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Aggravated Cognitive and Brain Functional Impairment in Mild Cognitive Impairment Patients with Type 2 Diabetes: A Resting-State Functional MRI Study

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Abstract. Type 2 diabetes mellitus is a metabolic disorder and a risk factor for dementia and mild cognitive impairment (MCI), which could also increase the risk of progression from MCI to dementia. The present study evaluated the spontaneous neuronal activity of 31 patients with MCI using resting-state functional MRI. The patients were divided into two groups (17 MCI patients without diabetes, and 14 patients with type 2 diabetes who were considered as the MCI-DM group) and 17 well-matched healthy controls were also recruited. The amplitude of low-frequency fluctuations (ALFF) of spontaneous blood oxygen level dependent signals was then applied to assess neuroimaging changes. To further investigate the impact of type 2 diabetes on cognition, the correlation of ALFF and the neuropsychological tests for the MCI-DM and MCI group were calculated. MCI-DM patients showed diffused ALFF changes in a variety of brain regions that were significantly related to cognitive performance, including the frontal lobe, the temporal lobe, the hippocampus, the amygdala, and the precuneus during a resting state; whereas, the alterations were much less pronounced in the MCI patients without diabetes. These findings provide new insights into understanding essential of diabetes mellitus and may help to clarify the relationship between diabetes mellitus and dementia.

Keywords: Functional MRI, mild cognitive impairment, resting-state, spontaneous brain activity, type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with changes in cognition, particularly in the domains of learning, memory, mental flexibility, and mental speed [1]. Several large longitudinal population-based studies have shown that T2DM is a risk factor for dementia and mild cognitive impairment (MCI) [2–4]. Furthermore, several studies have shown that T2DM increases the risk of conversion from MCI to dementia [5, 6]. MCI is a concept that defines a transitional state between normal aging and dementia, and is an independent risk factor for dementia. The conversion rates of MCI to dementia are reported to be in the range of 1% to 25% or more per year, with approximately 50% converting to dementia within 3 years [7–9]; when MCI co-occurs with diabetes, this risk is further increased [5].

Alzheimer's disease (AD) is a neurological disorder in which the death of brain cells causes memory loss and cognitive decline. Multiple epidemiological studies have provided direct evidence showing that T2DM is a strong risk factor for AD [10–12]. Some *in vitro* and *in vivo* studies have reported that T2DM could modulate the metabolism of the amyloid-β protein (Aβ), which plays a key role in the pathogenesis of AD [13].

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Although there are a lot of studies about the association between T2DM and cognitive changes, it remains unclear whether older adults with MCI show abnormalities across cognition and neuroimaging when T2DM is also present. The number of elderly people who are affected by T2DM is expected to increase over the next few decades [14]; thus, better insight into how T2DM modifies the brain's physiological responses to cognitive events is critical because such functional changes may represent early indicators of neurodegenerative diseases [15]. This early detection will allow the possibility of implementing a therapeutic intervention at the appropriate time and preventing or delaying the cognitive dysfunction. To achieve this goal, advanced magnetic resonance imaging (MRI) approaches have been extensively employed for the assessment of structural and functional alterations in the brains of patients with T2DM [16]. While research has noted that cerebral atrophy and white-matter lesions are thought to be mainly responsible for cognitive decline in older adults with T2DM [17, 18], there is evidence that functional imaging techniques may identify abnormal activation signatures before structural changes are observed [19]. Resting-state functional MRI (fMRI) provides a simple and noninvasive method to measure spontaneous low frequency (<0.08–0.1 Hz) fluctuations in the blood oxygen level dependent (BOLD) signal [20–22]. According to recent research, altered amplitude of low-frequency fluctuations (ALFF) has been found in many brain regions, e.g., decreased ALFF values in the bilateral-middle temporal gyrus, left fusiform gyrus, left-middle occipital gyrus, right inferior occipital gyrus; and increased ALFF values in both the bilateral cerebellum posterior lobe and right cerebellum culmen in T2DM patients [20]. However, decreased ALFF was observed in an MCI group compared to controls mainly in the prefrontal and left parietal regions, and right fusiform gyrus; whereas, increased ALFF/fALFF was found in the limbic and midbrain regions [22]. Thus, T2DM and MCI have different mechanisms of cognitive dysfunction. Resting-state ALFF has not been previously applied to MCI patients with T2DM to assess the effect of this concurrence.

