Altered hippocampal white matter connectivity and memory impairment in Type 2 Diabetes Mellitus

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Target audience: Investigators interested in neuroimaging, cognition and type 2 Diabetes Mellitus.

Purpose: Type 2 Diabetes Mellitus (T2DM) is associated with cognitive decline. A prominently affected cognitive domain is memory, for which the hippocampus plays an essential role. Diffusion MRI (dMRI) enables assessment of hippocampal microstructure through the fractional anisotropy (FA), mean diffusivity (MD), and tractographic connectivity. To examine whether hippocampal abnormalities are related to verbal memory performance, T2DM, and their potential interaction, we performed dMRI in participants with and without T2DM.

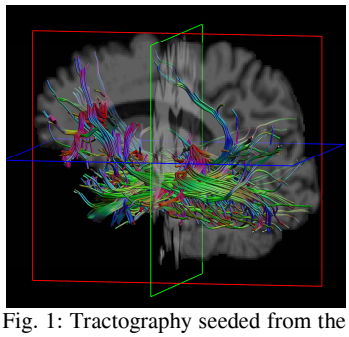

Fig. 1: Tractography seeded from the hippocampus

Methods: *Subjects and measurements*: 40 T2DM (age 64.9±6.1 y, 29 male, BMI 29.2±3.5 kg/m^2) and 38 non-T2DM (age 58.7±9.1 y, 14 male, BMI 24.7±2.9 kg/m^2) control participants were included. All participants underwent a 15-words learning memory task (15-WLT). Neuroradiological assessment revealed no abnormalities. dMRI and T1-weigthed images were obtained on a 3.0 Tesla MRI scanner (Philips Achieva TX) and a 32-element SENSE head coil. The dMRI sequence parameters are: TR/TE of 6980/84 ms, 2.4 mm isotropic voxel size, 128 diffusion sensitizing gradient directions, a b-value of 1500 s/mm^2, and acquisition time of 15 minutes. A single b0-scan was acquired. For anatomical reference, a 3D T1-weighted fast field-echo was acquired: TR/TE of 8.1/3.7 ms, 1.00 mm isotropic voxel size, 170 continuous slices, matrix size of 240x240, acquisition time of 8 minutes. *Analysis*: 3D T1-weighted fast field echo images were used for automatic segmentation of the left and right hippocampus, frontal lobe, parietal lobe, temporal lobe, occipital lobe, and subcortical gray matter with Freesurfer[1]. Motion and distortion correction of dMRI data was performed using ExploreDTI[2] (v4.8.2). The diffusion tensor was estimated using the RESTORE approach[3]. Whole brain probabilistic tractography was performed using constrained spherical deconvolution (CSD) to extract the fiber orientation distributions with a seed point volume of 1 mm^3 and a maximum deflection angle of 30°, yielding approximately 4.3M streamlines. Next, connectivity analysis was performed to obtain tract volumes seeded from each hippocampus (Fig.1). The total tract volumes seeded from both hippocampi to each brain lobe was calculated and normalized to the intracranial volume. *Statistics:* Linear regression analyses, adjusted for age, gender, education level, BMI, systolic blood pressure, relative hippocampal volume, and relative white matter lesion volume were performed (SPSS) to assess the association of hippocampal dMRI measures (FA, MD, and tractographic volumes) with verbal memory performance, T2DM status, and their interaction. When the tract volumes to specific brain lobes were significantly different between the groups, measures FA and MD of the tracts were also investigated in more detail. Furthermore, group characteristics were tested using independent samples t-test and Chi-Square tests.

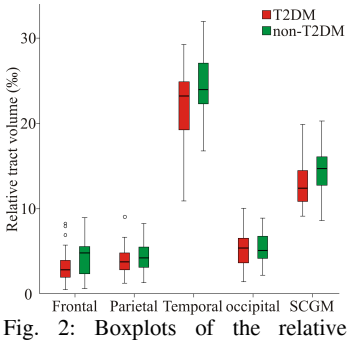

Fig. 2: Boxplots of the relative hippocampal tract volumes to the different brain lobes.

Results: T2DM participants scored significantly worse on 15-WLT total score than non-T2DM participants (39.8±10.8 vs 47.2±11.1, p≤0.05). Furthermore, age, gender, and education level were different between both groups (p<0.05). Linear regression (Fig. 3) revealed: i) no abnormalities of FA or MD in both hippocampi with T2DM or memory performance, ii) a T2DM specific decreased relative tract volume from both hippocampi to the frontal lobe (β= -0.720, p=0.017) (Fig.2,3), iii) tract volume to the temporal lobe (β= 0.235, p=0.017) decreased and tract volume to the parietal lobe (β= -0.268, p=0.042) increased for worse memory performance (Fig.3), and iv) no significant interaction of T2DM with memory performance. Additionally, the FA and MD of the tracts to the frontal lobe were not different between T2DM and non-T2DM participants.

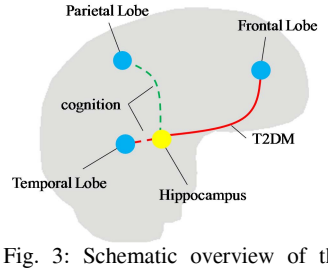

Fig. 3: Schematic overview of the connectivity results with dotted line fewer (red) and more (green) connections in participants with worse memory and less connectivity (red line) in T2DM.

Discussion & Conclusion: In this study we observed fewer connections from the hippocampus to the frontal lobe in participants with T2DM. This suggests that the transfer and integration of information between the hippocampus and frontal lobe might underlie the memory impairment. Hoogenboom et al. related impaired cognitive performance to reduced FA of specific white matter bundles in T2DM participants, although no differences in tract volumes were observed[4]. In contrary to Hoogenboom et al. our focus was specific to the hippocampus which could explain the different results. For participants who score worse on memory performance, we observed fewer hippocampal connections to the temporal lobe, but more to the parietal lobe. Possibly a compensatory mechanism is involved and therefore the cognitive reserve theory could be relevant, which specifies that individual differences in cognitive processes allow some individuals to cope better with pathology than others[5]. To conclude, impaired memory in T2DM seems to be associated with altered hippocampal white matter connectivity. The exact underlying mechanism needs to be elucidated in future studies.

References: [1] Fischl, B., et al., 2002, Neuron, vol.33, no.3, pp.341-355. [2] Leemans, A., et al, 2009, 17th Annual Meeting of ISMRM. [3] Chang, L., et al., 2005, Magn Reson Med, vol.53, no.5, pp.1088-1095. [4] Hoogenboom, W., et al., 2014, Diabetes, vol.63, no.2, pp.728-738. [5] Stern, Y. 2009, Neuropsychologia, vol.47, no. 10, pp.2015-2028.