Research Article

Assessment of structural brain changes in patients with type 2 diabetes mellitus using the MRI-based brain atrophy and lesion index

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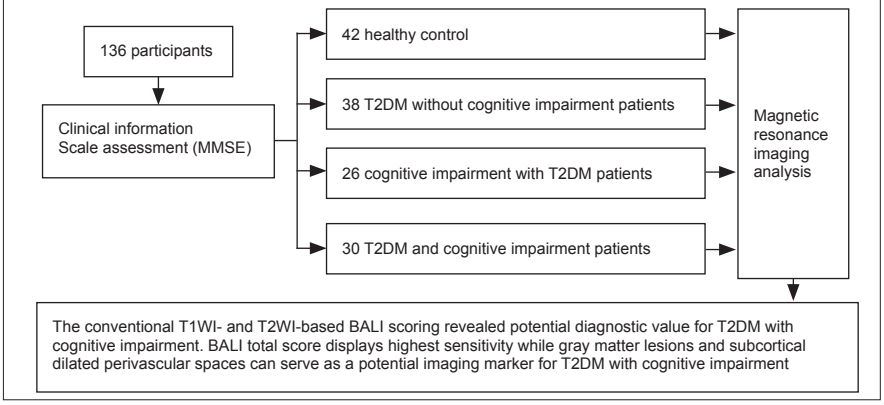
Graphical Abstract *Detecting brain structure changes with an magnetic resinance imaging-based brain atrophy and lesion index (BALI) in type 2 diabetes mellitus (T2DM) patients and determine the potential diagnostic value for T2DM with cognitive impairment*



Abstract

Patients with type 2 diabetes mellitus (T2DM) often have cognitive impairment and structural brain abnormalities. The magnetic resonance imaging (MRI)-based brain atrophy and lesion index can be used to evaluate common brain changes and their correlation with cognitive function, and can therefore also be used to reflect whole-brain structural changes related to T2DM. A total of 136 participants (64 men and 72 women, aged 55–86 years) were recruited for our study between January 2014 and December 2016. All participants underwent MRI and Mini-Mental State Examination assessment (including 42 healthy control, 38 T2DM without cognitive impairment, 26 with cognitive impairment but without T2DM, and 30 T2DM with cognitive impairment participants). The total and sub-category brain atrophy and lesion index scores in patients with T2DM with cognitive impairment were higher than those in healthy controls. Differences in the brain atrophy and lesion index of gray matter lesions and subcortical dilated perivascular spaces were found between non-T2DM patients with cognitive impairment and patients with T2DM and cognitive impairment. After adjusting for age, the brain atrophy and lesion index retained its capacity to identify patients with T2DM with cognitive impairment. These findings suggest that the brain atrophy and lesion index, based on T1-weighted and T2-weighted imaging, is of clinical value for identifying patients with T2DM and cognitive impairment. Gray matter lesions and subcortical dilated perivascular spaces may be potential diagnostic markers of T2DM that is complicated by cognitive impairment. This study was approved by the Medical Ethics Committee of University of South China (approval No. USC20131109003) on November 9, 2013, and was retrospectively registered with the Chinese Clinical Trial Registry (registration No. ChiCTR1900024150) on June 27, 2019.
Key Words: brain atrophy and lesion index; cognitive impairments; gray matter lesions; magnetic resonance imaging; Mini-Mental State Examination; structural brain; subcortical dilated perivascular spaces; T1-weighted image; T2-weighted image; type 2 diabetes mellitus

Chinese Library Classification No. R445.2; R742; R587.1

Introduction

Typically, type 2 diabetes mellitus (T2DM) has a negative impact on cognitive function, especially in aging individuals, and increases the risk of cognitive impairment (CI), including Alzheimer's disease (AD) and vascular dementia (Wang et al., 2014; Bangen et al., 2018; Biessels and Despa, 2018; Agatonovic-Kustrin et al., 2019; Callisaya et al., 2019; Chornenkyy et al., 2019; Groeneveld et al., 2019; International

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Diabetes Federation, 2020; Popa-Wagner et al., 2020). Previous research has indicated that individuals with T2DM are at ~60% greater risk for the development of dementia compared with those without diabetes (Kanaya et al., 2004). For vascular dementia, this risk is even greater in women with diabetes (Chatterjee et al., 2016). However, the difference between men and women has not been observed consistently in some similarly large, contemporary studies (Shah et al., 2015; Wright et al., 2019).

Both CI and structural brain abnormalities have been reported in T2DM. Previous research suggests that patients with diabetes mellitus represent a large proportion of adults with cerebral small vessel disease, the structural brain abnormalities correlates of which include lacunar infarcts, white matter hyperintensities, enlarged perivascular spaces, microbleeds, and brain atrophy (Funnell et al., 2017; Mankovsky et al., 2018). Compared with healthy older people, older patients with T2DM have more severe structural brain changes (Moran et al., 2013).

The brain atrophy and lesion index (BALI), which is a validated semi-quantitative global measure of structural degeneration, has been used to collectively assess common brain changes and their association with cognitive function. Previous studies have shown that BALIs are significantly associated with age and dementia progression (Chen et al., 2010; Zhang et al., 2012; Guo et al., 2014a, b, 2017). Thus, it is possible that the BALI could also be applied to assess T2DM-related whole-brain structural changes. The present study was designed to rapidly assess structural brain changes in patients with T2DM using the BALI, and to evaluate the ability of T1-weighted (T1WI) and T2-weighted (T2WI)-based BALI to identify which patients with T2DM have CI.

Participants and Methods

This retrospective observational study was approved by the Medical Ethics Committee of University of South China (approval No. USC20131109003) on November 9, 2013 (**Additional file 1**), and written informed consent (**Additional file 2**) was obtained from all participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidance (**Additional file 3**). The study was retrospectively registered with the Chinese Clinical Trial Registry (registration No. ChiCTR1900024150) on June 27, 2019.

Participants

The study was conducted between January 2014 and December 2016. All participants were recruited from The First Affiliated Hospital of University of South China. The inclusion criteria were as follows: aged more than 50 years and less than 90 years. The exclusion criteria were as follows: (1) patients who could not complete the Mini-Mental State Examination (MMSE); (2) patients with a history of mental and/or neurological diseases; (3) those with organic diseases of the nervous system; (4) a history of alcohol, smoking, or drug abuse; (5) patients with contraindications for magnetic resonance imaging (MRI). Diabetes was confirmed based on clinical records. A diagnosis of CI was established using the MMSE. A total of 141 randomly recruited participants completed MRI scanning and the MMSE assessment, but 5 participants were excluded because of poor MR image quality. The final 136 participants were divided into four groups (**Figure 1**), as follows: (a) the healthy control (HC) group (n = 42), with normal cognitive function and without T2DM; (b) the T2DM-nonCI group (n = 38), which comprised patients with T2DM without CI; (c) the nonT2DM-CI group (n = 26), which comprised participants with CI but without T2DM; and (d) the T2DM-CI group (n = 30), which included patients with both T2DM and CI. The enrolled participants included 64 men and 72 women aged from 50 to 86 years.