In this study, we used the ALFF of spontaneous BOLD signals [23] to assess neuroimaging changes. We hypothesized that there are group differences in ALFF among MCI-DM, MCI, and healthy controls (HC), and that MCI-DM differs from MCI in significantly different brain regions of the three groups. We also hypothesized that cognitive performance would be correlated with ALFF in these brain regions.

RESEARCH DESIGN AND METHODS

Participants

The participants in the present study were all from the Beijing Aging Brain Rejuvenation Initiative (BABRI), which is an ongoing, longitudinal study investigating aging and cognitive impairment of urban elderly individuals in Beijing, China. The present study included a total of 31 MCI (including T2DM and nondiabetes) patients (all right-handed; 14 males and 17 females; average age: 65.2 ± 7.4) and 17 healthy controls (all right-handed, 10 males and 7 females; average age: 63.8 ± 5.79). The participants were all native Chinese Mandarin speakers. The participants were selected according to the following criteria: (1) aged between 55 and 79 years old; (2) received no less than 6 years of education; (3) achieved scores greater than, or equal to, 24 on the Mini-Mental-Status Examination-Chinese version (MMSE); (4) had no history of coronary disease, nephritis, tumors, gastrointestinal disease, or psychiatric illness; and (5) were able to meet the physical demands of the imaging procedure. All of the participants gave written informed consent to our protocol, which was approved by the ethics committee of the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University.

All of the MCI subjects were identified according to the criteria for MCI [7], which included: (a) impaired memory performance on a normalized objective verbal memory delayed-recall test; (b) recent history of symptomatic worsening in memory; (c) normal or near-normal performance on global cognitive tests, including MMSE score $\geq$24, as well as on activities described in a daily living scale; (d) global rating of 0.5 on the CDR Scale, with a score of at least 0.5 on the memory domain; and (e) absence of dementia. T2DM subjects based on medical history, medication use, or a Fasting plasma glucose (FPG) level $\geq$7 mmol/l. Of the 14 MCI-DM subjects, 3 subjects were under treatment with insulin and 11 subjects controled blood glucose using oral hypoglycemic agents (we provide the therapeutic agents taken by the 14 subjects in Supplementary Table 1).

Neuropsychological testing

All of the participants received a battery of six categories of neuropsychological tests to assess general mental status and other cognitive domains, such as episodic memory, executive function, and language

Table 1
Demographic information and neuropsychological characterizations for each group

	HC ($n=17$)	MCI ($n=17$)	MCI-DM ($n=14$)	F-value (χ^2)	p-value
Age (y)	63.82 ± 5.79	67.00 ± 7.88	63.50 ± 6.91	1.27	0.289
Education (y)	11.70 ± 2.95	11.05 ± 3.34	10.64 ± 2.73	0.486	0.618
Gender (M/F)	10/7	8/9	6/8	0.874	0.646*
Diabetes duration (y)			6.5 ± 2.1		
HbA1 C (%)	5.41 ± 0.61	5.20 ± 0.22	7.78 ± 1.02	67.617	<0.001[b,c]
FPG (mmol/L)	5.40 ± 0.67	5.17 ± 0.61	7.90 ± 2.48	16.435	<0.001[b,c]
Cholesterol (mmol/L)	5.10 ± 0.63	5.62 ± 1.23	4.96 ± 0.98	2.025	0.144
TG (mmol/L)	1.57 ± 0.88	1.65 ± 0.93	2.28 ± 1.06	2.449	0.098
HDL (mmol/L)	1.29 ± 0.31	1.41 ± 0.32	1.22 ± 0.22	1.799	0.177
LDL (mmol/L)	3.17 ± 0.64	3.56 ± 0.94	2.75 ± 1.07	3.170	0.052
BMI (kg/m^2)	24.22 ± 2.85	23.86 ± 3.99	24.83 ± 2.66	0.346	0.710
Hypertension (n)[#]	–	3	4		
General mental status					
MMSE	28.58 ± 1.12	26.35 ± 2.06	25.11 ± 1.96	17.20	<0.001[a,b]
Memory function					
AVLT-delay recall	6.76 ± 2.33	2.07 ± 1.85	1.64 ± 1.49	35.89	<0.001[a,b]
AVLT-T	34.64 ± 7.04	18.21 ± 4.54	16.17 ± 6.14	46.08	<0.001[a,b]
ROCF-delay recall	16.76 ± 9.03	9.07 ± 6.41	4.17 ± 4.51	14.19	<0.001[a,b]
Spatial processing					
ROCF-Copy	33.52 ± 5.91	32.28 ± 2.55	29.17 ± 6.66	2.82	0.07
CDT	26.50 ± 6.2	23.5 ± 3.5	21.8 ± 4.9	6.93	0.002[a,b]
Language					
CVFT	47.29 ± 7.43	39.42 ± 5.99	32.23 ± 10.53	13.87	<0.001[a,b,c]
BNT	26.17 ± 2.69	22.50 ± 3.15	18.52 ± 6.35	12.54	<0.001[a,b,c]
Attention					
SDMT	40.47 ± 9.54	30.41 ± 11.15	20.52 ± 9.21	17.36	<0.001[a,b,c]
TMT-A time (s)	47.88 ± 11.92	65.92 ± 24.55	91.52 ± 36.86	11.49	<0.001[a,b,c]
Executive function					
SCWT-SIE	64.88 ± 11.59	82.57 ± 34.37	97.81 ± 33.71	5.715	0.023[b]
TMT-B time(s)	133.00 ± 30.30	190.46 ± 54.50	269.23 ± 96.31	17.578	<0.001[a,b,c]

