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ORIGINAL RESEARCH

Relationship Between Resting-State Functional Magnetic Resonance Imaging and Different Time in Target Glucose Range in Elderly Patients with Type 2 Diabetes Mellitus

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Purpose: This study aimed to investigate the relationship between the resting-state functional magnetic resonance imaging (rs-fMRI) indices and time in target glucose range (TIR) in elderly type 2 diabetes mellitus (T2DM) patients.

Methods: Ninety-eight elderly T2DM patients were divided into the low-TIR (TIR≤70%) and high-TIR groups (TIR>70%). The two groups' clinical variables, neuropsychological scale scores, and rs-fMRI scan data were collected. The rs-fMRI including low-frequency fluctuation (ALFF), fractional ALFF (fALFF), and regional homogeneity (ReHo). The changes and the interrelationships of these indicators were analyzed in the two groups.

Results: Compared with the high-TIR group, disease duration, blood urea nitrogen, urine microalbumin were significantly greater ($P<0.01$) diastolic blood pressure and albumin were significantly lower ($P<0.05$) in the low TIR group. In the low-TIR group, the Cerebelum_Crus2_R ReHo value was significantly increased (voxel $p<0.001$, cluster $p<0.05$), the Frontal_Inf_Orb_R ReHo value was significantly decreased, the Cerebelum_Crus2_R and Frontal_Mid_L ALFF values were significantly increased, the Temporal_Sup_L and Precuneus_R ALFF values were significantly decreased; the Lingual_L fALFF value was significantly decreased. Increased ReHo values in differential brain regions between the low and high TIR groups were positively correlated with HbA1c ($P = 0.042$), and decreased ReHo values were significantly negatively correlated with HbA1c ($P=0.026$) and urine microalbumin ($P=0.005$) levels. Decreased ALFF values in differential brain regions were significantly negatively correlated with the basal C-peptide level ($p=0.007$) and significantly positively correlated with the basal Mini-Mental State Examination (MMSE) score ($p = 0.048$).

Conclusion: ReHO, ALFF, and fALFF value differences were present between the low and high TIR groups. Elderly T2DM patients in the low-TIR group were more susceptible to impaired brain function, which presented mainly as abnormal reduction in and activation of functional activity in some temporal lobes, frontal lobes, and occipital lobes in the resting state, and more significant when glycemic control is poorer.

Keywords: type 2 diabetes mellitus, time in range, resting-state functional magnetic resonance imaging, low-frequency fluctuation, fractional low-frequency fluctuation, regional homogeneity

Introduction

With rapid urbanization and population aging, the prevalence of type 2 diabetes mellitus (T2DM) in the older population is increasing annually, and long-term poor glycemic control and disease progression can cause several complications, including central nervous system complications. A substantial body of prospective research indicates that individuals with diabetes are at a significantly higher risk of cognitive dysfunction, with the risk being 1.5 to 2.5 times greater than that of the general population.[1,2] This risk is particularly pronounced among the elderly. Studies have shown that in individuals aged 60 and above with diabetes, the prevalence of mild cognitive impairment (MCI) and dementia is 26.0%

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and 36.9%, respectively, which is substantially higher than in non-diabetic populations (MCI 20.8%, dementia 5.6%). Among those aged 70 and above with diabetes, the prevalence of cognitive impairment reaches as high as 28.8%.[3,4] Diabetes is recognized as one of the primary etiologies of cognitive impairment, accounting for 60%-70% of all cognitive impairment cases.[5] Key factors contributing to accelerated cognitive decline include insulin resistance,[6,7] abnormal blood glucose levels,[8] and the accumulation of advanced glycation end products.[9] Diabetes significantly increases the risk of cognitive dysfunction, which in turn impairs the ability to self-manage diabetes, thereby exacerbating disease progression and creating a vicious cycle. Type 2 diabetes-related cognitive impairment has emerged as a major global public health challenge due to its high prevalence, complex mechanisms, and severe consequences. Addressing this issue requires multidisciplinary collaboration and early intervention strategies.

With advances in magnetic resonance imaging techniques, an increasing number of neuroimaging studies have been conducted on cognitive impairment in T2DM patients. Resting-state functional magnetic resonance imaging (rs-fMRI) is a powerful tool for investigating spontaneous brain activity and functional connectivity in the absence of external stimuli. Among the most commonly used rs-fMRI parameters are Regional Homogeneity (ReHo), Amplitude of Low-Frequency Fluctuation (ALFF), and fractional ALFF (fALFF).[10] ReHo reflects the temporal synchronization of neural activity within localized brain regions, making it sensitive to disruptions in regional functional coherence associated with metabolic dysregulation (eg, insulin resistance) in T2DM.[11] ALFF/fALFF quantify the intensity and fractional contribution of low-frequency oscillations in the blood oxygen level-dependent (BOLD) signal, which are linked to neuronal baseline energy metabolism. Abnormal ALFF/fALFF patterns in T2DM may reflect glucose toxicity and vascular dysfunction impacting neural networks.[12] Resting-state functional magnetic resonance imaging (rs-fMRI) can reveal abnormal changes in spontaneous neuronal activity in the brains of diabetic patients.[13,14] In recent years, the glucose time in range (TIR) has become a critical marker for blood glucose monitoring that is recommended in the latest Chinese and international guidelines, as it can compensate for the shortcomings of HbA1c and can more comprehensively reflect the glycemic control status of patients.[15,16] TIR was selected as the glycemic control marker for grouping participants in this study. The flash glucose monitoring system (FGM) was used to obtain the TIR and combined with rs-fMRI data to examine the characteristics of resting-state brain functional activity markers in older T2DM patients and the relationships of these characteristics with clinical parameters to obtain new understanding of the pathogenesis of diabetic encephalopathy and options for formulating early intervention strategies.

Materials and Methods

Study Subjects and Grouping

Ninety-eight elderly T2DM patients hospitalized in the endocrinology department of the First People's Hospital of Jinan from March 2023 to May 2024 were included. Their ages ranged from 55–79 years. To improve consistency, reproducibility and allow for easier comparison and analysis of our findings with existing literature. All the participants were right-handed.[17,18]

All patients signed the informed consent form, and this study was approved by the ethics committee of the First People's Hospital of Jinan (No. 2022–03-01-01).