MRI protocol

MRI was performed using either a 1.5-T (Brivo MR355, GE Healthcare, Milwaukee, WI, USA; MAGNETOM, Siemens Healthcare, Erlangen, Germany) or a 3.0-T scanner (Achieva, Philips Healthcare, Best, the Netherlands) using either an 8-channel or 16-channel phased-array coil. Both conventional T1WI and T2WI images were acquired in the axial plane.

Evaluation of the BALI

The BALI scale was used to assess several common structural brain changes. The first category is gray matter lesions and subcortical dilated perivascular spaces (GM-SV) (Chen et al., 2010; Zhang et al., 2012; Guo et al., 2014a, b, 2017). Subsequent categories assess deep white matter lesions, periventricular white matter lesions, lesions in the basal ganglia and surrounding areas, lesions in the infratentorial compartment, and global atrophy. An "other findings" category records changes such as neoplasm, trauma, malformations, and hydrocephalus. Each category was assigned a value between 0 and 3, whereby a higher score indicates a more severe change. In two categories (deep white matter lesions and global atrophy), values of 4 and 5 were used to represent greater severity (Chen et al., 2010; Zhang et al., 2012; Guo et al., 2014a, b, 2017). The total BALI was calculated separately for T1W1 and T2W1 images by adding scores for the seven sub-categories, with a maximum total score of 25. The BALI scoring was performed by two radiologists (HZ and FW) with 20 and 8 years of experience in neural imaging, respectively. Evaluations for the two different MRI sequences were separated by one week to minimize possible recall bias. Scoring was performed independently, and the reviewers were blinded to all information, including participant demographics, diagnosis, and MMSE score. The scoring standard is presented in **Additional Figures 1** and **2**, and example images showing the BALI rating are shown in **Figure 2**.

Cognitive test

The MMSE was used to assess global cognitive function and was implemented by trained physicians and nurses (Zhang et al., 1999). There are 30 items in the MMSE, with a total possible score of 30. The MMSE measures the five following aspects of cognition: orientation (10 items), registration (3 items), attention and calculation (5 items), recall (3 items), and language (9 items). The MMSE cut-off score for defining normal cognition was as follows: a score ≥ 19 in illiterate individuals; ≥ 22 in those with a primary school education (education duration ≤ 6 years); and ≥ 26 in those with a middle school education and above (education duration > 6 years) (Zhang et al., 1999). Scores below these cut-off values were considered to indicate CI.

Statistical analysis

SPSS 23.0 (IBM Corp., Armonk, NY, USA) was used for all data analysis. Non-normally distributed data, as determined by the Kolmogorov–Smirnov test, were transformed logarithmically prior to analysis and are expressed as the median and interquartile range. Reliability of the ratings was examined using the inter-reviewer agreement rate (Cohen's kappa). Differences between groups regarding age, sex, and level of education were examined using Kruskal-Wallis nonparametric

tests for interval data and the chi-square test for categorical/ordinal data. Comparisons of the BALI between groups were performed using Kruskal-Wallis nonparametric tests, and correlations between the MMSE score and BALI were assessed using Spearman's correlation analysis. Evaluation of the ability of the BALI to identify patients with T2DM and CI was carried out using receiver operating characteristics curves. $P < 0.05$ (two-tailed) was considered statistically significant.

Results

Participant demographics

No significant difference in education level was found between the four groups ($\chi^2 = 1.66$, $P > 0.05$); however, significant differences were found in age ($\chi^2 = 21.65$, $P < 0.001$), sex ($\chi^2 = 8.03$, $P = 0.045$), and MMSE score ($\chi^2 = 18.04$ –85.40, $P < 0.01$) between the four groups (**Table 1**).

Intraclass correlation coefficient of BALI scoring between reviewers

With regard to reliability, the intraclass correlation coefficient of BALI scoring indicated an agreement that ranged from good to perfect (κ value: 0.64–0.90, $P < 0.001$). The κ coefficients for T1WI varied from 0.64, with lesions in GM-SV, to 0.90, with lesions in the infratentorial compartment. The κ coefficients for T2WI varied from 0.65, with lesions in DWM, to 0.82, with lesions in global atrophy (**Table 2**).

Between-group differences in the total and sub-category BALIs

Total and sub-category BALIs of the different groups are compared in **Table 3**. The non-T2DM-HC group had lower total and all sub-categories BALIs than the T2DM-CI group (both $P < 0.05$). Furthermore, the T2DM-HC group total BALI only was lower than that of the T2DM-CI group ($P < 0.05$), and sub-category BALIs exhibited no significant differences ($P > 0.05$). In addition, only the GM-SV index was significantly different between the nonT2DM-CI and T2DM-CI groups (reviewer 1: T1WI $\chi^2 = 24.54$, $P < 0.001$; T2WI $\chi^2 = 23.02$, $P = 0.017$; reviewer 2: T1WI $\chi^2 = 17.76$, $P = 0.012$; T2WI $\chi^2 = 5.30$, $P = 0.151$).

Ability of the BALI to discriminate patients with T2DM and CI

In T2DM subjects, T1WI- and T2WI-based BALIs showed comparable accuracy for the classification of patients with T2DM and CI at the individual level. After adjusting for age, the area under the curve ranged from 0.550 to 0.749, and the total BALI had the highest sensitivity (**Figure 3** and **Table 4**; the cut-off value was 9 in T1WI: 73.33% *vs.* 73.33% for reviewers 1 and 2; the cut-off value was 10.5 in T2WI: 70.00% *vs*. 76.67% for reviewers 1 and 2).

Correlation between the MMSE score and BALI in T2DM and nonT2DM groups

In the T2DM and non-T2DM groups, most BALIs and MMSE scores were significantly correlated. However, the GM-SV score was significantly correlated with the MMSE total ($|r| = 0.259$–0.267, $P < 0.05$ for reviewer 1's T1WI and T2WI-based score) and recall score ($|r| = 0.306$–0.325, $P < 0.05$ for reviewer 1's and reviewer 2's T1WI-based score and reviewer 1's T2WI-based score) within the T2DM groups, but no significant correlations were found within the nonT2DM groups (**Additional Tables 1** and **2**).

