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# Altered baseline brain activity in type 2 diabetes: A resting-state fMRI study

Wenqing Xia [c,1,*], Shaohua Wang [a,1,*], Zilin Sun [a], Feng Bai [b], Yi Zhou [c], Yue Yang [c], Pin Wang [c], Yan Huang [c], Yang Yuan [a]

[a] *Department of Endocrinology, Affiliated Zhongda Hospital of Southeast University, No. 87 Dingjiaqiao Road, Nanjing 210009, PR China*
[b] *Department of Neurology, Affiliated Zhongda Hospital of Southeast University, No. 87 DingJiaQiao Road, Nanjing 210009, PR China*
[c] *Medical School of Southeast University, Nanjing, China*

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**KEYWORDS**
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**Summary**
*Purpose:* This study aims to investigate whether altered baseline brain activity exists in type 2 diabetes mellitus (T2DM) patients using resting-state functional magnetic resonance imaging (rs-fMRI) and whether abnormal neural activity in the middle temporal gyrus (MTG) is correlated with cognitive function.
*Methods:* T2DM patients ($n = 28$) were compared with nondiabetic age-, sex-, and education-matched control subjects ($n = 29$) using rs-fMRI. We computed the amplitude of low-frequency fluctuations (ALFF) of fMRI signals to measure spontaneous neuronal activity and detect the relationship between rs-fMRI information and clinical data.
*Results:* Compared with healthy controls, T2DM patients had significantly 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. Moreover, we found an inverse correlation between the ALFF values in the MTG and both the HbA1c ($r = -0.451$, $p = 0.016$) and the score of Trail Making Test-B ($r = -0.420$, $p = 0.026$) in the patient group. On the other hand, C-peptide level and pancreatic β-cell function had a positive correlation ($r = 0.429$, $p = 0.023$; $r = 0.453$, $p = 0.016$, respectively) with the ALFF value in the middle temporal gyrus.
*Conclusion:* The present study confirms that T2DM patients have altered ALFF in many brain regions, which is associated with poor neurocognitive performances, severity of consistent hyperglycemic state and impaired β-cell function. ALFF disturbance in MTG may play a central role in cognitive decline associated with T2DM and serve as reference for future clinical diagnosis.


* Corresponding authors. Tel.: +86 25 83272261; fax: +86 25 83285132.
*E-mail address:* gyjwsh@gmail.com (S. Wang).
[1] Both authors contributed equally to this work.

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## 1. Introduction

Diabetes mellitus is associated with a 1.5–2-fold increased risk of Alzheimer's disease (AD) and a 2–2.5-fold increased risk of vascular dementia (Biessels et al., 2008). Type 2 diabetes mellitus (T2DM) is related to decrements in cognition, particularly learning and memory deficits (McCrimmon et al., 2012). Accumulating studies supported the fact that T2DM and AD share several same pathogenesis in the brain (Biessels et al., 2008; Vagelatos and Eslick, 2013), such as insulin deficits, glucose-mediated toxicity and Aβ accumulation. However, T2DM-related cognitive impairment is not comparable to the cognitive impairment found in mild cognitive impairment (MCI) or AD patients. For instance, recent longitudinal studies showed moderate decrements in cognitive function in the information-processing speed, attention and executive functioning domains, compared with individuals without diabetes (Van Den Berg et al., 2010; Spauwen et al., 2012). Particularly, to date, the hippocampus is largely proven to be specifically affected by T2DM (Gold et al., 2007; Bruehl et al., 2009), both structurally and functionally. Medial temporal lobe atrophy (MTA) is likewise observed in the brains of T2DM patients by brain magnetic resonance imaging (MRI) studies (Den Heijer et al., 2003; van Harten et al., 2006, 2007). However, the exact neuropatho-physiological mechanism of cognitive impairment related with T2DM has not yet been fully elucidated.