All subjects (HC, MCI, and MCI-DM) were matched for age, gender, and education. Values are mean ± standard deviation. The comparisons of demographic and clinical differences among the three groups (HC, MCI, and MCI-DM) were performed with separate one-way analysis of variance (ANOVA). Neuropsychological difference among the three groups were performed with analysis of covariance (ANCOVA) with all demographic factors (gender, age, and years of education) as covariates. *Post-hoc* comparisons were then performed with all demographic factors (gender, age, and years of education) as covariates. $p < 0.05$ was considered significant. HC, healthy control; MCI, mild cognitive impairment; MCI-DM, mild cognitive impairment patients with diabetes mellitus; HbA1 C, glycosylated hemoglobin; FPG, fasting plasma glucose; TG, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; BMI, body mass index; MMSE, Mini-Mental State Examination; AVLT, Auditory Verbal Learning Test; ROCF, Rey-Osterrrieth Complex Figure; CDT, Clock-Drawing Test; CVFT, Category Verbal Fluency Test; BNT, Boston Naming Test; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test; SCWT-SIE, Stroop interference effect of the Stroop Color and Word Test; [#]Other diseases were excluded except the hypertension. *The p-value for gender distribution in the three groups was obtained using a Chi-square test; [a]*Post-hoc* paired comparisons showed significant group differences between HC versus MCI, after least-significant difference (LSD) correction; [b]*Post-hoc* paired comparisons showed significant group differences between HC versus MCI-DM, after LSD correction; [c]*Post-hoc* paired comparisons showed significant group differences between MCI versus MCI-DM, after LSD correction.

ability. General mental status was assessed using the MMSE [24]. The consequent neuropsychological battery was composed of five cognition domains. The memory tests included the Auditory Verbal Learning Test [25] and the Rey-Osterrieth Complex Figure test (ROCF) (recall) [26]. The participants underwent visual-spatial tests, which included the ROCF (copy) and the Clock-Drawing Test [27]. The participants completed the Trail Making Test A (TMT-A) [28] and the Symbol Digit Modalities Test (SDMT) [29], which are measures of attention function. Executive function was assessed with the Stroop Color and Word Test, and Trail Making Test B (TMT-B) [28]. Finally, language ability was assessed with the Boston Naming Test [30] and the Category Verbal Fluency Test. The neuropsychological characteristics for each group are presented in Table 1.

MRI data acquisition

All participants were scanned on a 3.0 T Siemens scanner at Beijing Normal University during a single

session. Resting state functional images were collected using an echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2000 ms; echo time (TE) = 40 ms; flip angle = 90°; number of slices = 28; slice thickness = 4 mm; gap = 1 mm; voxel size = $4 \times 4 \times 4\,mm^3$; and matrix = 64×64. Participants were asked to lie quietly in the scanner with their eyes closed during data acquisition. The scan lasted for 478 s.

Data processing

All preprocessing was carried out using Statistical Parametric Mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm) Data Processing Assistant or Resting-State fMRI (DPARSF) [31]. The steps included: conversion of the DICOM data to NIFTI images; removal of the first 10 time points from each patient's data; slice timing correction; realignment to the middle image; spatial normalization to the Montreal Neurological Institute (MNI) template; and resampling of each voxel to $3 \times 3 \times 3\,mm^3$ with spatial filtering, and then spatially smoothed with an 8 mm full width at half maximum Gaussian kernel.