The inclusion criteria were as follows: (1) met the 1999 diabetes diagnosis and typing criteria recommended by the World Health Organization (WHO); (2) had a disease duration >1 year and were aged >60 years; (3) underwent continuous blood glucose monitoring via the FGM system and had complete data; and (4) underwent resting-state brain function magnetic resonance imaging.

The exclusion criteria were as follows: (1) had acute diabetes mellitus complications; (2) had a history of stroke, Parkinson's disease, epilepsy, severe depression, or other neuropsychiatric diseases; (3) had a history of brain trauma, hemorrhage, or tumor; (4) were contraindicated for magnetic resonance imaging; and (5) had intracerebral organic lesions on routine sequence scans via cranial magnetic resonance imaging.

Grouping: The 2019 Advanced Technologies & Treatments for Diabetes (ATTD) international consensus[19] and related studies[20,21] recommend a TIR>70% as a control target for diabetic patients. We divided the qualified participants

into two groups with a TIR>70% as the cutoff point: (1) the low-TIR group, with a TIR≤70% and 63 patients in total, and (2) the high-TIR group, with a TIR>70% and 35 patients in total.

Collection of Clinical Characteristics

Age, height, weight, other general data, fasting blood glucose, 2-hour postprandial blood glucose, glycated hemoglobin, total cholesterol, triglycerides, low-density lipoprotein, urine microalbumin, and other biochemical parameters were collected for all patients. The body mass index (BMI) was calculated as follows: BMI=weight (kg)/height^2 (m^2). Disease duration was calculated from the time of diagnosis of T2DM according to the patient's recollection to the day of the Magnetic Resonance Imaging (MRI) scan. The glucose-lowering pharmacotherapy usage status of the participants was determined. To make the study results more generalizable, we did not place specific restrictions on participant drug use due to individual differences in T2DM treatment regimens.

Instantaneous Scanning Glucose Monitoring System

A flash glucose monitoring (FGM) system (Abbott Laboratories, USA) was used for 3 days to continuously monitor blood glucose levels. The probe was located at the superolateral side of the patient's left arm, and a sensor was used to monitor glucose continuously in the interstitial fluid. The system automatically records 1 glucose reading every 15 minutes and uses finger-free blood correction. The FGM monitoring data were downloaded, and the system software was used to generate several reports, including the TIR. The blood glucose range for the TIR was 3.9–10.0 mmol/L.

MMSE and MoCA Evaluations

The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were used to evaluate the general cognitive function of each patient.[22,23] The total score was 30 points. The test results are intimately associated with education level. Since all our study participants have a junior high school education or above, combined with relevant literature, the cut-off points of MMSE and MoCA score was set <26 points to indicate cognitive impairment.[23–25]

Magnetic Resonance Imaging Data Collection

GE750 3.0T magnetic resonance imaging system with 8-channel cranial coils was used for routine T1-Weighted Imaging (T1WI), T2-Weighted Imaging (T2WI), and T2-Fluid Attenuated Inversion Recovery (T2-FLAIR) sequence scanning to rule out cranial organic lesions before conducting the rs-fMRI scan. For rs-fMRI, echo planar imaging sequence axial scans, Echo Time (TE) = 30 ms, Repetition Time (TR) = 2000 ms, field = 240×240 mm, rotation angle = 90°, matrix 80×80, slice thickness 3 mm, interslice distance 0, and 36-slice axial scans were used. The whole brain was scanned 220 times per patient. The patients were instructed to close their eyes, maintain a conscious status, and avoid any structural thinking activity or limb movement during the scanning process.

Resting-State BOLD fMRI Data Processing

Statistical Parametric Mapping 12 (SPM12) in Matrix Laboratory (MATLAB) and rs-fMRI data analysis toolkits (REST) plus were used to analyzed functional imaging data.[26,27]

Preprocessing of rs-fMRI data: The data were converted into the Neuroimaging Informatics Technology Initiative (NIFIT) data files, and the first 10 time points were removed. Time slice correction, head movement correction (subjects whose head movements exceeded 3 mm and 3° were removed), spatial standardization (two-step registration was used, and spatially normalized functional images were resampled to a voxel size of 3 mm×3 mm×3 mm), spatial smoothing using full width at half maximum (FWHM) 6×6×6 mm was used to remove linear drift, linear regression was used to remove confounding variables (white matter signal, cerebrospinal fluid signal, and 24 head movement noise signals), and filtering (filter frequency range: 0.01–0.08 hz) was conducted.

Indicator calculation: (1) ALFF: Pre-preprocessing for this step did not include filtering. The ALFF indicator was calculated, and *z* score conversion was conducted. (2) fALFF: Pre-preprocessing for this step included filtering. The ALFF indicator was calculated, and m conversion was conducted. The fALFF was calculated as the ratio of power in the

low-frequency range (0.01–0.08 hz) to that in the entire frequency range (0–0.25 hz), and *z* score conversion was conducted. (3) ReHo: Preprocessed data were filtered (0.01–0.08 hz) before the ReHo value was calculated, and a Gaussian filter with a FWHM kernel size of 4 mm was used for smoothing.

Statistical Analysis

1. SPSS 29.0 software was used for general clinical data statistical analyses. Levene's test and Shapiro–Wilk test were used for the assumptions of homogeneity of variance and normal distribution. P-value > 0.05 indicated that all continuous variables satisfied the assumption of normal distribution. Independent sample t tests were used for intergroup comparisons of quantitative data, and χ^2 tests were used for qualitative data. Both tests were two-tailed, and a difference of $P<0.05$ was considered significant.

2. Intergroup comparisons of various rs-fMRI indicators: The statistical module of the MATLAB-based REST plus software was used for two-sample t tests of ReHo, ALFF, and fALFF values, and statistical graphs of the two subjects were generated using sex, age, and history of diabetes as covariates and differential regions. The contrast was [−1 1], and Family-Wise Error (FWE) correction was used for multiple comparison correction. The significance criteria were voxels $P<0.001$ and cluster $P<0.05$.

