Impaired Biophysical Integrity of Default Mode Network in Type 2 Diabetes Revealed by Magnetization Transfer Imaging

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Target audience: Scientists and clinicians who involve in the research and treatment of type 2 diabetes mellitus (T2DM).

Purpose

Type 2 diabetes mellitus (T2DM) is associated with metabolic and vascular complications [1], linked to mood disorders, cognitive impairment, and at an increased risk of Alzheimer's disease [2-4]. Compared to healthy controls (HC), patients with T2DM exhibit reduced functional connectivity in default mode network (DMN)[5]. Further, disruption of DMN functional connectivity in T2DM is associated with declined integrity of white matter (WM) tracts connecting DMN nodal regions [6]. Besides impairment in WM tracts, it is unknown whether DMN nodal regions are compromised in T2DM, which may contribute to the reduced functional connectivity too. Therefore, using magnetization transfer (MT) imaging, this study examined the biophysical integrity of macromolecular protein pools in the DMN nodal regions in patients with T2DM and healthy controls.

Methods

Subject: 20 patients with T2DM and 26 non-diabetic HCs. Diagnosis of T2DM was confirmed using the American Diabetes Association guidelines. All participants had no history of depression, a score of 8 or lower on the 17-item Hamilton Depression Rating Scale (HAM-D), and were free of unstable medical conditions. For all participants, vascular comorbidities were assessed using the Framingham Stroke Risk Profile (FSRP) score [7] and glycated hemoglobin (HbA1c) levels were evaluated as an indicator of the glycemic control status.

Magnetization Transfer Imaging. MRI scans were performed on a Philips Achieva 3T scanner with an 8-element phased-array head coil. MT images were acquired using a 3D spoiled gradient-echo sequence with multi-shot EPI readout: TR/TE=64/15ms, flip angle=9°, FOV=24 cm, 67 axial slices, slice thickness/gap =2.2 mm/no gap, EPI factor=7, reconstructed voxel size = 0.83×0.83×2.2 mm^3, with a nonselective five-lobed Sinc-Gauss off-resonance MT prepulse (B_1/Δf/dur=10.5μT/1.5kHz/24.5ms) [8]. Parallel imaging was utilized with a reduction factor of 2.

Image Processing. The magnetization transfer ratio (MTR) values were calculated on the voxel-by-voxel basis. The ROIs encompassed nodal regions of the DMN [5,6], including posterior cingulate cortex (PCC), precuneus (PCu), medial prefrontal cortex (mPFC), middle temporal, inferior parietal, inferior frontal, fusiform, and medial temporal regions in both hemispheres (major nodal regions of DMN obtained using independent component analysis (ICA) on 10 healthy controls who were scanned for rsfMRI). The generation of the ROIs in the images and the calculation of MTR in each ROI were performed using in-house developed programs.

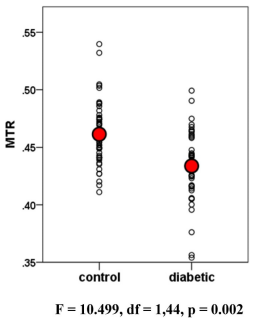

Fig.1 Scatterplot of PCC MTR

Results

Demographic and Clinical Measures. No significant group differences in demographic measures such as age, sex, handedness, education, IQ, MMSE, HAM-D. As expected, there were significant group differences in the diabetes-related clinical measures: FSRP and HbA1c (p's <0.006).

Group Differences in MTR. The mixed model analysis (with diagnostic group as the between-group factor and hemisphere as a within-subject factor) showed that among the examined nodal regions of the DMN, MTR was significantly lower in bilateral PCC (F = 10.499, df = 1,44, p = 0.002) (see Fig. 1) and was marginally significant in bilateral inferior parietal (F = 3.579, df = 1,44, p = 0.065) and mPFC regions (F = 3.542, df = 1,44, p = 0.066) in patients compared with controls. MTR change in PCC remained significant after the FDR multiple comparison correction.

Correlation between MTR and HbA1c or FSRP. For combined groups, MTR negatively correlated with the log-transformed HbA1c level [ln(HbA1c)] in bilateral PCC (left: r = -0.327, df = 43, p = 0.028 and right: r = -0.415, df = 43, p = 0.005) (see Fig. 2a) but not in bilateral mPFC and inferior parietal regions (p's > 0.115). Correlations of ln(HbA1c) and PCC MTR in both hemisphere remained significant after the FDR multiple comparison correction. Additionally, MTRs in right PCC were negatively correlated with FSRP scores across the entire sample (r = -0.363, df = 43, p = 0.014) (see Fig. 2b), while there was only a trend to significant correlation in left PCC MTR (r = -0.263, df = 43, p = 0.081). The significant correlation in right PCC remained significant after the FDR multiple comparison correction. There was no significant correlation between FSRP scores and MTRs in bilateral mPFC and inferior parietal regions (p's > 0.235).

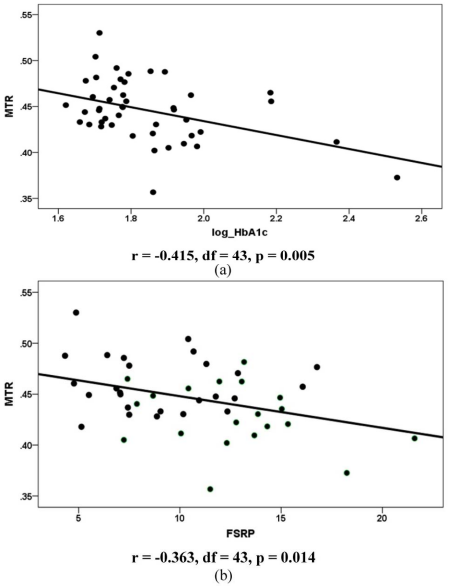

Fig.2 Scatterplots of right PCC MTR vs. (a) log-transformed HbA1c and (b) FSRP

Discussion and Conclusion

Findings from this study may provide complementary mechanistic explanation about reduced DMN functional connectivity in T2DM and aid in our understanding of the mechanisms underlying T2DM-related brain alterations and the neurobiology of diabetes.

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