Data analysis

Demographic, clinical, and neuropsychological data were analyzed in SPSS 17.0 (SPSS, Inc.). Comparisons of demographics and clinical difference among the three groups (HC, MCI and MCI-DM) were performed either with separate one-way analysis of variance (ANOVA) or χ^2 test. Neuropsychological difference among the three groups were performed with analysis of covariance (ANCOVA) and all demographic factors (gender, age, and years of education) as covariates. *Post-hoc* comparisons were then performed with all demographic factors (gender, age, and years of education) as covariates. $p < 0.05$ was considered significant.

We applied REST (State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University; http://resting-fmri.sourceforge.net/) to calculate the ALFF. Briefly, the time courses were first converted to the frequency domain using a Fast Fourier Transform. The square root of the power spectrum was computed and then averaged across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. To reduce the global effects of variability across participants, the ALFF of each voxel was divided by the global mean ALFF value for each subject, resulting in a relative ALFF. The global mean ALFF value was calculated for each participant within a mean grey matter mask of the whole group obtained by selecting a threshold of 0.2 on the mean GM map of all 48 subjects. The relative ALFF value in a given voxel reflects the degree of its raw ALFF value relative to the average ALFF value of the whole brain. Recent research into fMRI has suggested that functional results may be influenced by structural differences among groups [32]. To exclude this possible effect, apart from including gender, age, and years of education as covariates, we also performed all analyses with grey matter volume as a covariance. All of the statistical maps were corrected for multiple comparisons to a significance level of $p < 0.05$ by combining the individual voxel $p < 0.05$ with a cluster size larger than a certain amount of mm^3, based on using Monte Carlo simulations [33].

RESULTS

Clinical demographic characteristics and neuropsychological data

There were no significant differences in age, gender, education, body mass index, total cholesterol, triglycerides HDL-C or LDL-C among the three groups. As expected, HbA1c ($p < 0.001$) and FPG levels ($p < 0.001$), were elevated in MCI-DM group (Table 1). Regarding the neuropsychological tests, significant differences were found in the spatial processing, language, attention, and executive function domains. *Post-hoc* comparisons presented sharp differences between the two kinds of MCI patients and the HC group. Although no significant differences were found between MCI and MCI-DM, the MCI-DM group showed obvious trends of declining in nearly all cognitive tests (Table 1).

Group differences in ALFF maps

By comparing the whole brain ALFF map among the three groups, using ANCOVA, we found significant group differences in ALFF among MCI-MD, MCI, and HC in a variety of brain regions, including the fusiform gyrus, inferior temporal gyrus, parahippocampal gyrus, precuneus, posterior cingulate, inferior frontal gyrus, and superior frontal gyrus (Fig. 1). To exclude the influence of grey matter, all data were analyzed with concomitant variables of grey matter.

Post-hoc comparisons of the three groups were further calculated (Fig. 2). The MCI patients showed decreased ALFF in precuneus, posterior cingulate, frontal gyrus, and increased ALFF in fusiform, inferior temporal, and amygdala when compared with the

