Diffusion Tensor Imaging in Diabetes Mellitus Type 2 and memory impairment - initial findings -

Frank C.G. van Bussel[1], Walter H. Backes[1], Paul A.M. Hofman[1], Harm J. van de Haar[1], Martin P.J. van Boxtel[2], Miranda T. Schram[3], Coen D.A. Stehouwer[3], Joachim E. Wildberger[1], and Jacobus F.A. Jansen[1]

[1]Radiology, MUMC+, Maastricht, Netherlands, [2]Psychiatry and Neuropsychology, MUMC+, Maastricht, Netherlands, [3]Internal Medicine, MUMC+, Maastricht, Netherlands

Target audience:

Investigators with research related to neuroimaging and Diabetes Mellitus Type 2.

Introduction:

Diabetes Mellitus Type II (T2DM) is a common chronic metabolic disorder, characterized by chronic hyperglycemia. In addition to (cardio)vascular disease, T2DM is associated with various pathophysiological cerebral abnormalities, accelerated cognitive decline, and dementia in older subjects. A prominently affected cognitive domain is memory, for which the hippocampus plays an essential role. Diffusion Tensor Imaging (DTI), which probes microstructure, might be a good candidate for the identification of early biomarkers of memory decline in T2DM. To the best of our knowledge, we are the first to use DTI to study microstructural properties of the hippocampus in T2DM patients with memory impairment, compared to healthy controls.

Methods:

Subjects and MRI: Six subjects with T2DM (3 female) and impaired memory performance and five healthy subjects (4 female) with good cognitive performance were included in this preliminary study (Tab. 1). Subjects were selected based on cognitive performance (words learning task (15-WLT) from the existing 'Maastricht Study' population. Neuroradiological assessment revealed no hippocampal abnormalities. Whole brain DTI scans were performed using a 3.0 Tesla MRI scanner (Philips Achieva TX) and a 32-element SENSE head coil for parallel imaging. The DTI imaging parameters were: TR/TE of 6980/84ms, 2.4x2.4x2.4mm voxelsize, 128 diffusion sensitizing gradient directions, b-value of 1500 s/mm^2, acquisition time of 15 minutes. For anatomical reference, a 3D T1-weighted fast field-echo with the following parameters was acquired: TR/TE of 8.1/3.7ms, flip angle of 8^0, 1x1x1mm voxelsize, 180 continuous slices, slice thickness was 1mm and matrix size of 240x240, acquisition time of 8 minutes.

Analysis: A series of preprocessing steps common for DTI analysis was performed using ExploreDTI (v4.8.2 [1]). The preprocessing included motion and distortion correction. After these preprocessing steps further analysis was performed using 1) Region of Interest (ROI) based analysis and 2) Tract-Based Spatial Statistics (TBSS) toolbox [2] within FSL (FMRIB, Oxford, UK). *ROI-based analysis*: First, ROIs of the hippocampus (left and right separately) were manually delineated (Fig 1.) according to [3]. Second, the median of the left and right fractional anisotropy (FA) and mean diffusivity (MD) values corresponding to the ROIs were calculated and compared between the two groups using the non-parametric Mann-Whitney U Test in SPSS (IBM SPSS statistics v20). Finally, associations of FA and MD values with memory performance were assessed using non-parametric Spearman correlation coefficients. *TBSS*: Differences between the two groups in FA and MD within the white matter skeleton were characterized with permutation tests using the Randomize toolbox in FSL. For the TBSS analysis, the threshold-free cluster enhancement (TFCE) approach in FSL was used to find clusters, corrected for multiple comparisons [4].

Tab. 1. Characteristics	Maximum Test Score	Controls (n=5)	T2DM (n=6)
Age (y)		65±7	67±4
BMI (kg/m^2)		27±3.0	30±3.5
15-WLT total score	75	54.8±9.7	31.8±4.4*
15-WLT recall score	15	12.6±1.8	5.5±2.5*

*p<0.05

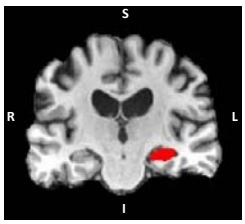

Fig 1. ROI (red) of the left hippo-

Results:

T2DM subjects score significantly worse on 15-WLT and recall 15-WLT in comparison to healthy controls (Tab. 1). *ROI-based analysis*: No significant group differences were found for MD and FA (p>0.32). Mean diffusivity of the left hippocampus significantly decreased with the total- (Spearman's ρ= -0.631, p=0.037) and recall- (Spearman's ρ= -0.659, p=0.027) 15-WLT scores (Fig 2.). A similar trend was present for the mean diffusivity in the right hippocampus (p = 0.07). *TBSS*: No significant differences in FA or MD skeletons were detected between controls and T2DM subjects using TBSS.

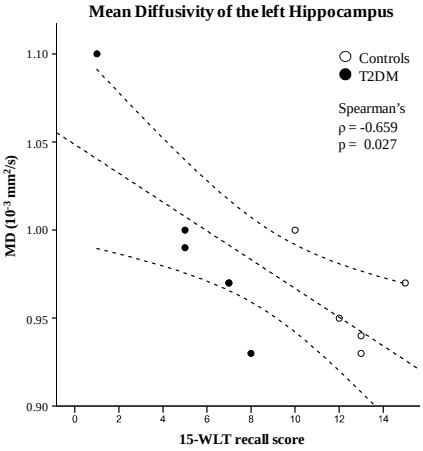

Fig 2. Correlation between Mean Diffusivity of the left hippo-campus and 15-WLT recall score over the entire subject group. Dashed lines represent the regression line with 95% mean confidence interval.

Discussion/Conclusion:

In the left hippocampus, a high MD was associated with poor memory performance, which suggests that injured hippocampal microstructure might underlie memory problems [5]. However, no significant group differences were found, which can possibly be attributed due to the limited number of included subjects. Also, the current preliminary study cannot disentangle the effects of T2DM from poor memory performance. Nonetheless, these promising results warrant further inclusion of more subjects (including T2DM with more subtle memory problems) to study altered hippocampal microstructure in T2DM related memory decline, which is currently ongoing.

References: [1] Leemans, A., et al, 2009, 17th Annual Meeting of Intl Soc Mag Reson Med; [2] Smith, S.M., et al, 2006, Neuroimage, vol.31, no.4, pp.1487-1505; [3] Jeukens, C.R., et al, 2009, Investigative Radiology, vol.44, no.9, pp. 509-517; [4] Smith, S.M., et al, 2009,Neuroimage, vol.44, no.1, pp. 83-98; [5] van Norden, A.G., et al, 2012, Human Brain Mapping, vol.33, no.3, pp. 542-551.