial ability. Higher HbA1c level that associated with worse glycemic control was a critical biochemical marker in T2DM with MCI patients, it was always correlated with lower MMSE and MoCA scores. The HbA1c difference that our study population shows is consistent with previous MCI researches [45, 46, 47, 48].

It worth noting that except for the significant changed brain regions presented in Table 3, many other investigated regions also present an obvious decrease in the order of healthy control, T2DM without MCI, and T2DM with MCI. This may suggest us that T2DM patients have a broader spectrum of brain regional volume change. Although some recent studies about T2DM patients have implied that gray matter atrophy play a pivotal role in cognitive decline in patients with T2DM-MCI [9, 10], but they failed to assess the regional volume changes by a systematic way of segmenting the whole brain.

However, there were several limitations in this cross-section study. First, the present study is relatively small in size. The structural indicators

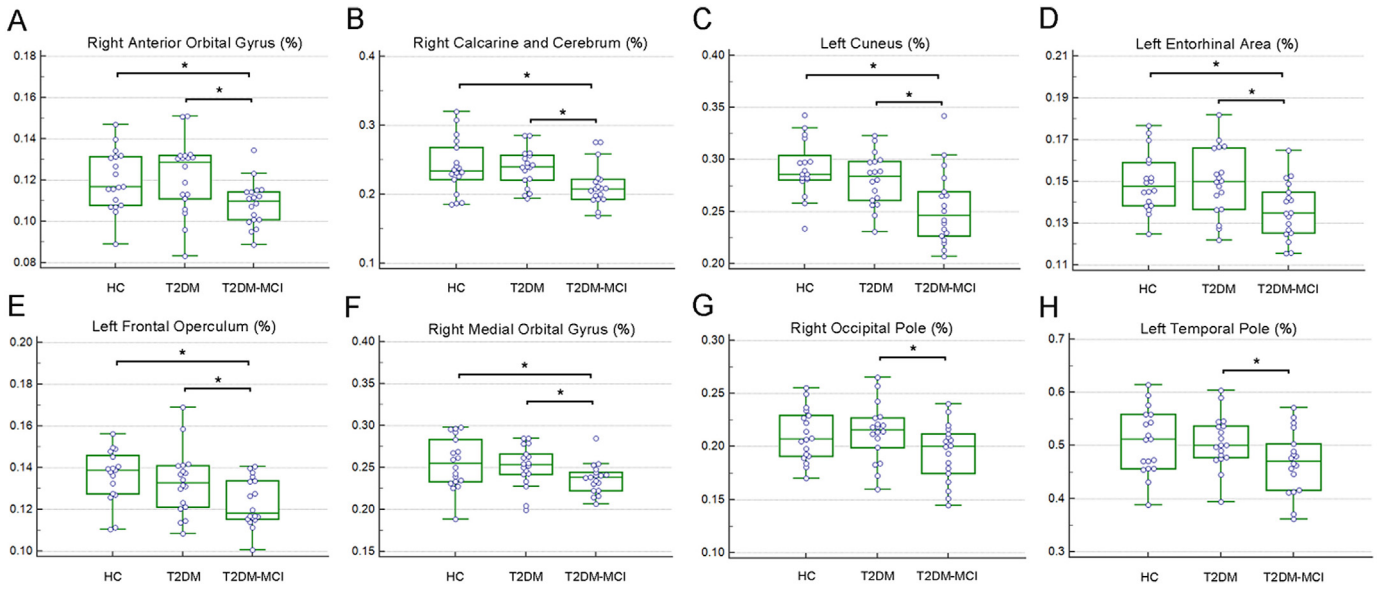


Figure 1. Atrophy of brain sub-structures which were associated with the occurrence of MCI in T2DM patients. A. Right anterior orbital gyrus, B. Right calcarine and cerebrum, C. Left cuneus, D. Left entorhinal area, E. Left frontal operculum, F. Right medial orbital gyrus, G. Right occipital pole, H. Left temporal pole. HC = healthy control; T2DM = type II diabetes mellitus; MCI = mild cognitive impairment, * indicates $p < 0.05$.