3. Correlation analysis: The time sequence signals of brain regions with significant differences in ReHo, ALFF, and fALFF values and diabetes duration, HbA1c, urine microalbumin, high-density lipoprotein, basal insulin, basal C-peptide, and MMSE and MoCA scores were used for Pearson correlation analysis. Age, sex, and education level were added as covariates for partial correlation analysis. A difference of $P<0.05$ was considered significant. Moreover, the Benjamini-Hochberg (BH) method was employed to control the False Discovery Rate (FDR) in multiple hypothesis testing.[28]

Results

Clinical Characteristics of Study Subjects

There were no significant differences in age, Sex, Education levels, BMI, systolic blood pressure, cholesterol, triglycerides, basal C-peptide, basal insulin, MMSE score, or MoCA score between the two groups (Table 1). Compared with those in the high-TIR group, disease duration, blood urea nitrogen, and urine microalbumin were significantly higher in the low-TIR group patients ($P<0.01$), and diastolic blood pressure and albumin were significantly lower ($P<0.05$).

Table 1 Demographic Information and Neurocognitive Tests Results of Two Groups

Group	TIR≤70%	TIR>70%	*P value*
Age (years)	66.49±6.59	63.88±11.65	0.153
Sex (male/female)	34/29	14/21	0.139
Education levels (years)	10.15±1.65	10.17±2.10	0.618
Disease duration (years)	13.99±14.84	8.89±6.72	0.020*
BMI (kg/m^2)	25.84±2.82	25.92±3.49	0.901
Basic C-peptide (ng/mL)	2.71±1.97	2.75±1.09	0.900
Basal insulin (uU/mL)	12.22±7.26	15.87±25.29	0.274
MMSE	25.49±1.65	25.74±1.71	0.491
MoCA	25.28±6.47	24.91±1.96	0.745
Diastolic blood pressure (mmHg)	79.97±9.95	85.35±8.35	0.008**
Systolic blood pressure (mmHg)	140.45±19.13	145.03±15.47	0.229
Albumin (g/L)	42.30±2.63	43.50±2.90	0.038*
Globulin (g/L)	26.52±4.14	27.22±4.07	0.424

(*Continued*)

Table 1 (Continued).

Group	TIR≤70%	TIR>70%	*P value*
Urea nitrogen (mmol/L)	5.83±1.53	5.16±1.28	0.030*
Creatinine (umol/L)	66.69±15.87	61.32±14.59	0.103
Uric acid (umol/L)	297.22±81.59	306.32±80.43	0.596
Total cholesterol (mmol/L)	5.27±1.39	5.13±0.90	0.534
Triglyceride (mmol/L)	1.89±1.88	1.66±0.89	0.509
Low density lipoprotein (mmol/L)	3.28±1.19	3.17±0.84	0.654
High density lipoprotein (mmol/L)	1.21±0.27	1.19±0.22	0.685
Fasting Glucose (mmol/L)	8.42±2.69	7.79±1.52	0.137
Postprandial blood glucose (mmol/L)	16.04±13.70	11.56±3.49	0.064
HbA1c (%)	8.13±1.70	7.67±1.57	0.190
Urinary microalbumin (mg/L)	83.68±230.88	11.72±19.35	0.014*

Note: *P<0.05, **P<0.01. The data are presented as the means ± SDs.

Comparison of ReHo Values Between the Two Groups and Correlation Analysis with Clinical Parameters

Compared with those in the high-TIR group, the brain regions with increased ReHo values in the low-TIR group were mainly concentrated in the right cerebellum and involved Cerebelum_Crus2_R (AAL) (Figure 1 and Table 2); using automatic anatomical labeling (AAL) mapping,[29] the brain regions with reduced ReHo values were mainly concentrated in the right cerebrum and involved the Frontal_Inf_Orb_R (AAL) (Figure 2 and Table 3).

Increased ReHo values in differential brain regions in the low TIR group were significantly positively correlated with HbA1c (r = 0.204, P = 0.042), and decreased ReHo values were significantly negatively correlated with Hb1Ac (r = −0.222, P = 0.026) and urine microalbumin (r = −0.280, P = 0.005) and significantly positively correlated with basal C peptide (r = 0.225, P = 0.026) (Figure 3).

Comparison of ALFF Values Between the Two Groups and Correlation Analysis with Clinical Data

Compared with those in the high-TIR group, the brain regions with increased ALFF values in the low-TIR group were mainly concentrated in the right cerebellum and involved mainly the Cerebelum_Crus2_R (AAL) and Frontal_Mid_L (Figure 4 and Table 4); the brain regions with decreased ALFF values were mainly concentrated in the left cerebrum and involved mainly the Precuneus_R and Temporal_Sup_L (AAL) (Figure 5 and Table 5).

Decreased ALFF values in the Precuneus_R brain region of the low-TIR group were significantly negatively correlated with the basal C-peptide level (r = −0.271, p = 0.007) and significantly positively correlated with the basal MMSE score (r = 0.199, p = 0.048). Cerebelum_Crus2_R, Frontal_Mid_L, and Temporal_Sup_L did not significantly correlate with various clinical parameters (Figure 6).

Comparison of fALFF Values Between the Two Groups and Correlation Analysis with Clinical Data

Compared with those in the high-TIR group, no brain regions with increased fALFF values were extracted in the low-TIR group, and the brain regions with decreased fALFF values were mainly concentrated in the left cerebrum and involved mainly the Lingual_L (AAL) (Figure 7 and Table 6).

Decreased fALFF values in the Lingual_L brain region in the low TIR group were not correlated with Hb1Ac, urine microalbumin, high-density lipoprotein, basal insulin, basal C-peptide, MMSE, or MoCA scores.