In recent years, functional neuroimaging, especially resting-state functional MRI (rs-fMRI), with high security, spatial resolution and easy application (He et al., 2007), has become a novel and widely used technique to investigate the pathogenesis of various neuropsychiatric disorder diseases. Musen and her colleagues showed reduced functional connectivity in the default mode network (DMN) of T2DM patients compared with control subjects, which indicated abnormal connectivity among several brain areas (Musen et al., 2012). DMN, consisting of several brain areas, such as the middle temporal gyrus (MTG), the posterior cingulate cortex (PCC), the anterior cingulate cortex (ACC), the middle frontal gyrus (MFG), and the inferior parietal lobe, is active at rest and suspended during cognitive activity (Raichle, 1996). Zhou et al. (2010) observed that the hippocampus displays decreased functional connectivity bilaterally to widespread regions in T2DM patients, which may predict cognitive dysfunction. Meanwhile, several studies focused on the structural changes in the brain of diabetes patients. Chen et al. (2011) demonstrated that T2DM patients showed gray and white matter atrophy in the right temporal lobes using voxel-based morphometry (VBM). Hsu et al. (2012) also found microstructural abnormalities in various white matter pathways using diffusion tensor imaging (DTI) in T2DM patients. Nevertheless, other MRI techniques, such as VBM and DTI, merely observe the atrophy or abnormal white matter changes. Besides, previous studies using rs-fMRI all focus on the abnormal functional connectivity between two remote areas. We still do not know which area is abnormal, and we cannot observe the spontaneous neuronal activity over the entire brain of T2DM patients from such an examination.

The amplitude of low frequency fluctuation (ALFF) of the blood oxygen level dependent (BOLD) signal, one of the rs-fMRI analysis algorithms, was highly coherent among motor cortices during resting state and likely reflects spontaneous neuronal activity (Biswal et al., 1995; Kiviniemi et al., 2000; Fransson, 2005). This technique has also been used as an effective method in evaluating the spontaneous neuronal activity of diseases, such as AD, MCI (Wang et al., 2011), schizophrenia (Hoptman et al., 2010), and hepatic encephalopathy (Chen et al., 2012). However, this method has never been applied in cognitive dysfunction related with diabetes. The ALFF is reported higher in gray matter than in white matter (Biswal et al., 1995) and is associated with intrinsic, regional brain responses in local brain regions. When comparing with functional connectivity analyses, which focus on the changes among different regions, ALFF can be used as an index to evaluate changes in brain function and to measure the amplitude of regional activity and physiological states.

On the basis of the conclusion of previous studies that T2DM increases the risk of cognitive dysfunction, accompanied by MTA and the high sensitivity of the ALFF method, we aim to investigate whether T2DM patients show different ALFF in selected brain areas compared with control subjects and whether ALFF in the MTG is correlated with the performance of some cognitive functions and some clinical characteristics. This investigation might contribute to provide revelations to early diagnosis and prevention of cognitive decline induced by diabetes such that timely and effective treatment can be received.

## 2. Experimental procedures

### 2.1. Subjects and study design

The current study was conducted from June 2012 to February 2013. The protocol and informed consent document were approved by the Research Ethics Committee of the Affiliated Zhongda Hospital of Southeast University. All individuals provided written informed consent before their participation in the study protocol.

Sixty subjects (all right handed, educated for at least 6 years), with 30 diabetic patients and 30 age-matched healthy subjects were recruited through community health screening or newspaper advertisements. Two of the patients and one of the healthy control subjects were subsequently excluded because the limits for head motion were exceeded during the imaging processing. All patients met the diagnosis of T2DM according to the World Health Organization 1999 criteria (Alberti and Zimmet, 1998) and did not use insulin secreting drugs, such as sulfonylureas and repaglinide. The patients were aged between 45 and 70 years (average age = 58.7 ± 8.1 years), with disease duration of 3–20 years (mean = 9.8 ± 5.5 years) and BMI index of 19.3–32.1 (mean = 25.4 ± 3.0). The normal controls were recruited during the same period from the community and were matched for sex, age, BMI, and education. The fasting glucose levels and postprandial glucose levels were measured, and individuals with fasting glucose $> 6.1$ mmol/l or postprandial glucose $> 7.8$ mmol/l were excluded.

Participants with a past history of known stroke, alcoholism, head injury, Parkinson's disease, epilepsy, major depression (excluded by self-rating depression scale) or other neurological or psychiatric illness (excluded by clinical assessment and case history), major medical illness (e.g.,