Biophysical Abnormalities in Fronto-Striato-Thalamic Circuits 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

T2DM is associated with metabolic, macro- and micro-vascular complications in multiple organ systems including the brain [1]. Neuroanatomical alterations has been found in T2DM patients by structural magnetic resonance imaging [2]. Diffusion tensor imaging (DTI) studies have revealed decreased fractional anisotropy (FA) in frontal white matter regions in T2DM [3]. Magnetization transfer (MT) imaging may provide supplementary information on the effects of T2DM on the human brain [4]. Fronto-striato-thalamic circuits have been implicated in the pathophysiology of several mood and associated cognitive disorders [5]. In this study, we were interested in examining the integrity of the macromolecular protein pool in patients with T2DM without mood disturbances. We were primarily interested in the fronto-striato-thalamic circuits – circuits that are neurobiologically relevant in human behavior [5], and were interested in examining the relationship between the compromised biophysical integrity and the T2DM-related clinical measures.

Methods

Subject: 20 patients with T2DM and 26 non-diabetic comparison controls. The diagnosis of T2DM was confirmed using the American Diabetes Association guidelines. Both control and patient subjects denied a history of depressed mood, required a score of 8 or lower on the 17-item Hamilton Depression Rating Scale (HAM-D), were free of unstable medical conditions. All participants were assessed for vascular comorbidities using the Framingham Stroke Risk Profile (FSRP) score [6]. Participants also received a non-fasting blood draw to document HbA1c levels, an indicator of glycemic control.

Magnetization Transfer Imaging. The MRI scan was performed on a Philips Achieva 3T scanner with an 8-element phased-array coil. The MT images were acquired using a 3D spoiled gradient-echo sequence with multi-shot EPI readout with the following parameters: 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) [7]. Parallel imaging was utilized with a reduction factor of 2.

Image Processing. The MTR values were calculated on the voxel-by-voxel basis. The ROIs were placed at the nodes of fronto-striato-thalamic circuits [5], including 4 subcortical regions, i.e., head of caudate nucleus (hCaud), putamen, globus pallidus, and thalamus, and 4 cortical regions, i.e., rostral and dorsal anterior cingulate cortex (rACC and dACC), dorsolateral prefrontal cortex (DLPFC), and lateral orbitofrontal cortex (lOFC) in both hemispheres. The slice displaying the most anterior margin of the genu of corpus callosum was chosen as the reference slice for placing the subcortical ROIs: hCaud, putamen, and thalamus. For the ROI of globus pallidus, the slice clearly displaying the anterior commissure was chosen as the reference slice. For the four cortical ROIs i.e., rACC, dACC, DLPFC, and lOFC, we used the FreeSurfer to automatically segment out these structures. We used constant volumes of ROIs in all of the defined regions except for the 4 cortical regions, i.e., the volume was fixed to 73.3 mm^3 for hCaud, putamen, and thalamus and was fixed to relatively smaller 55 mm^3 for globus pallidus. These two volumes were selected so that the MTR calculation in each subcortical ROI could be devoid of any partial volume effects from adjoining region tissues on all the involved subjects. For the four cortical regions, we calculated the MTR only in white matter.

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 ROIs examined, MTR was significantly lower in bilateral dACC ($F_{1,44}$ = 6.220, p = 0.016), bilateral hCaud ($F_{1,44}$ = 4.969, p = 0.031), and was close to significantly lower in bilateral rACC ($F_{1,44}$ = 3.992, p = 0.052) in T2DM patients compared with non-diabetic controls.

Correlation between MTR and HbA1c or FSRP. Only when groups were combined did MTR negatively correlate with the HbA1c level in bilateral dACC (left: r = -0.400, df = 43, p = 0.006 and right: r = -0.418, df = 43, p = 0.004), bilateral rACC (left: r = -0.360, df = 43, p = 0.015 and right: r = -0.340, df = 43, p = 0.022), and right hCaud (r = -0.313, df = 43, p = 0.036). MTRs in bilateral rACC were negatively correlated with the FSRP score across the entire sample (left: r = -0.344, df = 43, p = 0.021; right: r = -0.371, df = 43, p = 0.012).

Discussion and Conclusion

Our findings suggest that T2DM is associated with distinct, focal biophysical abnormalities that map on to the specific nodes of fronto-striato-thalamic circuits and are correlated with T2DM-related clinical measures.

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