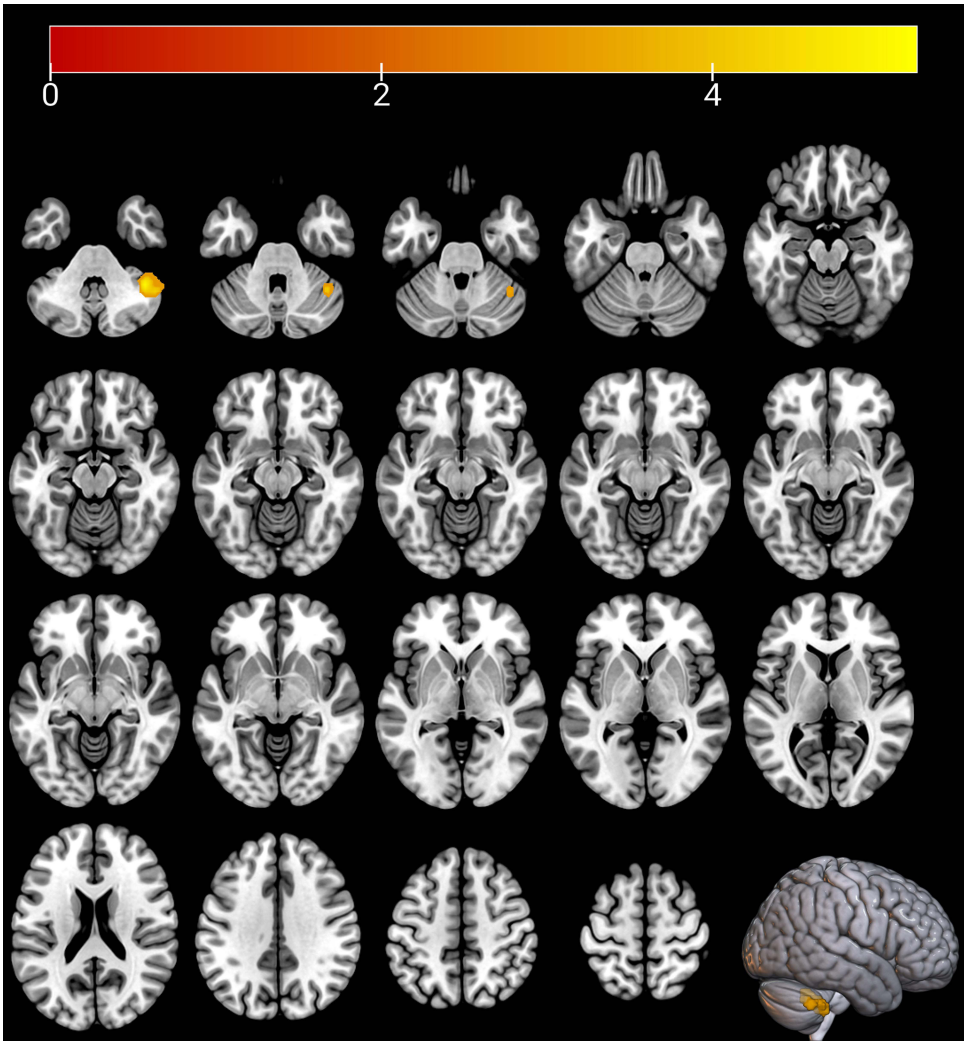

Figure 1 The area of increased ReHo in the low TIR group compared with that in the high TIR group.

Discussion

In recent years, the role of diabetes mellitus in cognitive decline and dementia progression has become a research focus.[30,31] Diabetes mellitus-induced cognitive impairment and neuropathophysiological and structural changes in the brain mainly present as memory decline and decreased learning ability, with an insidious onset and slow progression. Existing clinical treatments for dementia have poor efficacy, and treatments for mild cognitive impairment have good efficacy. Therefore, the early discovery and diagnosis of T2DM-induced cognitive impairment are important. With advances in magnetic resonance imaging, rs-fMRI has become a new examination method for the early discovery and diagnosis of cognitive impairment. This method is low-cost, has an easily controlled baseline, is highly repeatable, and

Table 2 The Brain Regions with Increased ReHo Values Between the Low TIR Group and the High TIR Group (Voxel P<0.001, Cluster P<0.05, FWE Corrected)

No. of Voxel Cluster	Brain Regions	Peak MNI (mm)			Peak t value	Cluster (voxels)
		X	Y	Z		
1	Cerebelum_Crus2_R	42	−48	−36	5.319	158

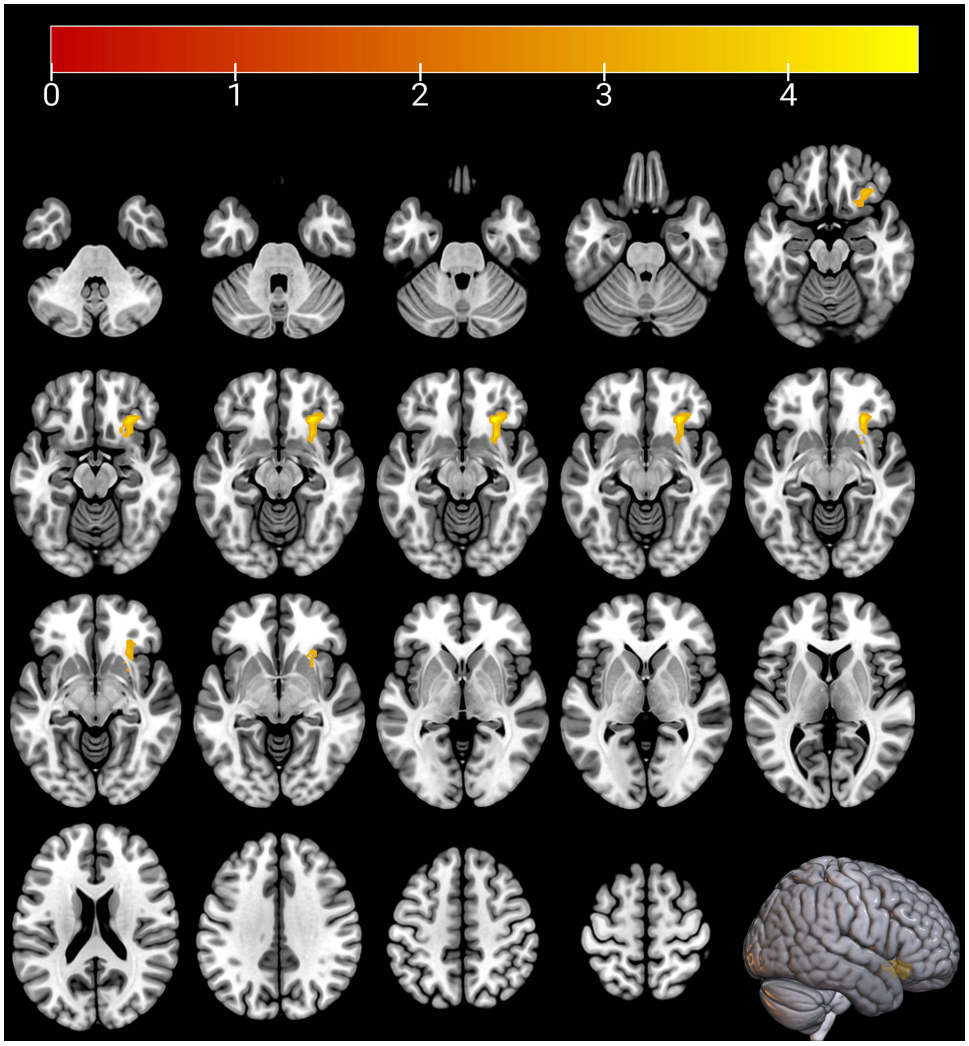

Figure 2 The area of decreased ReHo in the low TIR group compared with that in the high TIR group.

has high spatial resolution. Rs-fMRI can also provide information on structural and functional changes in the brain. In this study, rs-fMRI was used to investigate the brain function of T2DM patients; the effects of glycemic control on ReHo, ALFF, and fALFF in diabetic patients were examined, and the correlations between various brain function marker changes and clinical parameters in older diabetic patients in the two groups were analyzed. These findings provide a basis for early intervention and the diagnosis of brain impairment in diabetes mellitus patients.

