Understanding the role of amyloid to cerebral microvasculature in Alzheimer's disease: A pre-clinical Intra-Voxel Incoherent Motion (IVIM) study

Syed Salman Shahid[1,2], Jui-Hung Yen[4], Hallel C. Paraiso[4], Yu-Chien Wu[1,2,3], and I-Chen I. Yu[4]

[1]Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, [2]Indiana Alzheimer's Disease Research Center, Indiana University School of Medicine, Indianapolis, [3]Stark Neuroscience Research Institute, Indiana University School of Medicine, Indianapolis, [4]Indiana University School of Medicine, Fort Wayne, IN, USA

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Background

Vascular perturbation is emerging as an important contribution to Alzheimer's disease (AD) trajectory. However, the role of microvascular alterations in pathophysiological processes remains unclear. We hypothesized a direct link between β-amyloid (Aβ) and the cerebral microvasculature, leading to vascular stress, deteriorated blood-brain barrier, and impaired microcirculation.

The early detection of changes in the microvasculature can be used as an early biomarker to study underlying disease mechanisms. This study used intra-voxel incoherent motion (IVIM) technique to quantitatively map functional capillaries related to blood volume fraction as surrogate marker for microvasculature alterations in an Alzheimer's disease mouse model.

Abbreviations:

AD: Alzheimer's disease
Aβ: β-amyloid
DWI: diffusion weighted Imaging
D: Apparent diffusion coefficient
D*: Pseudo-diffusion coefficient
f_{IVIM}: Perfusion fraction
IVIM: Intra-voxel incoherent motion

Material and Methods

Male 5xFAD mice at 6-months-old and age-matched littermates (C57BL/6J) were scanned using high-resolution IVIM optimized diffusion weighted imaging (DWI). The DWI and anatomical images were acquired on a horizontal bore 9.4T Biospec micro-MRI system equipped with a ^{1}H cryogenic surface coil. 2D T2-weightd images were acquired with a voxel size of 60x60x300 μm^3 and DWIs were acquired with a voxel size of 120x120x300 μm^3.

T2-W images were nonlinearly registered to Badhwar hippocampal atlas. Hippocampal subfields, cornu ammonis 1 (CA1), cornu-ammonis 2 (CA2), cornu ammonis 3 (CA3), dentate gyrus (DG) and Subiculum in atlas space were transformed to individual T2-W space and then linearly transformed to individual DWI space.

Intra-voxel incoherent motion maps (Apparent diffusion coefficient [D], pseudo-diffusion coefficient [D*], and perfusion fraction [f_{IVIM}]) were calculated (voxel-wise) using a bi-exponential IVIM model. The mean f_{IVIM} of individual subfields were used for group-wise comparison, and the Hedges'g were used for effect-size analysis.

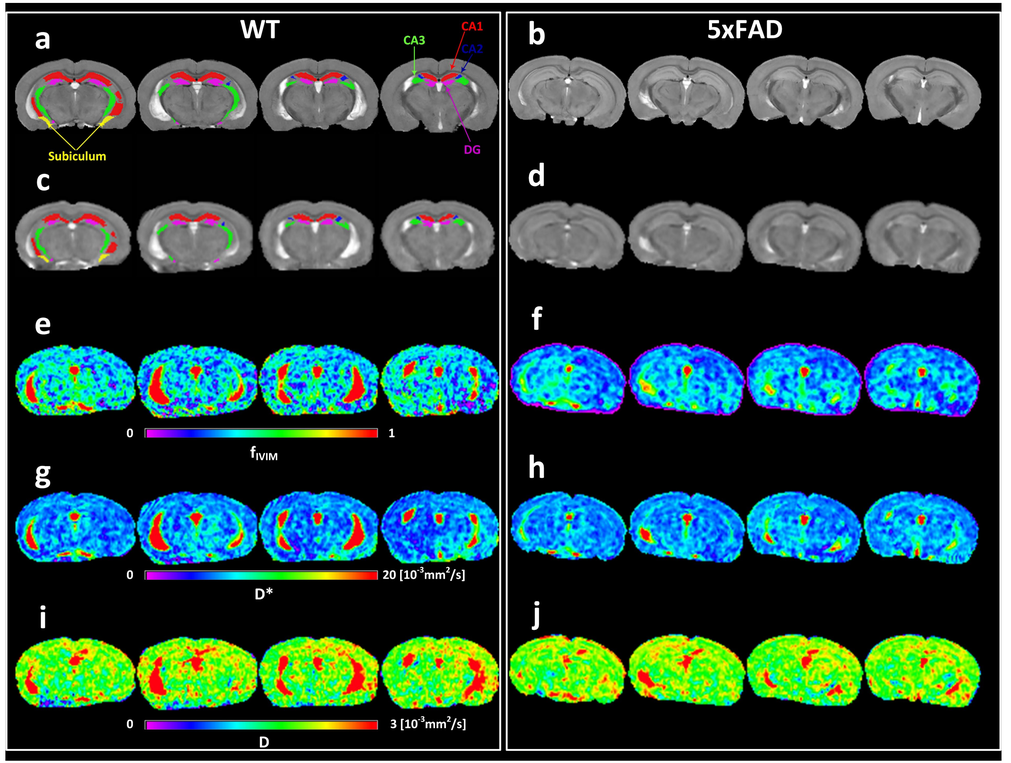

Figure: T2-W anatomical images and IVIM derived quantitative maps. (a, b) T2-W structural images. (c, d) averaged b0 images, (e, f) perfusion fraction maps (f_{IVIM}), (g, h) pseudo-diffusion maps (D*), and (I, j) apparent diffusion maps. In a and c, the Hippocampal subfields used for region of interest based statistical analysis are shown.

Results

Our preliminary results showed regional differences in microvascular perfusion fraction (f_{IVIM}) between control (n=6) and 5xFAD (n=8) mice at 6 months of age. f_{IVIM} was significantly lower in DG ($p<0.05$; Hedge's g =-1.4; 95% CI: 0.002, 0.031)[-2.552, -0.202] and in Subiculum ($p<0.05$; Hedge's g=-1.3; 95% CI: 0.002, 0.028) [-2.54, -0.194] of 5xFAD compared to wild-type mice . The f_{IVIM} remains unchanged in other subfields. The decreased f_{IVIM} suggested that deficits in the capillary network of DG and Subiculum develop early.

Conclusion

These findings support the sensitivity of IVIM to detect functional deficits in the hippocampal microvasculature associated with Aβ pathology. The IVIM may provide new insight into cerebral small vessel health in an early AD stage without a contrast agent administration and can be readily translated to the clinic.

Contacts

Syed Salman Shahid – shahids@iu.edu
Jui-Hung Yen - jimyen@iu.edu,
Hallel C. Paraiso - hparaiso@iu.edu
Yu-Chien Wu - yucwu@iu.edu,
I-Chen I. Yu - ivoyu@iu.edu