Table 1 | **Demographic characteristics of participants**

Characteristic	HC (n = 42)	T2DM-nonCI (n = 38)	nonT2DM-CI (n = 26)	T2DM-CI (n = 30)	χ^2	P
Female [n(%)]	15(36)	20(53)	18(69)	12(40)$^{*\#\#\dagger\dagger}$	8.03	0.045
Age (yr)	66.0(62.5, 73.3)	68.0(61.8, 72.0)	73.5(65.8, 76.3)$^{***\#\#}$	74.5(70.8, 80.3)$^{***\#\#}$	21.65	< 0.001
Education (yr)	6(6, 12)	6(6, 9)	6(6, 9)	9(6, 9)	1.66	0.646
MMSE total score (30)	27.00(25.00, 28.00)	27.00(24.75, 29.00)	17.00(15.00, 21.00)$^{***\#\#\#}$	18.00(15.00, 21.00)$^{***\#\#\#}$	85.4	< 0.001
Orientation	10.00(9.00, 10.00)	9.50(9.00, 10.00)	8.00(5.00, 9.00)$^{***\#\#}$	7.50(5.00, 9.25)$^{***\#\#\#}$	35.18	< 0.001
Registration	3.00(3.00, 3.00)	3.00(3.00, 3.00)	3.00(2.00,3.00)$^{**\#\#}$	3.00(3.00, 3.00)	18.04	0.006
Attention and calculation	5.00(4.00, 5.00)	5.00(4.00, 5.00)	1.00(0.00, 2.00)$^{***\#\#\#}$	1.00(0.00, 1.25)$^{***\#\#\#}$	78.87	< 0.001
Recall	2.00(2.00, 3.00)	2.00(2.00, 3.00)	0.00(0.00, 1.00)$^{***\#\#\#}$	1.00(0.00, 2.00)$^{***\#\#\#}$	47.43	< 0.001
Language	8.00(7.00, 9.00)	8.00(7.00, 9.00)	5500(4.75, 7.00)$^{***\#\#\#}$	7.00(4.75, 7.00)$^{**\#\#}$	38.96	< 0.001

Continuous variables are expressed as the median (interquartile range). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, *vs.* HC group; $\#\#P < 0.01$, $\#\#\#P < 0.001$, *vs.* T2DM-nonCI group; $\dagger\dagger P < 0.01$, *vs.* nonT2DM-CI group (Kolmogorov-Smirnov test). CI: Cognitive impairment; HC: healthy control; MMSE: Mini-Mental State Examination; T2DM: type 2 diabetes mellitus.

Table 2 | **Agreement in the total and sub-category BALIs between the two reviewers**

	T1WI		T2WI	
BALI scores	κ	P	κ	P
GM-SV	0.64	< 0.001	0.71	< 0.001
DWM	0.85	< 0.001	0.65	< 0.001
PV	0.79	< 0.001	0.7	< 0.001
BG	0.81	< 0.001	0.73	< 0.001
IT	0.9	< 0.001	0.77	< 0.001
GA	0.79	< 0.001	0.82	< 0.001

BALI: Brain atrophy and lesion index; BG: lesions in the basal ganglia and surrounding areas; DWM: deep white matter lesions; GA: global atrophy; GM-SV: gray matter lesions and subcortical dilated perivascular spaces; IT: lesions in the infratentorial regions; PV: periventricular white matter lesions; T1WI: T1-weighted image; T2WI: T2-weighted image. Data were analyzed using Cohen's kappa analysis.

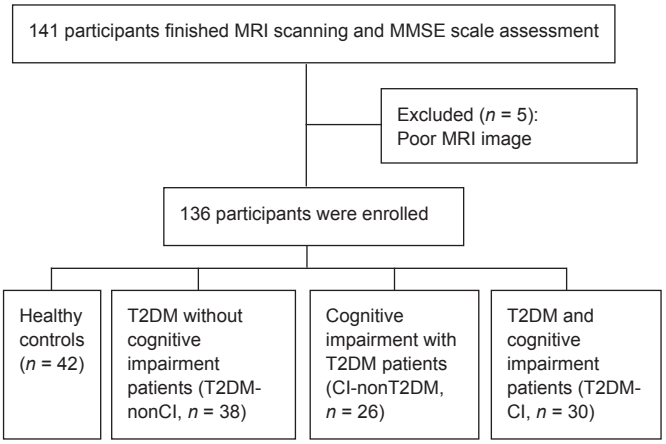

Figure 1 | **Trial flow chart.**
CI: Cognitive impairment; MMSE: Mini-Mental State Examination; T2DM: type 2 diabetes mellitus.

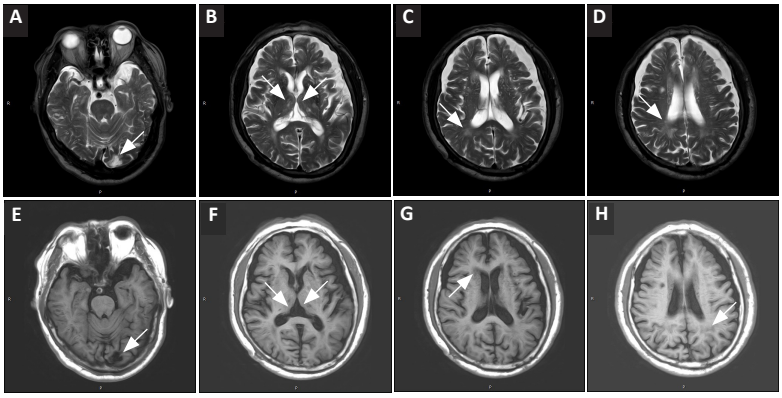

Figure 2 | T1- and T2-weighted-based BALI scoring in a 72-year-old woman diagnosed with T2DM-CI.
(A, E) This slice evaluated gray matter lesions and subcortical dilated perivascular spaces (arrows) and lesions in the infratentorial regions (without lesion). (B, F) Lesions in the basal ganglia and surrounding areas (arrows, excluding dilated perivascular spaces). (C, G) This slice evaluated lesions in the peri-ventricular white matter (arrows) and global atrophy. (D, H) Lesions in the deep white matter (arrows). T2-weighted based BALI rating score = 13 (3 + 3 + 3 + 2 + 0 + 2), T1-weighted based BALI rating score = 12 (3 + 3 + 2 + 2 + 0 + 2). Locations of specific deficits under evaluation are indicated by white arrows. BALI: Brain atrophy and lesion index; CI: cognitive impairment; T2DM: type 2 diabetes mellitus

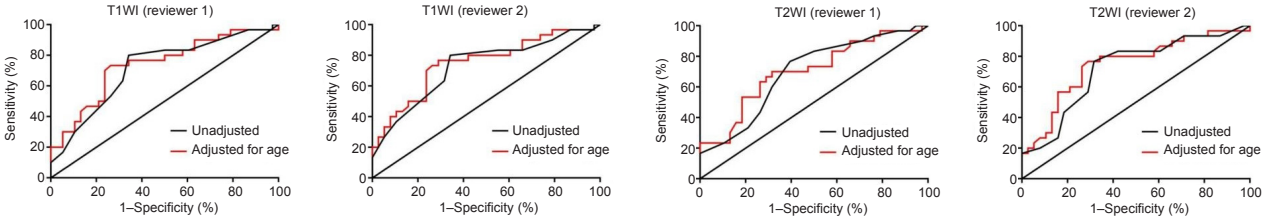

Figure 3 | Receiver operating characteristics curve analysis for the prediction of type 2 diabetes mellitus with cognitive impairment.
Black lines represent the results not adjusting for age, red lines represent the results adjusting for age. T1WI: T1-weighted image; T2WI: T2-weighted image.