ReHo was proposed by a renowned Chinese academic, Professor Yufeng Zang,[11] and refers to the homogeneity of a specific voxel and its neighboring voxels in a stationary time series using Kendall's coefficient of concordance,[32] thereby reflecting the synchronicity of spontaneous activity in local voxels and neighboring voxels in the brain. ReHO does not require a predefined region of interest and has high test–retest reliability. In recent years, processing methods for

Table 3 The Brain Regions with Decreased ReHo Values Between the Low TIR Group and the High TIR Group (Voxel P<0.001, Cluster P<0.05, FWE Corrected)

No. of Voxel	Brain Regions	Peak MNI (mm)			Peak t value	Cluster (voxels)
Cluster		X	Y	Z		
1	Frontal_Inf_Orb_R	27	30	−12	4.7906	78

https://doi.org/10.2147/DMSO.S510628

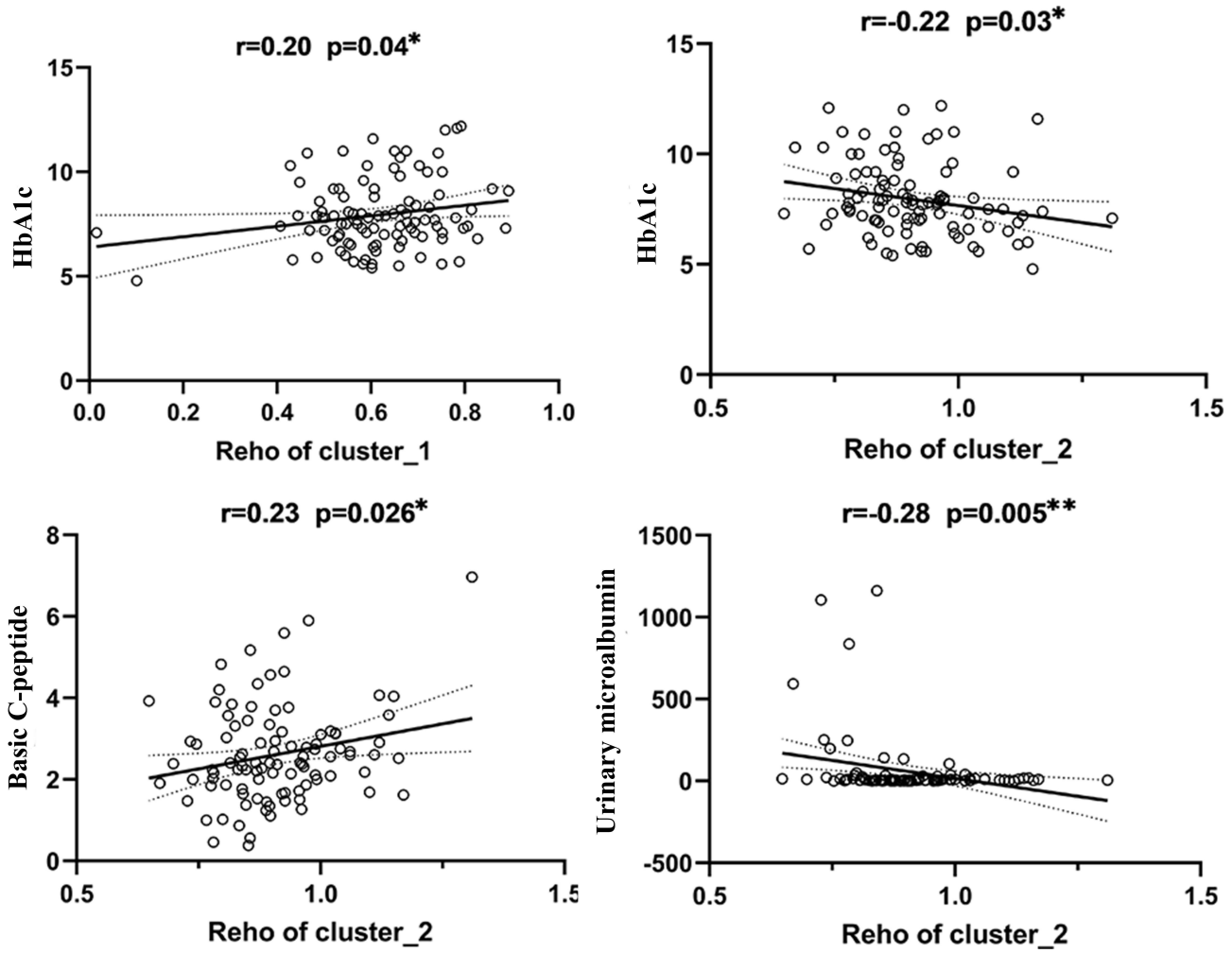

Figure 3 Correlation analysis between differential brain region ReHo values and clinical data in the low-TIR and high-TIR groups. Cluster 1 refers to differential regions in the low TIR group that had significantly higher ReHO values than those in the high TIR group did, and cluster 2 refers to differential regions in the high TIR group that had significantly higher ReHO values than those in the low TIR group did.

rs-FMRI ReHo data have been widely used in studies on many diseases, such as Alzheimer's disease,[33,34] epilepsy,[35] heroin addiction,[36] and schizophrenia,[37] demonstrating that ReHO is an effective method for examining neural mechanisms in the brain. An increase (decrease) in ReHo values indicates increased (decreased) temporal homogeneity in local neuronal activity and tends to present as temporal synchronicity (stochasticity). In the present study, the right cerebellum demonstrated ReHo value differences between the two groups of older T2DM patients. The ReHo values in part of this region were increased in the low-TIR group patients and involved mainly Cerebelum_Crus2_R (aa1). Increased ReHo values were significantly positively correlated with HbA1c. The ReHo values of another brain region were decreased and were mainly involved in Frontal_Inf_Orb_R (aal). Decreased ReHo values were significantly negatively correlated with HbA1c and urine microalbumin and significantly positively correlated with basal C-peptide. Abnormal TIR increases and decreases were present in older T2DM patients in the low TIR group, indicating that the TIR is positively or negatively correlated with ReHo value changes in these brain regions and that the specific relationship varies according to the brain region. This finding shows that the effects of glycemic control on brain function in T2DM patients show regional specificity and that this effect is more significant when glycemic control is poorer.

