Identifying cognitive impairment in Type 2 Diabetes with functional connectivity: a multivariate pattern analysis of resting state fMRI data

Zhenyu Liu[a], Xingwei Cui[b], Zhenchao Tang[c], Di Dong[a], Yali Zang[a], Jie Tian*[a]

[a] Key Lab of Molecular Imaging, CAS, Institute of Automation, Chinese Academy of Sciences, Beijing, 100190, China

[b] Cooperative Innovation Center of Internet Healthcare, Zhengzhou University, Zhengzhou, Henan Province, 450002, China

[c] School of Mechanical, Electrical & Information Engineering, Shandong University, Weihai, Shandong Province, 264209, China

* Corresponding author, E-mail: tian@ieee.org, Tel.: 86-10-82618465; Fax: 86-10-62527995

Abstract: Previous researches have shown that type 2 diabetes mellitus (T2DM) is associated with an increased risk of cognitive impairment. Early detection of brain abnormalities at the preclinical stage can be useful for developing preventive interventions to abate cognitive decline. We aimed to investigate the whole-brain resting-state functional connectivity (RSFC) patterns of T2DM patients between 90 regions of interest (ROIs) based on the RS-fMRI data, which can be used to test the feasibility of identifying T2DM patients with cognitive impairment from other T2DM patients. 74 patients were recruited in this study and multivariate pattern analysis was utilized to assess the prediction performance. Elastic net was firstly used to select the key features for prediction, and then a linear discrimination model was constructed. 23 RSFCs were selected and it achieved the performance with classification accuracy of 90.54% and areas under the receiver operating characteristic curve (AUC) of 0.944 using ten-fold cross-validation. The results provide strong evidence that functional interactions of brain regions undergo notable alterations between T2DM patients with cognitive impairment or not. By analyzing the RSFCs that were selected as key features, we found that most of them involved the frontal or temporal. We speculated that cognitive impairment in T2DM patients mainly impacted these two lobes. Overall, the present study indicated that RSFCs undergo notable alterations associated with the cognitive impairment in T2DM patients, and it is possible to predicted cognitive impairment early with RSFCs.

Description of purpose

In the present study, we attempted to investigate the whole brain RSFC patterns to discriminate the T2DM patients with cognitive impairments from other T2DM patients with a multivariate pattern analysis method-Elastic net.

Methods

From Henan Provincial People's Hospital, we recruited 74 right-handed T2DM patients according to the latest criteria published by the American Diabetes Association. Each patient provided written informed consents approved by Institutional Review Board of the Henan Provincial People's Hospital Subcommittee on Human Studies. Demographics findings of T2DM patients were shown in Table 1. All patients underwent a neuropsychological test, and the education corrected MoCA was used to assess their general cognition.

All experiments were performed on a Siemens Trio 3-Tesla MRI system at Henan Provincial People's Hospital. A custom-built head holder was used to prevent head movements. The resting state scan lasted for 8 minutes and 20 senconds. Functional MR images were obtained using a gradient echo T2*-weighted pulse sequence with TR = 2000 ms, TE = 30 ms, matrix = 64 × 64, FOV = 256 mm × 256 mm and FA = 85°. After the functional run, a high-resolution T1-weighted 3D MRI sequence was used (voxel size = 1 × 1 × 1 mm3, no gap, TR = 2100 ms, TE = 3.25 ms, matrix = 256 × 256, FOV = 230 mm x 230 mm, and FA = 10°).

Table 1 Subject characteristics

	MoCA <26	MoCA >26	P-value
Age (years)	57.29±10.03	51.14±7.22	0.004*
Sex (Male/Female)	22/16	25/11	0.035† *
Disease Duration (years)	10.39±6.25	8.89±6.20	0.302
Body Mass Index	26.13±3.14	25.07±2.87	0.134
HbA_{1c} (%) (mmol/mol)	8.30±1.66	7.93±1.66	0.345
Fasting glucose (mmol/L)	8.97±2.87	8.97±2.53	0.992
MoCA	23.91±1.10	27.81±1.04	<0.001*

Data are mean±SD, n (%), or median (range) unless otherwise stated. MoCA, Montreal Cognitive Assessment. †The P value for proportions was obtained by X^2 test. *P < 0.05.