Table 3 | Between-group differences in the total and sub-category BALIs

Category	Image type	HC	T2DM-nonCI	nonT2DM-CI	T2DM-CI	χ^2	*P*-value
Reviewer 1							
Total scores	T1WI	6.0(4.0, 9.3)	7.5(5.0, 12.0)	9.0(6.8, 13.3)*	12.0(10.0, 13.3)$^{***\#}$	22.59	< 0.001
	T2WI	7.0(4.8, 12.0)	8.5(6.8, 13.0)	12.0(6.8, 14.3)*	12.0(10.8, 14.3)***	18.14	< 0.001
GM-SV	T1WI	1.0(1.0, 1.0)	1.0(1.0, 1.0)	1.0(1.0, 1.0)	1.0(1.0, 2.3)**†††	17.47	0.002
	T2WI	1.0(1.0, 2.0)	1.0(1.0, 1.0)	1.0(1.0, 1.0)	1.0(1.0, 2.0)†	10.30	0.016
DWM	T1WI	2.0(1.0, 3.0)	2.0(2.0, 3.0)	3.0(2.0, 3.0)	3.0(2.0, 3.0)**	12.33	0.005
	T2WI	2.0(1.0, 3.0)	2.5(2.0, 3.0)	3.0(2.0, 3.3)	3.0(2.8, 3.3)*	10.49	0.007
PV	T1WI	1.0(1.0, 2.3)	1.0(1.0, 2.0)	2.0(1.0, 3.0)	3.0(1.8, 3.0)$^{*\#}$	11.44	0.010
	T2WI	1.5(1.0, 3.0)	2.0(1.0, 3.0)	3.0(2.0, 3.0)	3.0(2.0, 3.0)*	12.36	0.008
BG	T1WI	0.0(0.0, 2.0)	1.0(0.0, 2.0)	1.0(0.0, 3.0)	2.0(1.0, 3.0)**	13.12	0.001
	T2WI	0.0(0.0, 2.0)	2.0(0.0, 2.0)	2.0(0.0, 3.0)	2.0(2.0, 3.0)**	15.10	0.001
IT	T1WI	0.0(0.0, 0.0)	0.0(0.0, 0.0)	0.0(0.0, 2.0)*	0.0(0.0, 2.0)*	12.12	0.008
	T2WI	0.0(0.0, 0.0)	0.0(0.0, 2.0)	0.0(0.0, 2.0)	0.0(0.0, 2.0)	6.62	0.114
GA	T1WI	1.0(1.0, 2.0)	2.0(1.0, 2.0)	2.0(1.8, 3.0)**	2.0(2.0, 2.0)**	17.20	0.002
	T2WI	2.0(1.0, 2.0)	2.0(1.0, 3.0)	2.0(1.0, 3.0)	2.0(2.0, 3.0)*	10.60	0.012
Reviewer 2							
Total scores	T1WI	6.0(4.0, 10.0)	8.0(6.0, 11.0)	8.5(6.0, 13.3)	11.5(10.0, 15.0)$^{***\#}$	21.38	< 0.001
	T2WI	7.0(4.0, 11.0)	8.0(6.0, 12.0)	11.0(7.0, 13.5)*	12.0(10.8, 14.0)$^{***\#}$	20.72	< 0.001
GM-SV	T1WI	1.0(1.0, 1.0)	1.0(1.0, 1.0)	1.0(1.0, 1.0)	1.0(1.0, 2.3)$^{**\#\dagger}$	13.63	0.001
	T2WI	1.0(1.0, 1.0)	1.0(1.0, 1.3)	1.0(1.0, 1.0)	1.0(1.0, 3.0)	5.30	0.226
DWM	T1WI	2.0(1.0, 3.0)	2.0(2.0, 3.0)	3.0(2.0, 3.0)	3.0(2.0, 3.0)**	12.08	0.004
	T2WI	2.0(1.0, 3.0)	2.0(2.0, 3.0)	3.0(2.0, 3.0)	3.0(2.0, 3.0)**	12.61	0.003
PV	T1WI	1.0(1.0, 3.0)	1.5(1.0, 2.3)	2.0(1.0, 3.0)	3.0(1.8, 3.0)*	11.29	0.009
	T2WI	1.0(1.0, 3.0)	2.0(1.0, 3.0)	2.5(2.0, 3.0)*	3.0(2.0, 3.0)**	14.73	0.004
BG	T1WI	0.0(0.0, 2.0)	1.0(0.0, 2.0)	1.0(0.0, 2.3)	2.0(1.8, 3.0)$^{*\#}$	10.94	0.003
	T2WI	0.0(0.0, 2.0)	1.0(0.0, 2.0)	1.5(0.0, 3.0)	2.0(1.8, 3.0)$^{**\#}$	16.40	< 0.001
IT	T1WI	0.0(0.0, 0.0)	0.0(0.0, 0.0)	0.0(0.0, 2.0)*	0.5(0.0, 2.0)*	15.65	0.001
	T2WI	0.0(0.0, 0.0)	0.0(0.0, 1.0)	0.0(0.0, 2.0)	0.5(0.0, 2.0)	8.52	0.042
GA	T1WI	1.5(1.0, 2.0)	2.0(1.0, 2.0)	2.0(1.0, 3.0)*	2.0(2.0, 2.0)**	15.75	0.002
	T2WI	2.0(1.0, 2.0)	2.0(1.0, 2.0)	2.0(1.8, 3.0)	2.0(2.0, 3.0)*	11.89	0.010

Data are expressed as the median (interquartile range). *P < 0.05, **P < 0.01, ***P < 0.001, *vs*. HC group; #P < 0.05, *vs*. T2DM-nonCI group; †P < 0.05, †††P < 0.001, *vs.* nonT2DM-CI group (Kolmogorov–Smirnov test). BALI: Brain atrophy and lesion index; BG: lesions in the basal ganglia and surrounding areas; CI: cognitive impairment; DWM: deep white matter lesions; GA: global atrophy; GM-SV: gray matter lesions and subcortical dilated perivascular spaces; HC: healthy control; IT: lesions in the infratentorial regions; PV: periventricular white matter lesions; T2DM: type 2 diabetes mellitus

Table 4 | **Sensitivity, specificity, and AUC for the BALI in predicting type 2 diabetes mellitus with cognitive impairment**

Variables	Cut-off	Area (95% CI)	Sensitivity (%)	Specificity (%)	*P*-value
T1WI					
Reviewer 1	9.00	0.716(0.582,0.841)	80.00	65.79	0.002
Reviewer 1 (age adjusted)	0.498[a]	0.738(0.616,0.859)	73.33	73.68	0.001
Reviewer 2	9.00	0.727(0.603,0.851)	80.00	65.79	0.002
Reviewer 2 (age adjusted)	0.485[a]	0.749(0.630,0.869)	73.33	73.68	< 0.001
T2WI					
Reviewer 1	10.50	0.696(0.571,0.822)	76.67	60.53	0.006
Reviewer 1 (age adjusted)	0.455[a]	0.703(0.577,0.828)	70.00	68.42	0.004
Reviewer 2	10.50	0.718(0.594,0.843)	76.67	68.42	0.002
Reviewer 2 (age adjusted)	0.457[a]	0.745(0.625,0.866)	76.67	71.05	< 0.001

[a]age-adjusted predicted value from a logistic model. T1WI: T1-weighted image; T2WI: T2-weighted image.