The ALFF is a 0.01–0.10 hz low-frequency fluctuation BOLD signal value[38] that reflects the intensity of spontaneous activity in local nerves but may be affected by nonneurophysiological fluctuations from breathing, cardiac activity, and movement. A modified measurement was introduced to improve the original ALFF method, namely, the fALFF. The

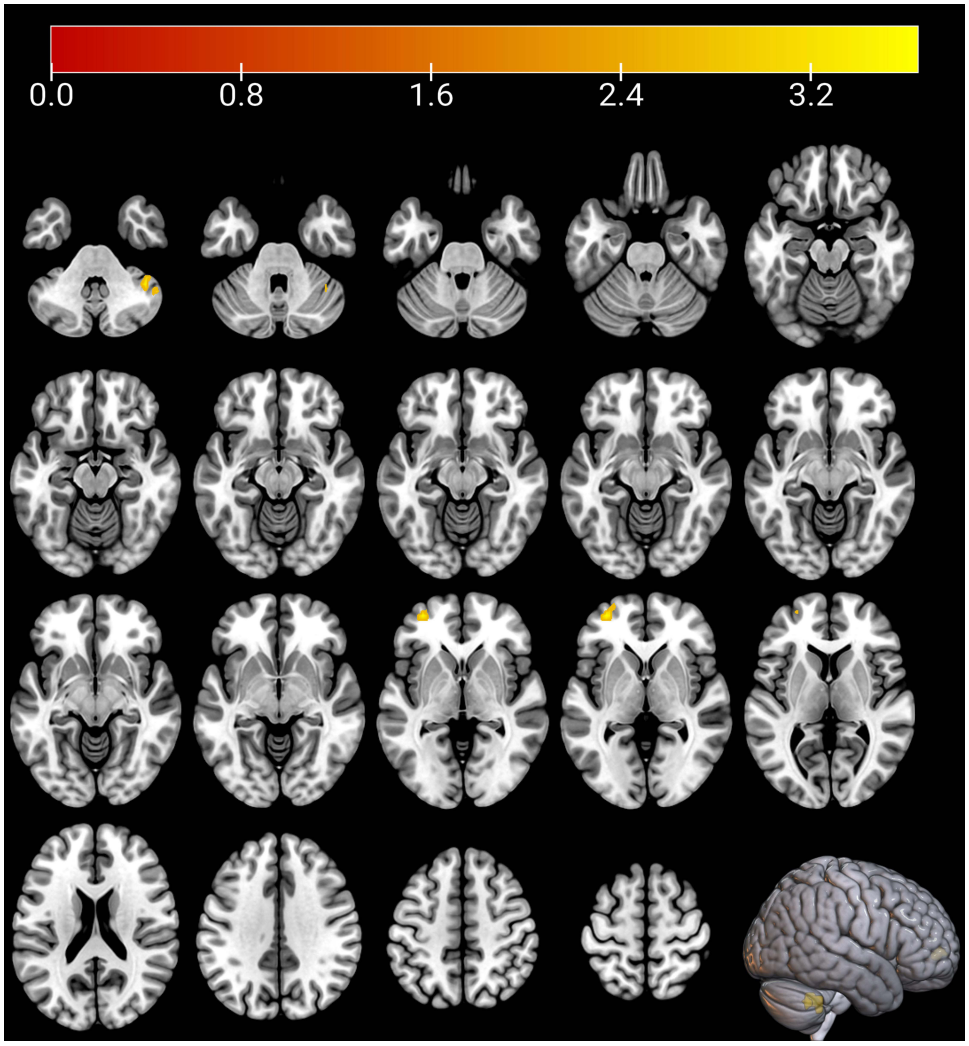

Figure 4 Areas with increased ALFF values in the low-TIR group compared with those in the high-TIR group.

fALFF is the power of the low-frequency range divided by the total power of the entire measurable frequency range[39] and can effectively eliminate physiological noise. Although ALFF and fALFF are related, they are not identical. The reliability of ALFF in gray matter is better than that of fALFF, and it is more sensitive to intergroup and interindividual differences. However, the ALFF may be affected by noise from physiological sources. Yang et al[40] extracted standardized ALFF and fALFF values from 116 brain regions to classify 44 subjective cognitive decline (SCD) patients and 57 healthy controls. The results revealed that the accuracy and AUC of the ALFF were 71.38% and 0.67, respectively, and the accuracy and AUC of the fALFF were 63.81% and 0.59, respectively. After combining the ALFF and fALFF values, the accuracy and AUC increased to 76.44% and 0.69, respectively. Therefore, to evaluate brain function changes more comprehensively, ALFF and fALFF values were evaluated and reported simultaneously in this study. Our study

Table 4 The Brain Regions with Increased ALFF Values Between the Low TIR Group and the High TIR Group (Voxel P<0.001, Cluster P<0.05, FWE Corrected)

No. of Voxel	Brain Regions	Peak MNI (mm)			Peak t value	Cluster (voxels)
Cluster		X	Y	Z		
1	Cerebelum_Crus2_R	42	−48	−36	3.6782	49
2	Frontal_mid_L	−33	54	0	3.7269	26