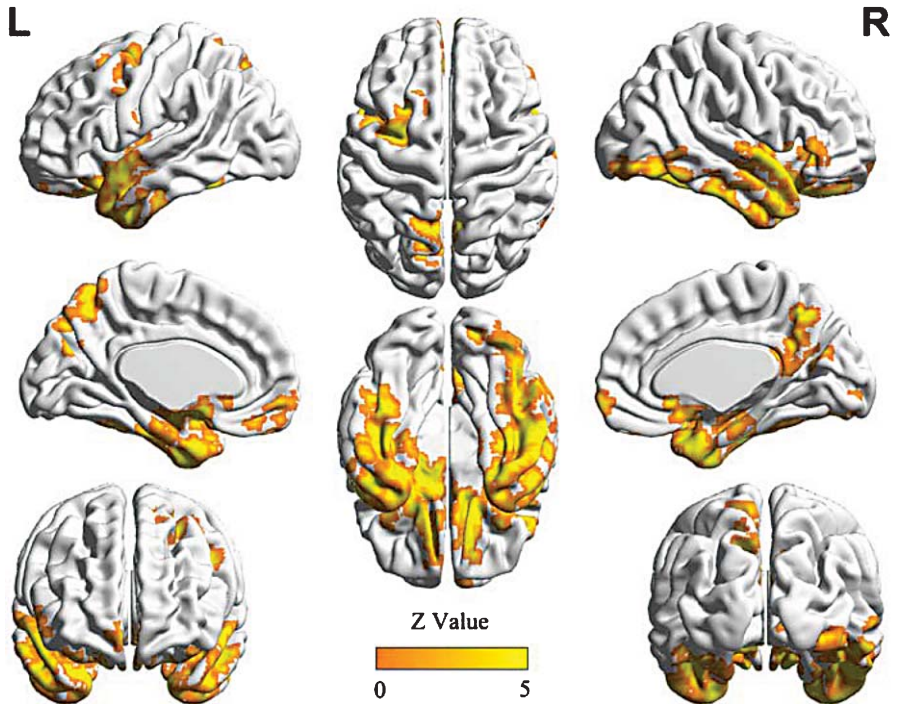

Fig. 1. Z-statistical maps difference (with grey matter correction) of ALFF among the MCI-DM patients, MCI patients, and HC. There are significant differences among three groups in the fusiform gyrus, inferior temporal gyrus, parahippocampa gyrus, precuneus, posterior cingulate, inferior frontal gyrus, and superior frontal gyrus. The comparisons among the three groups (HC, MCI, and MCI-DM) were performed with separate one-way analysis of covariance (ANCOVA); gender, age, years of education, and grey matter volume were included as covariates. The statistical threshold was set at $p < 0.05$ and cluster size >181 mm^3, which corresponded to a corrected $p < 0.05$.

HC group (Table 2, Fig. 2A). The MCI-MD group showed decreased ALFF in frontal gyrus, precuneus, cuneus, and insula and increased ALFF in fusiform and temporal gyrus, which is nearly the combination of the influence of MCI and T2DM compared with healthy controls (Table 2, Fig. 2B). When comparing the MCI-MD group with the MCI group in the significantly different brain regions of three groups, the MCI-MD group showed significantly decreased ALFF in the inferior temporal gyrus, fusiform gyrus, inferior frontal gyrus, parahippocampal gyrus, hippocampus, amygdala; and increased ALFF in the precuneus and superior temporal gyrus (Table 2, Fig. 2C).

Correlation between ALFF and cognitive performance

To identify the meaning of the group differences between MCI-DM and MCI, we calculated the relation between ALFF and cognitive performance to obtain correlation maps between the ALFF and cognitive performance (Fig. 3). In the MCI-DM group, significant positive correlations were found between the left fusiform gyrus, left parahippocampal gyrus, and the Stroop test; and between the left paracentral gyrus, precuneus, superior parietal gyrus, and the TMT test. Significant negative correlations were found between the left fusiform gyrus, left parahippocampal gyrus, and the MMSE; and between the left paracentral gyrus, precuneus, superior parietal gyrus, and the SDMT. In the MCI group, none of these correlations were found to be significant. The statistical threshold was set at $p < 0.05$ and cluster size >810 mm^3, which corresponded to a corrected $p < 0.05$ for multiple comparisons.

DISCUSSION

To the best of our knowledge, this study was the first to examine resting-state ALFF values to investigate the difference in cognitive dysfunction in MCI-DM with, MCI and healthy controls. In addition, we focused on the correlation between the ALFF and neuropsychological test information in the MCI-DM group.

In this study, six different cognitive domains were evaluated, i.e., general mental status, episodic memory,

