European Journal of Radiology 85 (2016) 607–615

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Abnormal spontaneous brain activity in type 2 diabetes with and without microangiopathy revealed by regional homogeneity

Juan Peng[a], Hang Qu[a], Jing Peng[b], Tian-You Luo[a,*], Fa-Jin Lv[a], Li chen[a], Zhuo-Nan Wang[a], Yu Ouyang[a], Qing-Feng Cheng[c]

[a] Department of Radiology, the First Affiliated Hospital, Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing 400016, China
[b] Department of Clinical Laboratory, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030 China
[c] Department of Endocrinology, the First Affiliated Hospital, Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing 400016, China

ARTICLE INFO

Article history:
Received 18 August 2015
Received in revised form
12 December 2015
Accepted 27 December 2015

Keywords:
Type 2 diabetes
Cognitive impairment
Regional homogeneity
Resting-state fMRI
Microangiopathy

ABSTRACT

Purpose: To investigate whether global spontaneous brain activity changes in type 2 diabetes mellitus (T2DM) patients and these changes vary according to the degree of microangiopathy.
Materials and methods: T2DM patients with (M^+, n = 26) and without (M^-, n = 22) microangiopathy as well as 28 healthy nondiabetic subjects were enrolled in this study. All the subjects completed a resting-state functional magnetic resonance imaging (rs-fMRI) examination and neuropsychological assessment. Regional homogeneity (ReHo) values, representing spontaneous brain activity, were calculated and compared between M^+ and M^- T2DM patients and nondiabetic controls.
Results: In both M^+ and M^- T2DM patients, ReHo values were decreased in the occipital lobe, temporal lobe, postcentral gyrus, and cerebellum, while increased in the bilateral precuneus, superior/middle frontal gyrus, and insula. Compared with the M^- group, M^+ patients showed decreased ReHo values in the left cuneus and superior occipital gyrus. The ReHo values in the lingual gyrus/calcarine cortex and MTG were related to clinical parameters in T2DM patients.
Conclusion: The abnormalities of spontaneous brain activity revealed by ReHo values in both $M^+$and M^- T2DM patients may provide insights into the neurological pathophysiology underlying diabetes-related cognitive impairments. M^+ patients showed more decreased brain activity related to severely impaired function of visual processing and visual memory.

1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with impaired cognition which mainly presented as declined mental speed, attention, memory, and executive function [1], although the exact pathophysiological mechanism of T2DM-induced cognitive impairment has not yet been fully elucidated. Longitudinal epidemiological studies have shown that chronic hyperglycaemia and microangiopathy are associated with increased risk of cognitive dysfunction in both type 2 and type 1 diabetes [2,3]. Since the retinal and cerebral microvasculature share some common features, including similar embryological origin, size, and structure, and physiological characteristics, microangiopathy in the retina might be an indirect marker for changes in the cerebral microangiopathy [4].

Resting-state functional magnetic resonance imaging (rs-fMRI) has become a promising technique to exhibit neurophysiological mechanism in various neuropsychiatric disorders [5–8]. Recently, rs-fMRI has been used to investigate whether altered spontaneous brain activity exists in DM patients. Musen et al. observed that T2DM patients had abnormal functional connectivity among several brain regions in the default mode network (DMN) when compared with controls [9]. Meanwhile, Xia et al. demonstrated altered amplitude of low-frequency fluctuations (ALFF) in some

Abbreviations: FG, fusiform gyrus; IPL, inferior parietal lobe; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MPFC, medial prefrontal cortex; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; PCu, precuneus; PoCG, post-central gyrus; PrCG, pre-central gyrus; SFG, superior frontal gyrus; SOG, superior occipital gyrus; STG, superior temporal gyrus.

* Corresponding author. Fax: +86 23 68811487.
E-mail addresses: pengjuan1209@126.com (J. Peng), quhang126@126.com (H. Qu), ppjj6@126.com (J. Peng), ltycqfs@126.com (T.-Y. Luo), fajinlv@hotmail.com (F.-J. Lv), 30733281@qq.com (L. chen), wangzhuonan424@hotmail.com (Z.-N. Wang), 1957ouyangyu@sina.com (Y. Ouyang), cqf19760516@163.com (Q.-F. Cheng).

http://dx.doi.org/10.1016/j.ejrad.2015.12.024
0720-048X/

brain areas in T2DM patients which was correlated with declined neurocognitive function, severity of hyperglycemic state and damaged β-cell function [10]. In a previous rs-fMRI study, van Duinkerken et al. suggested that cognitive decrements in T1DM patients were related to changes in resting-state neural connectivity and that these alterations dependent on the degree of microangiopathy [11].

Regional homogeneity (ReHo) analysis is an important method for depicting the various characteristics of global rs-fMRI signals, in which Kendall coefficient of concordace (KCC) was used to measure the similarity of the time series of a given voxel to those of its nearest neighbors in a voxel-wise way [12]. It has been widely used to evaluate the functional abnormities in various diseases such as Parkinson's disease [6], major depression [7], Alzheimer's disease [8], and essential tremor [13]. However, few studies [14] have been conducted to investigate whether global spontaneous brain activity changes in T2DM patients and these changes vary according to the degree of microangiopathy using ReHo techniques.

In this study, ReHo analysis was used to assess whether spontaneous brain activity changed prior to structural abnormalities in T2DM patients. We hypothesized that (1) cognitive decrements in T2DM patients are associated with alterations in ReHo values and that these changes may vary according to the degree of microangiopathy; and (2) the spontaneous brain activity changes would be correlated with cognitive dysfunction and T2DM-related clinical parameters.