Discussion

This study investigated the use of routine clinical MRI examinations in the evaluation of brain health in patients with T2DM. Previous research has shown that the BALI allows us to simultaneously assess multiple structural changes in the aging and AD brain (Guo et al., 2014a, 2017). This previous work has not only shown that both T1WI and T2WI at 1.5T or 3.0T have good reliability when evaluating global structural brain changes (Guo et al., 2014a), but also that this method is quick and easy to perform, which could be particularly beneficial to and have widespread usefulness in clinical contexts (Guo et al., 2014a). Our data revealed the consistency of both T1WI and T2WI-based BALI total and sub-category scores between reviewers, which ranged from good to perfect.

In recent years, many studies have focused on the effect of structural brain changes on the progression of CI in older people, and have revealed that several common structural brain changes are related to CI (Li and Huang, 2016; Cuadrado-Godia et al., 2018; Shibata et al., 2019; Li et al., 2020; Lu and Deng, 2020). However, few recent studies have attempted to account for more than one type of structural brain change. For instance, the widely used Fazekas and Scholten scores only assess white matter hyperintensity and medial temporal lobe atrophy, and do not assess multiple changes. Previous research has shown that the BALI is a global measure that can evaluate multiple common changes that take place during aging and AD; furthermore, these changes can be independently related to dementia, and, when BALI sub-categories are evaluated together, the negative association with cognitive function becomes stronger (Manschot et al., 2006; Szémán et al., 2012; Guo et al., 2014b; Zhang et al., 2014; Bouvy et al., 2016; Hilal et al., 2018). Our results not only showed that cognition was consistently correlated with multiple structural brain changes, but also indicated that T2DM-CI patients had more severe, or higher sub-category BALI values, than T2DM-HC patients. Therefore, we speculate that worsening cognitive function in T2DM patients indicates that structural brain changes are also worsening.

To our knowledge, this is the first study to use the BALI to evaluate the T2DM brain. One of the most important findings of the present study is that only the GM-SV score was significantly different between CI subjects with and without T2DM. We also found that the GM-SV score was significantly correlated with the MMSE total and recall score in T2DM subjects, but no such correlation was found in nonT2DM subjects. Previous research has highlighted cortical infarction and perivascular spaces as increasingly recognized markers of cerebral small vessel disease in aging and dementia (Martinez-Ramirez et al., 2013). Some *in vivo* MRI studies have not only shown an association between severe centrum semiovale perivascular spaces and lobar (micro) hemorrhages, which are markers of cerebral amyloid angiopathy (Peila et al., 2002; Charidimou et al., 2013, 2014, 2017), but have also found that cerebral amyloid angiopathy severity is linked to the dilation of juxtacortical perivascular spaces (van Veluw et al., 2016). In addition, diabetes has been associated with a higher prevalence of cerebral amyloid angiopathy (Wardlaw et al., 2013). Considering these previous findings and our own results, GM-SV could represent a potential imaging marker of patients with T2DM and CI.

Previous research has demonstrated that the total BALI can help to improve AD and mild cognitive impairment diagnoses in aging (Chen et al., 2010; Zhang et al., 2012; Guo et al., 2014a, b, 2017). After adjusting for age, we found that both the total and sub-category BALIs could predict which patients had T2DM with CI; the total BALI had the highest sensitivity and a good specificity. This indicates that several subtle structural changes, measured by the BALI sub-categories, can be collectively evaluated by the total BALI and that this achieved a greater ability to predict T2DM with CI.

This study has some limitations. First, the relatively small sample size in our study limits the generalizability of our results. Second, the lesion size judgment (e.g., "large patchy lesions") may differ for different categories, because "large" can vary depending on brain structure. For example, a "large" change in the relatively smaller lesions in the infratentorial regions may not be considered "large" in the basal ganglia and surrounding areas or DWM. Future research could adopt quantitative measurements (in mm) to improve precision. In addition, several advanced MR techniques have more precise morphometric or volumetric quantifications than conventional MR sequences (Kanaan et al., 2012; Xie et al., 2017; Gatto and Weissmann, 2019; Sanjari Moghaddam et al., 2019). Adopting these more advanced measures in future studies could improve the detection of gray and white matter changes, especially for lesions that occur in the early stages of T2DM, which would in turn enhance the diagnostic specificity and sensibility.

In conclusion, we found associations between structural brain changes, T2DM, and cognitive function. T1WI- and T2WI-based BALIs have potential diagnostic value in the assessment of CI caused by T2DM. The total BALI exhibited the highest sensitivity, and the GM-SV BALI could be a potential imaging marker of T2DM with CI. Therefore, we suggest that BALI is an easy and convenient method that could provide more information to aid the clinical diagnosis and treatment of T2DM with CI.

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Institutional review board statement: *This study was approved by the Medical Ethics Review Form of University of South China (approval No. USC20131109003) on November 9, 2013, and was retrospectively registrated at Chinese Clinical Trial Registry (Registration No. ChiCTR1900024150) on June 27, 2019.*
Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms from the patients. In the forms, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.*
Reporting statement: *This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidance.*
Biostatistics statement: *The statistical methods of this study were reviewed by the biostatistician of Shengjing Hospital of China Medical University.*

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Plagiarism check: *Checked twice by iThenticate.*
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Open peer reviewer: *Rodolfo Gabriel Gatto, University of Illinois at Chicago, USA.*
Additional files:
Additional file 1: *Hospital Ethics Approval.*
Additional file 2: *Informed consent form.*
Additional file 3: *STROBE checklist.*
Additional file 4: *Open peer review report 1.*
Additional Table 1: *Spearman correlation coefficients between MMSE scores and BALI scores in type 2 diabetes mellitus patients.*
Additional Table 2: *Spearman correlation coefficients between MMSE scores and BALI scores in HC and nonT2DM-CI patients.*
Additional Figure 1: *Evaluation of the brain atrophy and lesion index (BALI) based on T1WI.*
Additional Figure 2: *Evaluation of the brain atrophy and lesion index based on T2WI.*

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STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how matching of cases and controls was addressed	
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of

Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Additional Table 1 Spearman correlation coefficients between MMSE scores and BALI scores in type 2 diabetes mellitus patients