All preprocessing steps were carried out using Matlab 7.6.0 with Statistical Parametric Mapping software (SPM5). The first five volumes of the resting state fMRI data were discarded to allow for equilibrations of the magnetic field. The following processing was applied to all the remaining volumes: motion correction using the least-squares minimization, spatial normalization based on the Montreal Neurological Institute (MNI) space, temporal band-pass filters (0.01~ 0.08Hz), and spatial smooth with FWHM of 6 mm. After preprocessing, the fMRI data were segmented into 90 regions (45 regions for each hemisphere), using the anatomically labeled template. For each patient, the representative time series of each region were estimated simply by averaging the fMRI time series over all voxels in the region. Based on the 90 ROI-time series obtained, we then performed RSFC analyses on each subject by first performing Pearson's correlation analysis on each pair of ROI-time series and then transforming the correlation coefficients into z-scores using Fisher's r-to-z transformation. The 4,005 z-transformed correlation coefficients were taken as the RSFCs between ROIs, and the following classification of cognition were all based on the RSFCs and clinical characteristics of patients, including age, sex, disease duration, body mass index, HbA_{1c}, and fasting glucose.

Glmnet ((http://statweb.stanford.edu/~tibs/lasso.html) was used in this study to obtain the linear model parameters for MoCA classification. As the sample size of this study was relatively small, ten-fold cross-validation was used to estimate the performance of the predictors. For the cognition classification analysis, each T2DM patients was labeled either as cognition impairment (MoCA < 26, $y_i = 0$) or as a normal cognition one (MoCA > 26, $y_i = 1$). The labels were entered into the linear model to estimate the classification performance of the model. The performance of classification was evaluated by the classification rate, which is defined as the percent of the accurately classified samples, as well as the area under the receiver operating characteristic curve (AUC).

Results

A classification rate of 90.54% and AUC of 0.944 were obtained when classifying the cognitive impairment T2DM patients from other T2DM patients based on the whole brain RSFCs and clinical characteristics of patients (the receiver operating characteristic curve was shown in Figure 1). Meanwhile, we were able to analyze the contributions of the RSFCs to cognition classification of T2DM patients by virtue of using a linear model-based method. A total of 23 RSFCs were selected as key features with the linear model, while no clinical characteristics were selected (the selected 23 RSFCs were shown in Table 2).