2. Materials and methods

2.1. Subjects

The present study was conducted from February 2012 to October 2013 and was approved by the institutional review board. Written informed consents were obtained from all the subjects. Eighty-five participants were enrolled in this study, including 29 T2DM patients with microangiopathy (M^+) and 26 patients without microangiopathy (M^-) and 30 nondiabetic subjects. Three of the M^+ patients, four of the M^- patients and two of the nondiabetic controls were excluded because their head motion was out of range during the MRI data acquisition. The patients were recruited from the endocrinology department of the affiliated hospital of our university, while the control subjects were from the local community during the same period. All the participants were at least 40 years of age, receiving at least 5 years of education and right handed. T2DM was diagnosed according to the latest criteria published by the American Diabetes Association [15]. M^+ patients were chosen on the basis of diabetic retinopathy, but other microangiopathy, such as microalbuminuria and peripheral neuropathy, could also be accompanied, while M^- patients were free of any of the microvascular complications. Diabetic retinopathy was diagnosed using fundus photography, which was assessed according to the EURODIAB classification criteria [16] and patients with scores from 1 (minimal non-proliferative retinopathy) to 5 (proliferative retinopathy) were included in the M^+ group. Microalbuminuria was defined by an albumin/creatinine ratio (ACR) >30 mg/gCr [17]. Peripheral neuropathy was assessed for all subjects in accordance with the Diabetes Control and Complications Trial criteria using electrophysiology tests [18].

Exclusion criteria for all participants included a history of T2DM-related acute metabolic complications, severe hypoglycemia episode, stroke, epilepsy, dementia, head injury, major depression or other psychiatric illness, major medical illness (e.g., anemia, cancer and thyroid dysfunction), alcoholism or drug abuse, severe visual or hearing loss, and contraindication for MRI.

2.2. Clinical data and cognitive assessment

Clinical data were recorded, including blood pressure, weight and height, body mass index (BMI) = (weight in kg)/(height in m)^2. Blood samples were obtained by venepuncture at 8 A.M. after overnight fasting to assess the levels of fasting blood glucose (FBG), glycosylated hemoglobin (HbAlc), total cholesterol, triglyceride and low density lipoprotein cholesterol.

A battery of neuropsychological assessments was completed, which based on previous studies concerning cognitive impairment in T2DM patients [10,19,20]. The Mini Mental State Examination (MMSE), which usually used to screen for dementia, was included as a general psychological assessment [19]. The Trail-Making Test (TMT) Parts A and B (TMT-A and -B) were used to evaluate attention, psychomotor speed, and executive function; these parameters were then assessed with ΔTMT, which is calculated as the difference between the times for each part (TMT-B minus TMT-A) and thought to be a more accurate measure of executive functions than performance on TMT-A or TMT-B [20]. The Auditory Verbal Learning Test (AVLT), a test of verbal memory, assesses registration and recall of words, while Rey–Osterrieth Complex Figure Test (CFT) assesses visuospatial memory and visual spatial skills [10,14]. The Clock Drawing Test (CDT) was used to evaluate executive function and visual spatial skills [10]. All of the tests took approximately 50 min to complete.

2.3. MRI data acquisition

MRI scanning was performed on a GE Signa Hdxt 3.0 T scanner (General Electric Medical Systems, USA) using an eight-channel phased-array head coil. Foam padding was used to restrict head movement and ear plugs were used to minimise scanner noise. During rs-fMRI acquisition, all subjects were instructed to keep their eyes closed and not to think of anything.

Rs-fMRI data were acquired using an echo-planar image (EPI) pulse sequence with parameters as follows: TR = 2000 ms, TE = 40 ms, flip angle = 90°, thickness/gap = 4.0/0 mm, FOV = 240 × 240 mm, and matrix = 64 × 64. A total of 240 time points were obtained in 8 min. High-resolution 3D-T1-weighted axial image (TR = 8.3 ms, TE = 3.3 ms, flip angle = 15°, thickness/gap = 1.0/0 mm, FOV = 240 × 240 mm, and matrix = 256 × 192) and T2-FLAIR-weighted image (TR = 8000 ms, TE = 126 ms, TI = 1500 ms, thickness/gap = 5.0/1.5 mm, FOV = 240 × 240 mm, and matrix = 256 × 192) were also acquired.

2.4. VBM analysis

To check out whether there were structural differences between M^+ and M^- T2DM patients and control subjects, the high-resolution 3D-T1-weighted images were processed using the VBM8 toolbox software (http://dbm.neuro.uni-jena.de/vbm). In brief, the T1-weighted images were segmented into gray matter (GM), whiter matter (WM), and cerebrospinal fluid (CSF) using the unified segmentation model. After that, one-way analysis of variance (ANOVA) with false discovery rate (FDR) corrections was carried out to evaluate between-group differences in GM and WM volume.

2.5. Data preprocessing and ReHo analysis

We excluded participants with obvious lacunar infarction, cerebral atrophy or WM lesions, which were assessed separately by two experienced radiologists on conventional MRI. After careful evaluation of the quality of raw functional images, data preprocessing, including slice timing, realignment, and normalization, was performed with the Data Processing Assistant for rs-fMRI (DPARSF; http://www.restfmri.net/forum/DPARSF) through SPM8 software