BALI scores	Image type	Reviewer	MMSE total		Orientation		Registration		Attention and calculation		Recall		Language	
			r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
BALI total	T1WI	1	-0.399	0.001	-0.366	0.002	0.043	0.725	-0.403	0.001	-0.279	0.021	-0.289	0.017
		2	-0.406	0.001	-0.342	0.004	0.072	0.559	-0.419	<0.001	-0.279	0.021	-0.302	0.012
	T2WI	1	-0.352	0.003	-0.294	0.015	0.053	0.669	-0.338	0.005	-0.271	0.025	-0.252	0.038
		2	-0.383	0.001	-0.325	0.007	0.092	0.454	-0.382	0.001	-0.241	0.048	-0.292	0.016
GM-SV	T1WI	1	-0.259	0.033	-0.178	0.146	0.040	0.748	-0.233	0.056	-0.325	0.007	-0.217	0.075
		2	-0.267	0.028	-0.222	0.069	0.140	0.254	-0.240	0.049	-0.378	0.001	-0.161	0.190
	T2WI	1	-0.194	0.112	-0.115	0.348	0.109	0.375	-0.225	0.065	-0.306	0.011	-0.162	0.187
		2	-0.044	0.720	-0.018	0.882	0.208	0.089	-0.048	0.696	-0.118	0.339	-0.097	0.432
DWM	T1WI	1	-0.296	0.014	-0.302	0.012	0.080	0.518	-0.311	0.010	-0.184	0.134	-0.212	0.083
		2	-0.323	0.007	-0.288	0.017	0.074	0.549	-0.333	0.005	-0.200	0.103	-0.238	0.050
	T2WI	1	-0.284	0.019	-0.184	0.133	0.041	0.742	-0.299	0.013	-0.236	0.053	-0.209	0.088
		2	-0.275	0.023	-0.272	0.025	0.116	0.347	-0.298	0.014	-0.230	0.060	-0.177	0.149
PV	T1WI	1	-0.375	0.002	-0.201	0.100	-0.055	0.655	-0.441	<0.001	-0.185	0.132	-0.324	0.007
		2	-0.348	0.004	-0.188	0.125	-0.035	0.778	-0.404	0.001	-0.172	0.160	-0.312	0.010
	T2WI	1	-0.322	0.007	-0.208	0.089	-0.045	0.718	-0.302	0.012	-0.209	0.088	-0.255	0.036
		2	-0.410	0.001	-0.292	0.016	-0.030	0.805	-0.406	0.001	-0.164	0.183	-0.366	0.002
BG	T1WI	1	-0.386	0.001	-0.393	0.001	-0.002	0.984	-0.354	0.003	-0.075	0.544	-0.393	0.001
		2	-0.398	0.001	-0.392	0.001	0.008	0.949	-0.359	0.003	-0.108	0.380	-0.402	0.001
	T2WI	1	-0.364	0.002	-0.330	0.006	0.095	0.442	-0.354	0.003	-0.120	0.328	-0.364	0.002
		2	-0.419	<0.001	-0.356	0.003	0.032	0.793	-0.417	<0.001	-0.180	0.142	-0.367	0.002
IT	T1WI	1	-0.090	0.464	-0.192	0.117	0.229	0.060	-0.170	0.165	-0.109	0.377	0.073	0.553
		2	-0.098	0.427	-0.148	0.228	0.236	0.053	-0.177	0.150	-0.146	0.236	0.055	0.657
	T2WI	1	0.017	0.889	-0.048	0.696	0.085	0.490	0.021	0.866	-0.090	0.464	0.070	0.573
		2	0.006	0.960	-0.031	0.802	0.099	0.420	-0.060	0.626	-0.090	0.467	0.057	0.642
GA	T1WI	1	-0.320	0.008	-0.184	0.133	-0.229	0.060	-0.306	0.011	-0.238	0.051	-0.198	0.106
		2	-0.318	0.008	-0.185	0.130	-0.121	0.325	-0.309	0.010	-0.261	0.031	-0.160	0.192
	T2WI	1	-0.353	0.003	-0.240	0.049	-0.187	0.126	-0.299	0.013	-0.215	0.078	-0.190	0.120
		2	-0.377	0.002	-0.270	0.026	-0.176	0.150	-0.303	0.012	-0.230	0.060	-0.207	0.090

BALI: Brain atrophy and lesion index; BG: basal ganglia and surrounding areas; DWM: deep white matter lesions; GA: global atrophy; GM-SV: gray matter lesions and subcortical dilated perivascular spaces; IT:

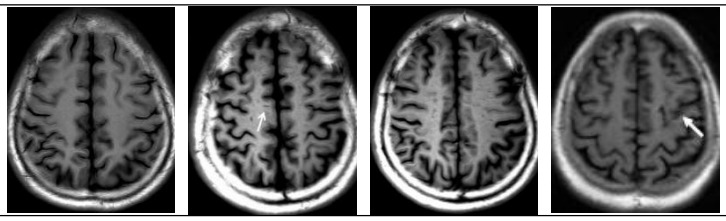
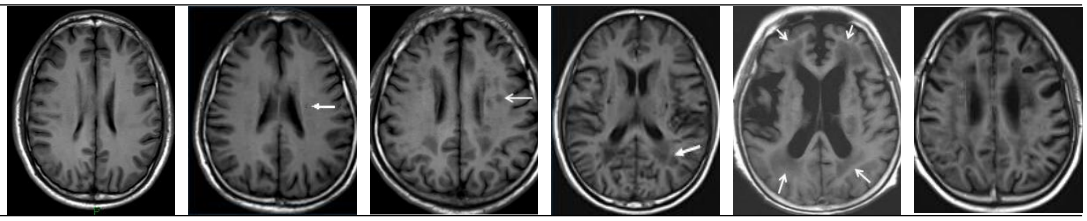
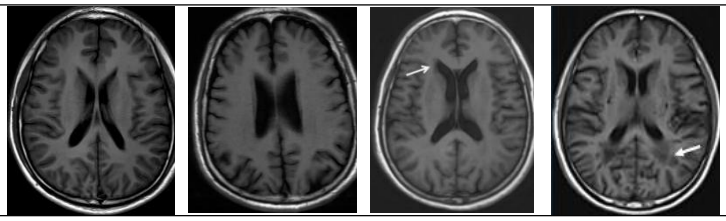
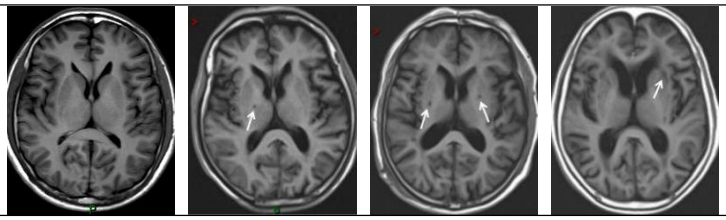
infratentorial compartment; MMSE: Mini-Mental State Examination; PV: periventricular white matter lesions; r: correlation coefficient; T1WI: T1-weighted image; T2WI: T2-weighted image.