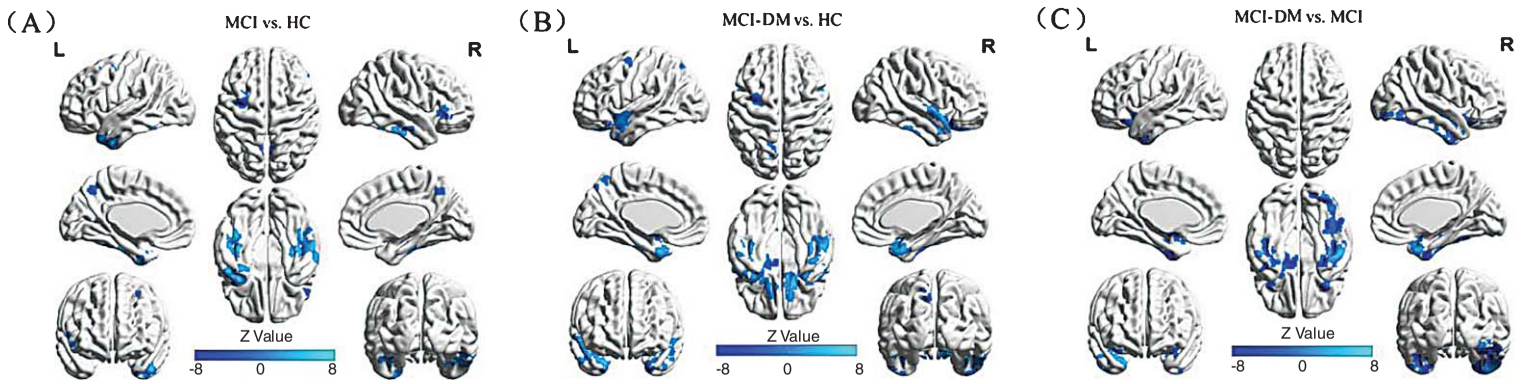

Fig. 2. Z-statistical difference maps of the ALFF between groups (with GM correction). A) Z-statistical difference maps between the MCI and healthy controls. The MCI patients showed significantly decreased ALFF in the bilateral precuneus, posterior cingulate, and bilateral inferior frontal gyrus; and increased ALFF in the temporal gyrus and furisom. B) Z-statistical difference maps between the MCI-DM patients and healthy elderly. The MCI-DM showed significantly decreased ALFF in the bilateral insula, left-middle frontal gyrus, left precuneus, and left cuneus; and increase in the temporal gyrus and fusiform. C) Z-statistical difference maps between the MCI-DM patients and MCI. The MCI-DM showed significantly decreased ALFF in the temporal gyrus, bilateral fusiform gyrus, inferior frontal gyrus, left hippocampus, right insula, and left precuneus; and increased ALFF in the temporal gyrus. Note: The two sample *t*-tests were performed within a mask, showing significant group differences in the ANCOVA analysis, and gender, age, years of education, and grey matter volume were included as covariates. The statistical threshold was set at $p < 0.05$ and cluster size >28 mm^3, which corresponded to a corrected $p < 0.05$.

Table 2
Brain areas with significant ALFF differences among the HC, MCI, and MCI-DM

Brain regions	MNI coordinates (mm)			Vol (mm^3)	Maximum Z
	X	Y	Z		
MCI-DM>MCI					
Right TP/STG	24	9	−36	2592	7.14
Left TP/STG	−30	12	−36	1971	7.35
MCI-DM<MCI					
Right Ins/IFG	36	15	−18	1647	−6.22
Right ITG/ FG	48	−12	−33	1242	−4.93
Left FG /PHG	−45	−51	−18	675	−6.92
Left PCu/PCC/SPG	−15	−60	63	783	−6.37
MCI>HC					
Right FG/ITG	42	−33	−27	1728	4.25
Right TP	30	9	−42	2538	4.06
Left ITG	−42	−30	−27	1080	4.65
Left Amy/IFG	−27	−6	−15	837	4.43
HC>MCI					
Right IFG	42	27	−3	1485	−4.36
Right PCu	12	−57	21	648	−3.74
Left PrCG /IFG	−6	−63	48	702	−3.99
Left PCu/PCC	−6	−63	48	675	−3.58
MCI-DM>HC					
Right FG	42	−21	−36	810	7.62
Left ITG	−42	−30	−27	891	6.09
Left MTG/STG/TP	−39	6	−27	2484	6.31
HC>MCI-DM					
Right Ins	33	12	−15	621	−4.67
Left Ins	−30	12	−15	1350	−5.53
Left PrCG	−33	0	60	1053	−7.62
Left PCu	−9	−63	57	648	−4.58

x, y, z, coordinates of primary peak locations in the MNI space; Z, statistical value of peak voxel showing significant ALFF differences among HC, MCI, and MCI-DM-MCI; PCC, posterior cingulate cortex; FG, fusiform gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; PCC, posterior cingulate cortex; PCu, precuneus; PrCG, precentral gyrus; TP, temporal pole; PHG, parahippocampal gyrus; Ins, insular; Amy, amygdala. $p < 0.05$, corrected for multiple comparisons.

reasoning, spatial processing, language ability, and executive function. There were significant differences between these three groups in the spatial processing, language, attention, and executive function domains, consistent with another study of T2DM patients [34]. Although no significant difference between MCI and MCI-DM was found, the MCI-DM group showed obvious trends of declining in nearly all cognitive tests, including verbal and nonverbal episodic memory, working memory, short-term memory, executive function, reasoning, and language ability, this would seem to suggest that T2DM may contribute to multidimensional abnormal brain function before declining cognitive performance.