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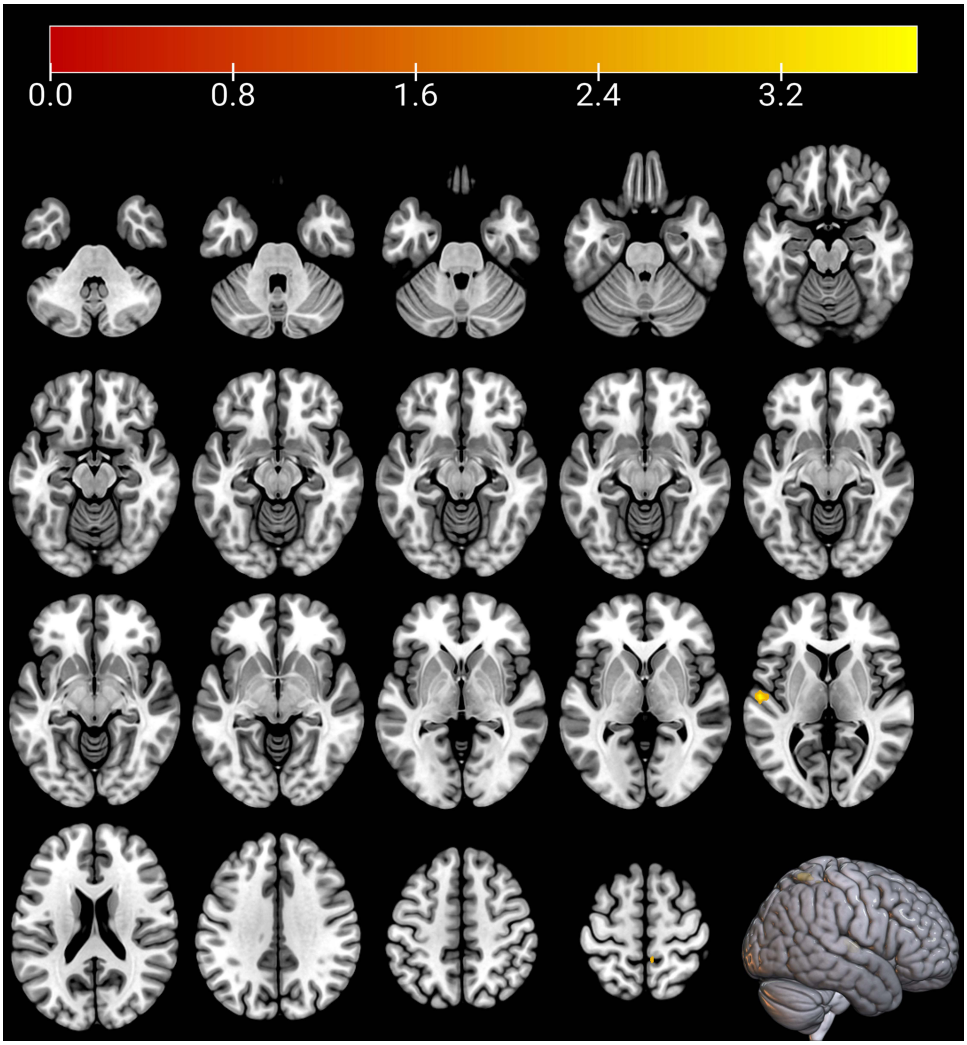

Figure 5 Areas with decreased ALFF in the low-TIR group compared with those in the high-TIR group.

revealed that the brain regions with differences in ALFF values between the two groups of older T2DM patients were the right cerebellum and left cerebrum. In the low-TIR group, the brain regions with increased ALFF values were mainly Cerebelum_Crus2_R (aal) and Frontal_Mid_L, and increased ALFF values were not correlated with the clinical data. The brain regions with decreased ALFF values were mainly the Precuneus_R and Temporal_Sup_L (aal), and decreased ALFF values were significantly negatively correlated with the basal C peptide and significantly positively correlated with the basal MMSE score. Moreover, the brain region with fALFF value differences was the left cerebrum, and the region with decreased fALFF values in the low TIR group was mainly Lingual_L (aal). No correlations were found between decreased fALFF values and clinical data, and brain regions with increased fALFF values were extracted. Our study revealed that some brain regions have bidirectional changes in the form of increased and decreased ALFF values,

Table 5 The Brain Regions with Decreased ALFF Values Between the Low TIR Group and the High TIR Group (Voxel P<0.001, Cluster P<0.05, FWE Corrected)

No. of Voxel	Brain Regions	Peak MNI (mm)			Peak t value	Cluster (voxels)
Cluster		X	Y	Z		
1	Temporal_Sup_L	−57	−15	6	3.9368	26
2	Precuneus_R	9	−57	66	3.6803	21

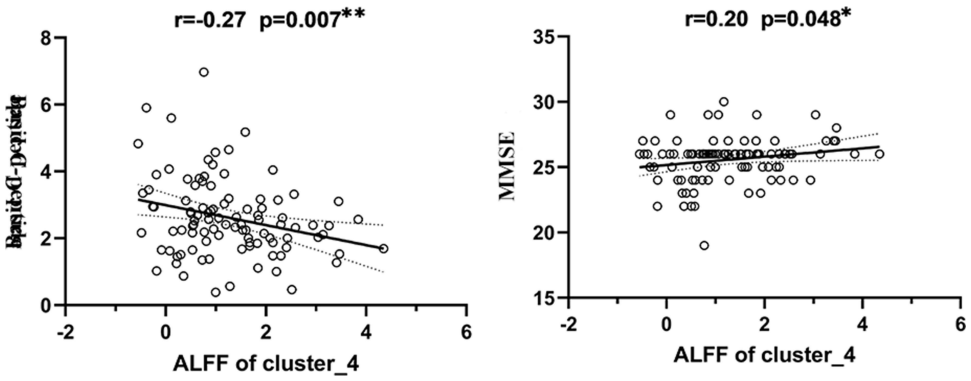

Figure 6 Correlation analysis between differential brain region ALFF values and clinical data in the low-TIR and high-TIR groups. Cluster 4 refers to differential regions in the low-TIR group whose ALFF values were significantly lower than those in the high-TIR group.