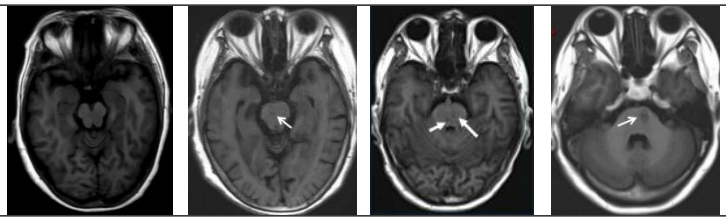
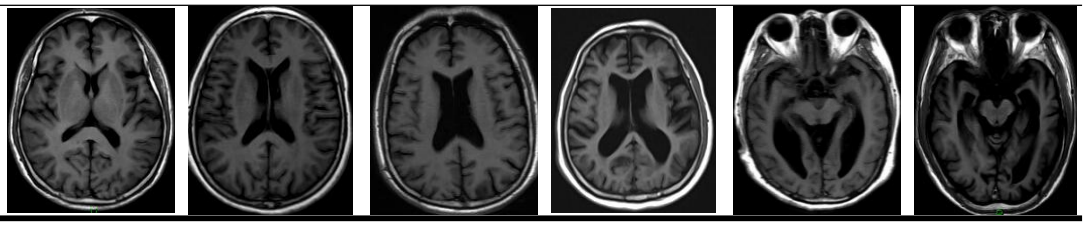
Additional Table 2 Spearman correlation coefficients between MMSE scores and BALI scores in HC and nonT2DM-CI patients

BALI scores	Image type	Reviewer	MMSE total		Orientation		Registration		Attention and calculation		Recall		Language	
			r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
BALI total	T1WI	1	-0.388	0.001	-0.272	0.025	-0.235	0.053	-0.307	0.011	-0.261	0.032	-0.352	0.003
		2	-0.356	0.003	-0.265	0.029	0.223	0.067	-0.276	0.023	-0.222	0.068	-0.343	0.003
	T2WI	1	-0.348	0.004	-0.267	0.028	-0.233	0.056	-0.284	0.019	-0.213	0.082	-0.310	0.010
		2	-0.413	<0.001	-0.326	0.007	-0.297	0.014	-0.318	0.008	-0.262	0.031	-0.383	0.001
GM-SV	T1WI	1	0.180	0.142	0.225	0.066	0.120	0.330	0.112	0.364	0.117	0.340	0.064	0.603
		2	0.161	0.191	0.076	0.538	0.213	0.081	0.123	0.316	0.149	0.226	0.178	0.146
	T2WI	1	-0.189	0.124	0.035	0.777	0.069	0.575	0.237	0.052	0.092	0.457	0.139	0.260
		2	0.059	0.630	-0.057	0.647	0.058	0.638	0.134	0.277	-0.012	0.923	0.068	0.580
DWM	T1WI	1	-0.372	0.002	-0.317	0.008	-0.221	0.071	-0.312	0.010	-0.264	0.030	-0.281	0.020
		2	-0.364	0.002	-0.277	0.022	-0.243	0.046	-0.306	0.011	-0.258	0.033	-0.334	0.005
	T2WI	1	-0.316	0.009	-0.170	0.165	-0.240	0.048	-0.323	0.007	-0.197	0.108	-0.254	0.037
		2	-0.375	0.002	-0.223	0.067	0.316	0.009	-0.337	0.005	-0.219	0.072	-0.316	0.009
PV	T1WI	1	-0.349	0.003	-0.136	0.269	-0.196	0.108	-0.358	0.003	-0.248	0.041	-0.317	0.008
		2	-0.326	0.007	-0.140	0.256	-0.203	0.097	-0.297	0.014	-0.218	0.074	-0.329	0.006
	T2WI	1	-0.412	<0.001	-0.255	0.035	-0.255	0.036	-0.354	0.003	-0.247	0.042	-0.382	0.001
		2	-0.446	<0.001	-0.285	0.018	-0.220	0.071	-0.391	0.001	-0.298	0.013	-0.382	0.001
BG	T1WI	1	-0.183	0.136	-0.217	0.075	-0.194	0.114	-0.173	0.159	-0.101	0.411	-0.140	0.256
		2	-0.105	0.394	-0.140	0.256	0.190	0.120	-0.121	0.326	-0.093	0.448	-0.067	0.586
	T2WI	1	-0.246	0.043	-0.176	0.150	-0.330	0.006	-0.269	0.026	-0.182	0.138	-0.164	0.182
		2	-0.248	0.041	-0.208	0.089	0.310	0.010	-0.253	0.037	-0.182	0.137	-0.187	0.126
IT	T1WI	1	-0.294	0.015	-0.262	0.031	0.153	0.213	-0.134	0.277	-0.096	0.434	0.347	0.004
		2	-0.295	0.014	-0.259	0.033	-0.178	0.147	-0.165	0.180	-0.107	0.385	0.325	0.007
	T2WI	1	-0.231	0.058	-0.242	0.047	-0.074	0.549	-0.119	0.332	-0.045	0.717	-0.236	0.053
		2	-0.239	0.050	-0.278	0.022	-0.177	0.149	-0.096	0.437	-0.085	0.491	-0.297	0.014
GA	T1WI	1	-0.413	<0.001	-0.328	0.006	-0.233	0.056	-0.291	0.016	-0.355	0.003	-0.358	0.003
		2	-0.374	0.002	-0.348	0.004	-0.191	0.118	-0.250	0.040	-0.328	0.006	-0.345	0.004
	T2WI	1	-0.344	0.004	-0.338	0.005	-0.186	0.129	-0.218	0.074	-0.301	0.013	-0.326	0.007
		2	-0.401	0.001	-0.357	0.003	-0225	0.065	-0.267	0.028	-0.311	0.010	-0.426	<0.001

HC: Healthy control; nonT2DM-CI: participants with cognitive impairment but without T2DM; BALI: Brain atrophy and lesion index; BG: basal ganglia and surrounding areas; DWM: deep white matter lesions; GA: global atrophy; GM-SV: gray matter lesions and subcortical dilated perivascular spaces; IT: infratentorial compartment; MMSE: Mini-Mental State Examination; PV: periventricular white matter lesions; r: correlation