In recent years, the ALFF of BOLD signals has been suggested to be physiologically meaningful for measuring intrinsic or spontaneous neuronal activity of the brain through resting fMRI studies. We found that there were widespread differences in ALFF values among MCI-DM, MCI, and healthy controls throughout the various brain regions of the fusiform gyrus, inferior temporal gyrus, parahippocampal gyrus, precuneus posterior cingulate, inferior frontal gyrus, and superior frontal gyrus. In T2DM patients, the hippocampus showed reduced functional connectivity bilaterally to widespread regions, including the fusiform gyrus, frontal gyrus, temporal gyrus, anterior cingulate gyrus, medial frontal gyrus, posterior cingulate gyrus, precuneus, and inferior parietal lobule [34]. These differences revealed, therefore, that MCI-DM, MCI, and T2DM patients do indeed share some cognitive decline in multidimensional aspects. This abnormality of resting brain activity has been recently demonstrated using positron emission tomography in older individuals in a mixed sample with T2DM or prediabetes [35]; our study extends these findings. Although the mechanisms linking T2DM and the risk of AD are not yet understood, several hypotheses have been suggested. Spontaneous neuronal activity is highly metabolically active and is a site of increased aerobic glycolysis, making these regions more susceptible to amyloid accumulation [36]. Altered glucose

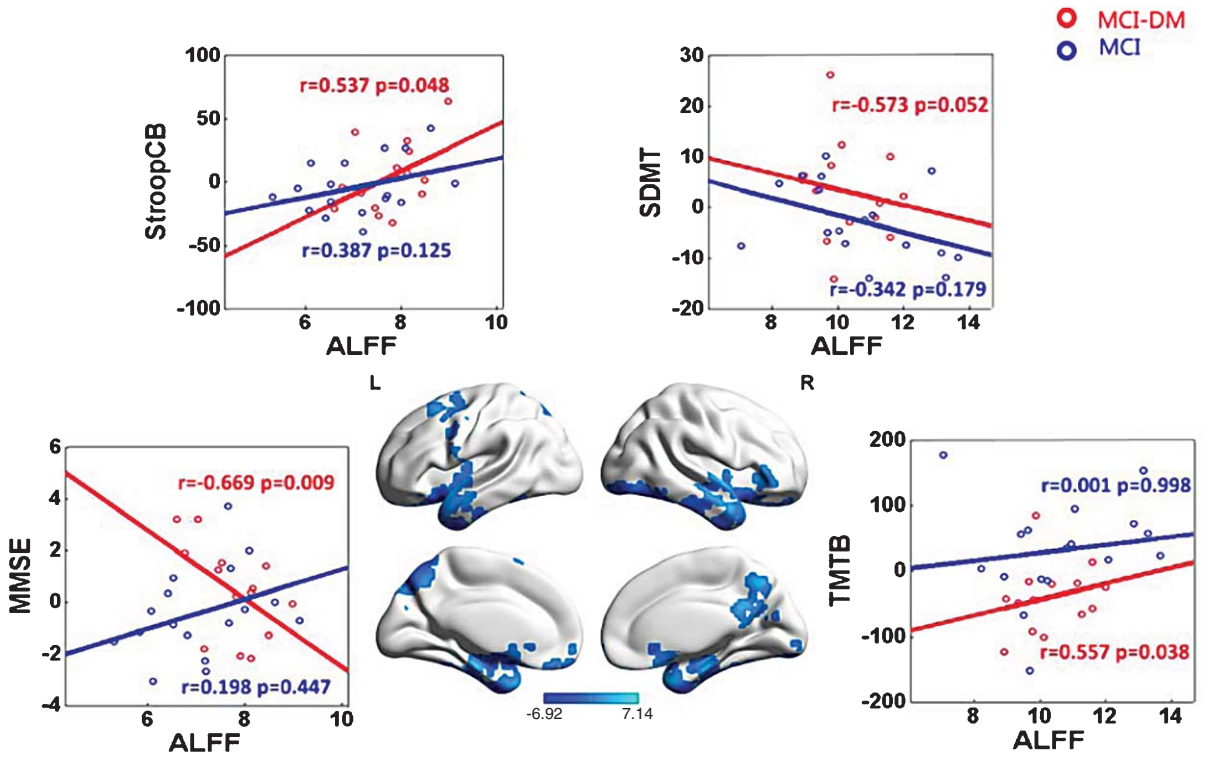

Fig. 3. Correlation maps of ALFF and neuropsychological tests for the MCI-DM and MCI group (with grey matter correction), and the scatter plots of the peak voxel. In the MCI-DM group, significant positive correlations were found between the left fusiform gyrus, left parahippocampal gyrus, and Stroop test; and between the left paracentral gyrus, precuneus, superior parietal gyrus, and TMTB test. Significant negative correlations were found between the left fusiform gyrus, left parahippocampal gyrus, and MMSE; and between the left paracentral gyrus, precuneus, superior parietal gyrus, and SDMT. In the MCI group, none of these correlations were found to be significant. In all analyses, gender, age, years of education, and grey matter volume were included as covariates. The statistical threshold was set at $p < 0.05$ and cluster size >810 mm^3 which corresponded to a corrected $p < 0.05$.

metabolism inherent in T2DM may augment this process.