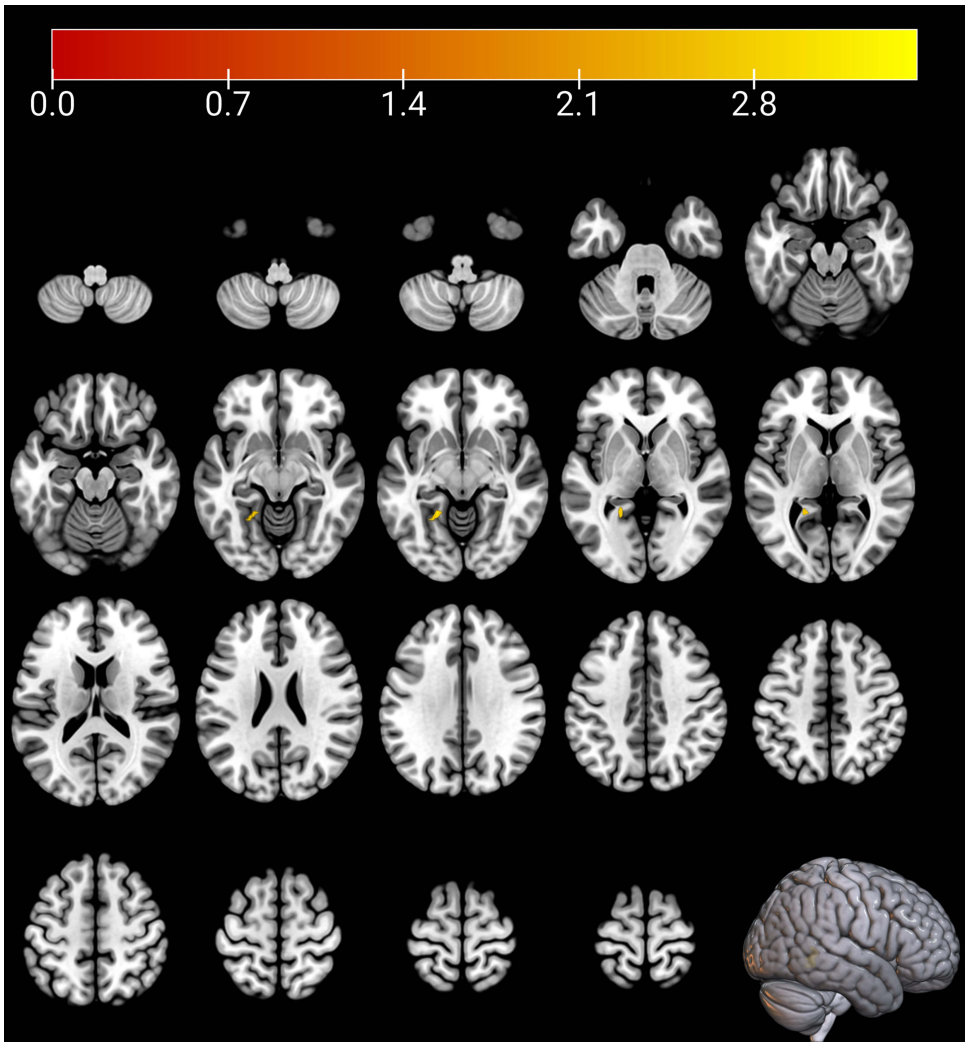

Figure 7 The area of decreased fALFF in the low TIR group compared with that in the high TIR group.

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Table 6 The Brain Regions with Decreased fALFF Values Between the Low-TIR Group and High-TIR Group (Voxel P<0.001, Cluster P<0.05, FWE Corrected P<0.05, GRF Corrected)

No. of Voxel	Brain Regions	Peak MNI (mm)			Peak t value	Cluster (voxels)
Cluster		X	Y	Z		
1	Lingual_L	−21	−51	−3	3.6925	21

indicating abnormal local neuronal activity and the presence of brain impairment. In addition, coexisting injury and compensatory mechanisms may be present. Poor glycemic control may further weaken neuron activity in related brain regions.

Recent studies[41–43] have shown that autonomic nervous activity changes are present in different brain regions in T2DM patients. However, few studies have investigated brain function changes in diabetic patients with different glycemic control statuses. In this study, older T2DM patients were recruited as study participants and grouped according to the TIR. Abnormal changes in ReHo, ALFF, and fALFF values were present in certain brain regions in patients in the low TIR versus high TIR group, and these brain regions were mainly concentrated in the right cerebellum and Crus2, frontal lobe, and temporal lobe in the left cerebrum. These regions control hearing, language, vision, and executive ability and are associated mainly with impaired auditory processing, semantic memory, decision-making, and executive ability. Moreover, the ReHO and ALFF values in neighboring brain regions and related brain regions were increased, which may be due to compensation. One study in China[44] revealed that increased and decreased ALFF values and fALFF values are present in different brain regions at rest in T2DM patients with mild cognitive impairment and that the regions with decreased ALFF values were mostly core brain regions in the DMN; conversely, regions with increased ALFF values were usually peripheral brain regions associated with cognitive impairment. Subsequent follow-up studies revealed that related brain region function continuously decreased with T2DM progression and that new compensatory brain function regions did not appear. Our study revealed that brain impairment further worsened in the low TIR group and that patients with good glycemic control could benefit from delayed cognitive impairment.

TIR is a new marker for evaluating glycemic control quality, and its optimization could help improve brain functional activities and decrease the risk of cognitive impairment. This study combined FGM and rs-fMRI data to provide a new method for the early identification of brain functional changes in older T2DM patients and provides a scientific basis for formulating personalized treatment regimens. Future studies should further explore the direct relationship between TIR and cognitive function, potential mechanisms by which TIR improves brain function, and how to prevent or delay cognitive impairment by optimizing glycemic control. Moreover, developing effective intervention measures for diabetic encephalopathy is an important direction for future research. The limitations of this study include its small sample size, which lacks the representativeness of a large sample size, and sampling errors in the data. Second, some T2DM patients in this study had complications such as diabetic retinopathy and peripheral neuropathy, and the inclusion criteria did not include the presence/absence or type of complications. Further targeted studies with more detailed groupings are needed to obtain more useful information.

Conclusion

ReHO, ALFF, and fALFF value differences were present between the low and high TIR groups. Older T2DM patients in the low-TIR group were more susceptible to impaired brain function, which presented mainly as abnormal reduction in and activation of functional activity in some temporal lobes, frontal lobes, and occipital lobes in the resting state. These factors may coexist with injury and compensatory mechanisms, and are more significant when glycemic control is poorer.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Research Ethics and Consent

This study was approved by the Ethics committee of First People's Hospital of Jinan (No. 2022-03-01-01) and was adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants, ensuring that the collected data were used anonymously and confidentially for scientific purposes.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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