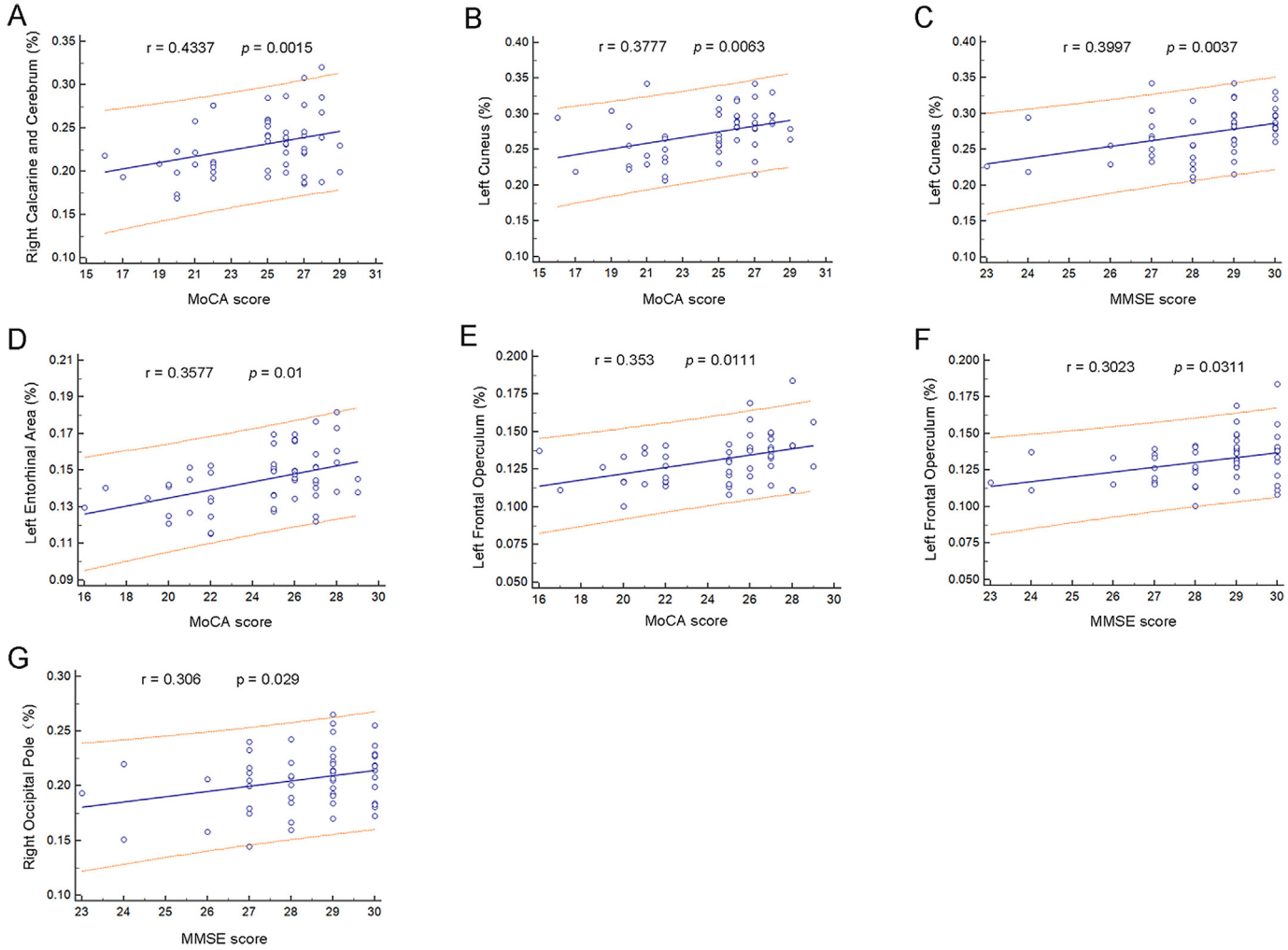


Figure 2. Partial correlations between the relative volume of brain sub-structures and the rating scale (MoCA and MMSE). The partial correlation coefficients were adjusted for age, gender, and education level. MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination. Significant p-value < 0.05.

Table 4. Diagnostic accuracy of the brain sub-structures for diagnosing MCI by ROC curve analysis in T2DM patients.