Compared with the healthy controls, the MCI-DM group showed significantly decreased ALFF in the bilateral insula, left-middle frontal gyrus, left precuneus, left cuneus; and significantly increased ALFF in temporal gyrus and fusiform. However, compared with the MCI group, the MCI-DM group showed significantly decreased ALFF in the temporal gyrus, bilateral fusiform gyrus, inferior frontal gyrus, left hippocampus, right insula, and left precuneus; and increased ALFF in the temporal gyrus. It is interesting to note that the temporal gyrus presented decreased and increased ALFF in the MCI-DM group; a study found that T2DM decreased the ALFF amplitude of the bilateral middle temporal gyrus [20]. Otherwise, when MCI-DM group was compared with healthy controls, MCI patients showed significantly decreased ALFF in the bilateral precuneus, posterior cingulate, and bilateral inferior frontal gyrus; and increased ALFF in the temporal gyrus and gurisom. AD patients were found to have increased ALFF in several frontal and temporal regions, as compared with MCI patients [37]. This increase in ALFF in the temporal gyrus may be a compensatory reallocation or recruitment of cognitive resources from other regions; thus, the DM may contribute to the progression from MCI to AD through increasing the compensation of temporal gyrus in MCI patients. It was determined early in animal models that reduced insulin secretion or reduced insulin tissue sensitivity can increase neuronal death through focal and global ischemia [38]. Insulin signal pathway impairment caused by diabetic conditions may contribute to AD progression, and insulin-signaling is involved in a variety of neuronal functions [39–41]. Other evidence has suggested that advanced glycation end products (RAGE) could bind to Aβ and trigger many neuronal degenerative processes [42]. The altered RAGE might affect cognitive function in MCI-DM patients, accelerating the progression from MCI to AD.

Patterns of intrinsic brain activity were measured by examining the ALFF of BOLD signals during resting state fMRI [43]. Assessments of cognitive function, such as MMSE, StroopCB, SDMT, and TMT-B all reflect the outcome of intrinsic or spontaneous neuronal activity denoted by ALFF [44, 45]. Normal brain function requires a steady supply of energy to support all of its cellular and molecular processes. The maintenance of oxidative phosphorylation (OXPHOS) capacity is extremely important in the brain, since about 90% of the ATP required for the normal functioning of neurons is provided by mitochondria [46, 47]. In the present study, ALFF showed a negative correlation with cognitive performance in MD-MCI subjects. A number of studies have reported that mitochondria impairment and decrement in (OXPHOS) efficiency in the brain are major pathological changes in T2DM [46, 48, 49]. Due to the impaired respiratory chain, an elevated blood oxygen level does not provide enough ATP for cognitive activity; however it results in a higher level of consumption of stored energy and, therefore, exacerbates cognitive impairment. Early prevention strategies to reduce the risk of cognitive impairment are needed because of the increased number of diabetes patients and their longevity [50]. Therefore, identifying possible biomarkers of cognitive impairment resulted from diabetes is clinically critical for formulating and developing early and optimum treatment strategies to improve glycemic control, which could mitigate the adverse effects of T2DM on the brain.

There are some improvable areas in our study. One limitation is that we have not considered whether participants carry the APOE-ε4 allele or other risk factors. Future studies in this line of research should include this factor. In addition, it would be important to explore changes in intrinsic brain activity between those who do and do not progress to AD, and to investigate longitudinal changes in MCI/AD subjects. Furthermore, our sample size is small, and this may have reduced our ability to detect changes in cognition in our T2DM group.

CONCLUSION

In this study, we found that MCI-DM patients showed diffused ALFF changes in a variety of brain regions that were significantly related to cognitive performance, including the frontal lobe, temporal lobe, hippocampus, amygdala, and precuneus during resting state; whereas, the alterations were much less pronounced in the MCI patients without T2DM. MCI patients with T2DM showed more abnormalities in cognition and ALFF. These findings might contribute to a deeper understanding of the relationship between T2DM and dementia.

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SUPPLEMENTARY MATERIAL

The supplementary table is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-132354.

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