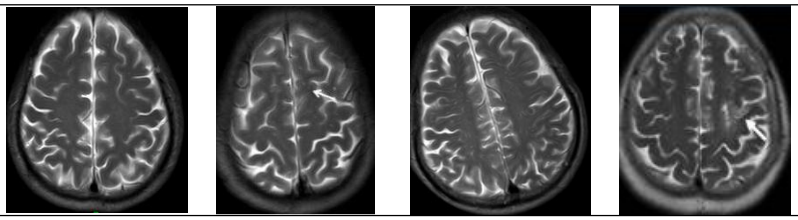
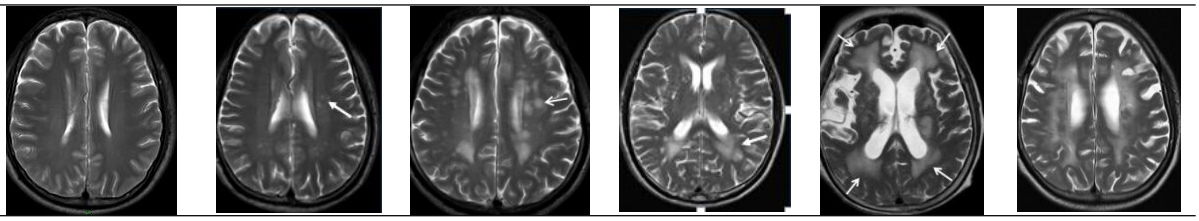
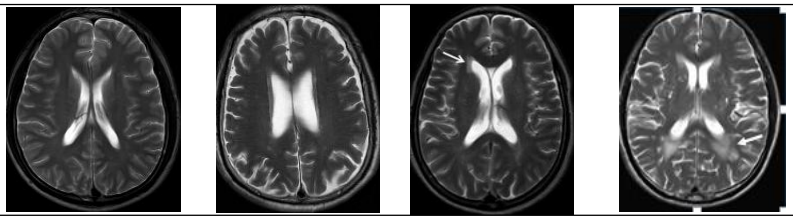
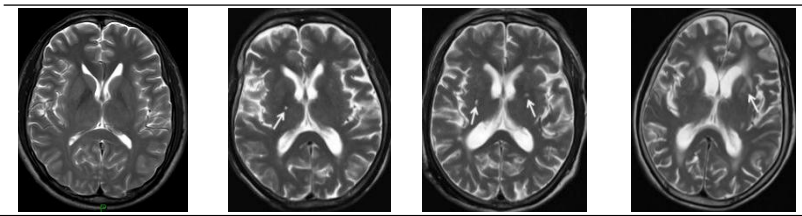
coefficient; T1WI: T1-weighted image; T2WI: T2-weighted image.

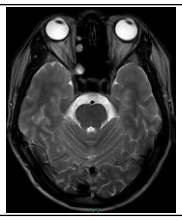
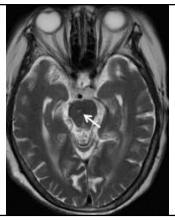
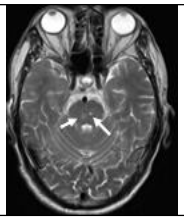
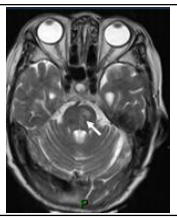
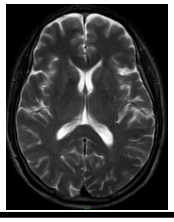
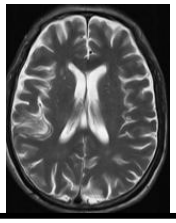
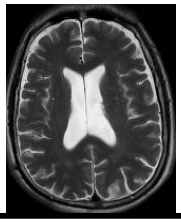
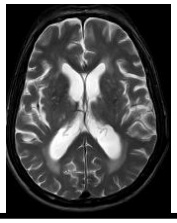
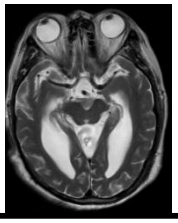
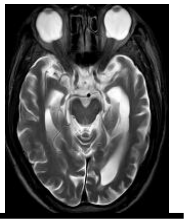
Categories	Score					
	0	1	2	3	4	5
GM-SV	Homogeneous signal intensity (SI) in the GM and adjacent subcortical WM	Few punctate low SI in GM or multiple punctate/linear low SI in adjacent subcortical WM	Small patchy focus of low SI in GM or punctate/linear low SI in the adjacent subcortical WM	Patchy foci of low SI in GM	—	—
					—	—
DWM	Normal homogenous SI	Punctate low SI lesion	Small patchy low SI lesions	Large patchy low SI lesions	Large patchy low SI lesions involving deep WM in all cerebral lobes	Low SI extending throughout all the deep WM
						
PV	Normal homogenous SI	Cap or pencil line shaped low SI	Patchy halo low SI with blurred margin	Patchy low SI lesions connected with lesions in the deep WM		
					—	—
BG	Normal homogenous SI	Only one punctate low SI lesion	More than one punctate low SI lesions	Patchy low SI lesions	—	—
					—	—

IT	Normal homogenous SI	Only one punctate low SI lesion	More than one punctate low SI lesions	Patchy low SI lesions	—	—
					—	—
GA	No enlargement of ventricles and no widen of sulci	Mild enlargement of ventricles and no widen of sulci	Moderate enlargement of ventricles and no widen of sulci	Severe enlargement of ventricles and no widen of sulci	Most severe atrophy of medial temporal lobes	Most severe atrophy of medial temporal lobes and also atrophy throughout the cerebral cortex
						

Additional Figure 1 Evaluation of the brain atrophy and lesion index (BALI) based on T1WI.

BG: basal ganglia and surrounding areas; DWM: deep white matter lesions; GA: global atrophy; GM: gray matter; GM-SV: gray matter lesions and subcortical dilated perivascular spaces; IT: infratentorial compartment; PV: periventricular white matter lesions; T1WI: T1-weighted image; WM: white matter. White arrows indicate targeted lesions.

Categories	Score					
	0	1	2	3	4	5
GM-SV	Homogeneous signal intensity (SI) in the GM and adjacent subcortical WM	Few punctate high SI in GM or multiple punctate/linear high SI in adjacent subcortical WM	Small patchy focus of high SI in GM or punctate/linear high SI in the adjacent subcortical WM	Patchy foci of high SI in GM	—	—
					—	—
DWM	Normal homogenous SI	Punctate high SI lesion	Small patchy high SI lesions	Large patchy high SI lesions	Large patchy high SI lesions involving deep WM in all cerebral lobes	High SI extending throughout all the deep WM
						
PV	Normal homogenous SI	Cap or pencil line shaped high SI	Patchy halo high SI with blurred margin	Patchy high SI lesions connected with lesions in the deep WM		
					—	—
BG	Normal homogenous SI	Only one punctate high SI lesion	More than one punctate high SI lesions	Patchy high SI lesions		
					—	—

IT	Normal homogenous SI	Only one punctate high SI lesion	More than one punctate high SI lesions	Patchy high SI lesions	—	—
					—	—
GA	No enlargement of ventricles and no widen of sulci	Mild enlargement of ventricles and no widen of sulci	Moderate enlargement of ventricles and no widen of sulci	Severe enlargement of ventricles and no widen of sulci	Most severe atrophy of medial temporal lobes	Most severe atrophy of medial temporal lobes and also atrophy throughout the cerebral cortex
						

Additional Figure 2 Evaluation of the brain atrophy and lesion index based on T2WI.

BG: basal ganglia and surrounding areas; DWM: deep white matter lesions; GA: global atrophy; GM: gray matter; GM-SV: gray matter lesions and subcortical dilated perivascular spaces; IT: infratentorial compartment; PV: periventricular white matter lesions; T2WI: T2-weighted image; WM: white matter. White arrows indicate targeted lesions.