

Hippocampal Intravoxel Incoherent Motion Imaging in Type 2 Diabetes Mellitus and memory impairment

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Target audience: Investigators interested in neuroimaging and Type 2 Diabetes Mellitus.

Introduction: Type 2 Diabetes Mellitus (T2DM) is a common chronic metabolic disorder, characterized by chronic hyperglycemia and associated with cerebral abnormalities, accelerated cognitive decline, and dementia. A prominently affected cognitive domain is memory, for which the hippocampus plays an essential role. Higher blood glucose levels have been shown to affect hippocampal microstructure and memory performance in healthy elderly¹. Intravoxel Incoherent Motion MR imaging (IVIM) enables assessment of hippocampal microstructure through the diffusion coefficient (D) and perfusion fraction (f), which is maybe sensitive to vascular pathology. The aim of this study is to examine if IVIM metrics are good candidates as MRI biomarkers for i) verbal memory performance, ii) T2DM and/or iii) blood glucose measures (fasting blood glucose and HbA1c).

Methods: Subjects and measurements: 34 non-T2DM (age 58.3±9.2 y, 12 male, BMI 24.7±2.7 kg/m²) and 40 T2DM (age 64.7±6.1 y, 30 male, BMI 29.2±3.5 kg/m²) participants were included in this study. All participants underwent a 15-words learning memory task (15-WLT). Neuroradiological assessment revealed no (macro)structural hippocampal abnormalities. IVIM diffusion weighted (IVIM) and 3D T1-weighted fast field echo data were obtained on a 3.0 Tesla MRI scanner (Philips Achieva TX) and a 32-element SENSE head coil for parallel imaging. Inversion recovery (to eliminate CSF contamination) IVIM sequence parameters are: TR/TE of 6800/84, 2.4x2.4x2.4mm voxelsize, IR delay of 2230ms. We acquired images at multiple b-values (0, 5, 7, 10, 15, 20, 30, 40, 50, 60, 100, 200, 400, 700, 1000, 1500 s/mm²) in one direction and number of averages (nsa) for highest three b-values were 2, 3, and 3, respectively. For anatomical reference, a 3D T1-weighted fast field-echo with the following parameters was acquired: TR/TE of 8.1/3.7ms, 1x1x1mm voxelsize, 180 continuous slices, slice thickness was 1 mm and matrix size of 240x240. **Analysis:** 3D T1-weighted fast field echo data was used for automatically segmentation of the left and right hippocampus with Freesurfer² (Fig.1). Motion and distortion correction for IVIM data was performed using ExploreDTI³ (v4.8.2).

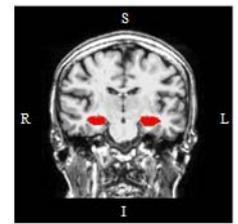


Fig. 1: Coronal view of the segmented right and left hippocampus (red).

After preprocessing, signal intensity of the left and right hippocampus were calculated and the IVIM signal versus b-value curve was fitted (Fig.2) with a two-step approach⁴ in Matlab: 1) mono-exponential fit for signal intensities of b-values 200-1500 s/mm², yielding the diffusion coefficient (D), 2) bi-exponential fit for signal intensities of all b-values with fixed D, yielding pseudodiffusion coefficient (D*) and perfusion fraction (f). Weighting was implemented in the fitting algorithm according to nsa per b-value. **Statistics:** Linear regression was performed (IBM SPSS statistics v20) for the left and right hippocampus, with D, D* and f as dependent, and T2DM, 15-WLT, T2DM*15-WLT, age, gender and relative (to intracranial) hippocampal volume as independent variables (*model 1*). Additionally, T2DM risk factors (fasting blood glucose (*model 2*) and HbA1c (*model 3*)) were added separately to the linear regression *model 1*. Furthermore, group characteristics were tested using independent samples t-test and Chi-Square tests.

Results: T2DM participants scored significantly worse on 15-WLT total score than non-T2DM participants (40.2±10.6 vs 46.4±11.2, p<0.05). Furthermore, age, gender, fasting blood glucose (5.0±0.3 vs 7.7±1.6 mmol/l), and HbA1c (5.6±0.4 vs 6.8±0.5%) were significantly different between both groups (p<0.01). Linear regression revealed increased D with lower 15-WLT scores ($\beta = -0.5$, p<0.01) in the left hippocampus and the same trend was present in the right hippocampus ($\beta = -0.36$, p=0.08) (*all models*). D was increased in participants with lower fasting blood glucose levels ($\beta = -0.5$, p<0.01; *model 2*) in left and right hippocampi. Perfusion fraction f was increased with higher fasting blood glucose levels ($\beta = 0.72$, p<0.001) in both hippocampi. No significant results were found regarding diabetic status ($\beta = -0.39$, p=0.431) and HbA1c ($\beta = -0.34$, p=0.050).

Discussion & Conclusion: In this study we observed that a higher D in the left hippocampus is associated with poor memory performance with the IVIM technique. These results suggests that the microstructure of the left hippocampus is injured, which might underlie memory impairments⁵. In addition to D, a measure of the perfusion fraction f can be obtained, indicative of vascular pathology. The association of f with increased fasting blood glucose levels might indicate that the increased risk of high glucose levels for dementia⁶ is mediated by vascular pathology. To conclude, higher hippocampal D is associated with lower memory performance. The interplay of vascular pathology, blood glucose and memory performance remains to be elucidated in future studies.

References: [1] Kerti, L., et al., 2013, Neurology, Epub ahead of print. [2] Fischl, B., et al., 2002, Neuron, vol.33, no.3, pp.341-355. [3] Leemans, A., et al, 2009, 17th Annual Meeting of ISMRM. [4] Federau, C., et al., 2012, Radiology, vol.265, no.3, pp.874-881.[5] van Norden, A.G., et al., 2012, Human Brain Mapping, vol.33, no.3, pp.542-551. [6] Crane, P.K., et al., 2013, N Engl J Med, vol.369, no.15, pp.540-548.

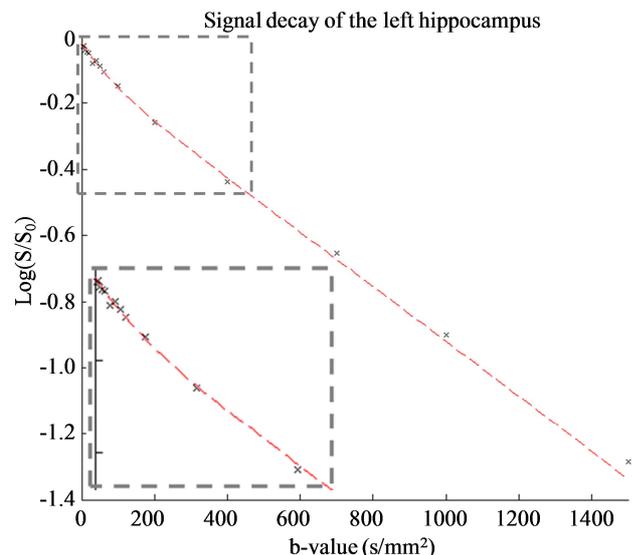


Fig. 2: Bi-exponential fit (dashed red line) of signal (x) decay in the left hippocampus. Magnified section in black dotted box highlights a non-linear fit for the low b-value range (upto a b-value of 500 s/mm²).