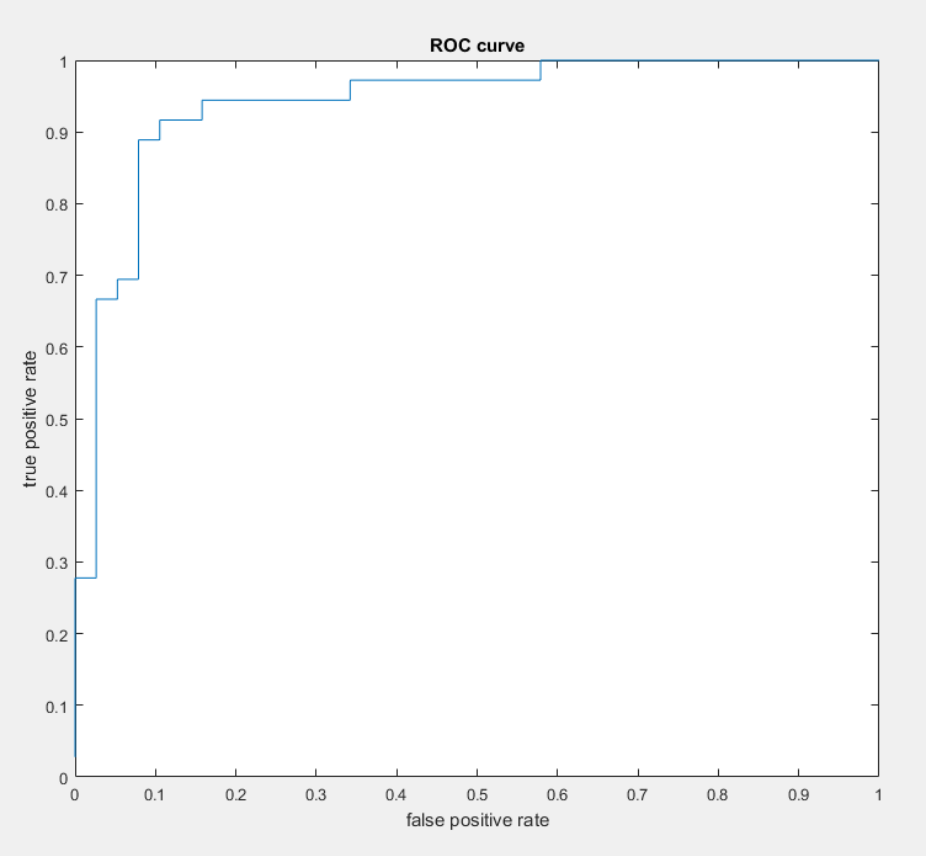

Figure 1. The receiver operating characteristic curve of the classification. The classification accuracy is 90.54% and the AUC is 0.944.

New or breakthrough work to be presented

In this study, we investigated the whole brain RSFC patterns to identify the T2DM patients with cognitive impairments from other T2DM patients with a multivariate pattern analysis method. The main findings of the present study were as follows: (1) 23 RSFCs mainly involving the frontal or temporal brain regions were selected as key features for the cognition classification in T2DM patients, while no clinical characteristics were selected, and (2) utilizing the multivariate pattern analysis, a relatively well classification performance was achieved. The results provide strong evidence that functional interactions of brain regions undergo notable alterations between T2DM patients with cognitive impairment or not.

Conclusions

In the present study, we constructed a multivariate linear model that could identify cognitive impairment T2DM patients from other T2DM patients. With this model, we detected 23 key RSFCs mainly involving the frontal or temporal brain regions for cognition classification. We speculated that cognitive impairment in T2DM patients may mainly impact these two lobes. Overall, the present study indicated that RSFCs undergo notable alterations associated with the cognitive impairment in T2DM patients, and it is possible to predicted cognitive impairment early with RSFCs.

Announcement: This work is not being and has not been submitted for any publication or presentation elsewhere.

Table 2 Selected key features for classification (23 RSFCs were selected as key features)

ROI1		ROI2	
Name (BA)	Coordinate	Name (BA)	Coordinate
Frontal_Sup_Orb_R.	18, 48, -14	Frontal_Sup_R	9, 51, 30
Frontal_Inf_Orb_L.	-36, 31, -12	Frontal_Inf_Oper_L	-48, 13, 19
Rectus_R.	8, 36, -18	Frontal_Sup_Orb_L	-17, 47, -13
Hippocampus_L.	-25, -21, -10	Frontal_Inf_Oper_L	-48, 13, 19
Calcarine_R.	16, -73, 9	Frontal_Inf_Tri_L	-46, 30, 14
Parietal_Inf_L.	-43, -46, 47	Frontal_Inf_Oper_L	-48, 13, 19
Caudate_R.	15, 12, 9	Hippocampus_R	29, -20, -10
Pallidum_L.	-18, 0, 0	Rolandic_Oper_R	53, -6, 15
Heschl_L.	-42, -19, 10	Occipital_Inf_R	38, -82, -8
Temporal_Pole_Sup_L.	-40, 15,-20	Cingulum_Ant_R	8, 37, 16
Temporal_Pole_Sup_R.	48, 15, -17	Occipital_Inf_L	-36, -78, -8
Temporal_Pole_Mid_L.	-36, 15, -34	Frontal_Mid_L	-33, 33, 35
Frontal_Inf_Orb_L.	-36, 31, -12	Precentral_L	-39, -6, 51
Rolandic_Oper_L.	-47, -8, 14	Frontal_Mid_R	38, 33, 34
Cingulum_Mid_R.	8, -9, 40	Frontal_Sup _R	9, 51, 30
ParaHippocampal_R.	25, -15, -20	Frontal_Mid_L	-33, 33, 35
Lingual_R.	16, -67, -4	Frontal_Inf_Tri_R	50, 30, 14
Paracentral_Lobule_R.	10.-56, 44	Frontal_Sup_Medial_L	-5, 49, 31
Putamen_R.	28, 5, 2	Frontal_Inf_Oper_L	-48, 13, 19
Heschl_L.	-42, -19, 10	Insula_L	-35, 7, 3
Heschl_R.	46, -17, 10	Precuneus_R	7, -32, 68
Temporal_Pole_Sup_R.	48, 15, -17	Occipital_Sup_R	24, -81, 31
Temporal_Mid_L.	-56, -34, -2	Frontal_Med_Orb_L	-31, 50, -10