Brain sub-structures	Sensitivity (%)	Specificity (%)	AUC area (95% CI)	*p*-value[a]
Right Anterior Orbital Gyrus	94.12	55.56	0.725 (0.549–0.862)	0.0116*
Right Calcarine and Cerebrum	82.35	66.67	0.742 (0.566–0.874)	0.0058*
Left Cuneus	88.89	58.82	0.745 (0.570–0.877)	0.0047*
Left Entorhinal Area	70.59	72.22	0.752 (0.577–0.882)	0.0021*
Left Frontal Operculum	52.94	83.33	0.676 (0.498–0.824)	0.055
Right Medial Orbital Gyrus	70.59	77.78	0.719 (0.542–0.857)	0.0176*
Right Occipital Pole	76.47	66.67	0.696 (0.518–0.840)	0.0301*
Left Temporal Pole	70.59	66.67	0.676 (0.498–0.824)	0.058

Notes: MCI = mild cognitive impairment; ROC = receiver operating characteristic; T2DM = type II diabetes mellitus; AUC = area under the curve; CI = confidence interval; [a] Compared with AUC area = 0.5. * indicates $p < 0.05$.

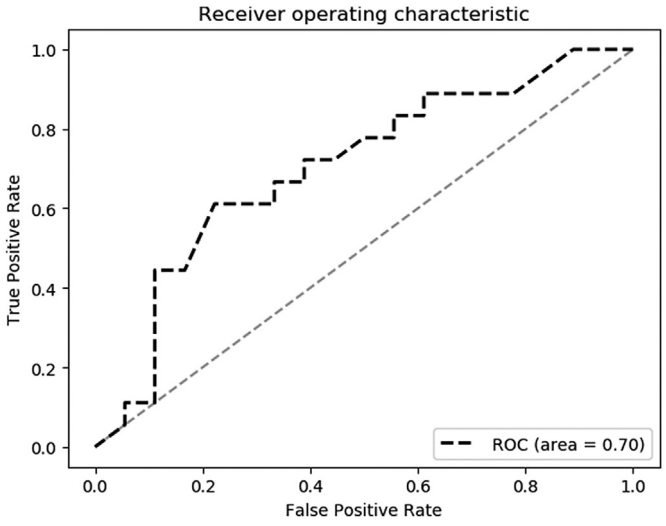


Figure 3. Random forest classification results between T2DM and DMCI based on the critical 8 brain regions deduced from ROC curve analysis gave an accuracy of 0.69 and AUC of 0.70.

found in this study should be further confirmed with a greater size of population in the future. Second, all the MCI in T2DM patients were primarily diagnosed, and the determination were according to the rating scales. MCI can be classified as amnestic MCI and non-amnestic MCI, but we did not distinguish these MCI subtypes in this study. Moreover, the evaluation of cognitive function by rating scale is subjective, and more objective and accurate mental status assessment method should be used for a more reliable result. Third, to disentangle the relationship between age and brain structure regression triggered by MCI, more individuals with different age group should be enrolled for a validation study.

By using an automatic brain quantification tool, we aimed to find effective imaging indicators for predicting the presence of MCI in patients with T2DM. In present study, we screened out 5 brain regions: right calcarine and cerebrum, left cuneus, left entorhinal area, left frontal operculum, right occipital pole.) The relative volume changes of these regions may have a potential for the evaluation of cognitive function in T2DM patients, and may benefit for MCI diagnosing.

5. Conclusions

The present study showed that multiple brain regions show structural alterations in T2DM patients, and these lesions are more serious in T2DM patients with MCI. Moreover, we found that relative volume of several brain regions has a positive correlation with MoCA or MMSE scores. Our analysis based on ROC and RF classification indicated that specific brain volumetric alternations could be a potential indicator for MCI in T2DM patients.

Declarations

Author contribution statement

Jing Gu: Conceived and designed the experiments.
Siyuan Cui: Performed the experiments.
Huihui Qi, Jing Li: Analyzed and interpreted the data.
Wenjuan Wu, Silun Wang: Contributed reagents, materials, analysis tools or data.
Zengli Miao and Jianming Ni: Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

The authors do not have permission to share data.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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