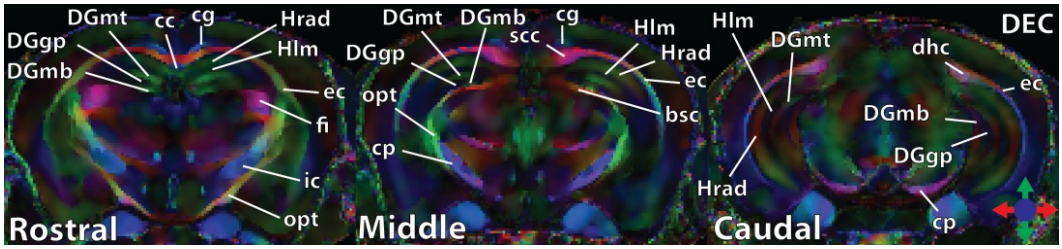
Comparison of Relaxation, Magnetization Transfer, and Diffusion Tensor Measurements in the Hippocampal Formation between APP, PS1, and Control Mice

Sheryl L Herrera[1], Heather Whittaker[2], Shenghua Zhu[3], Vanessa L Palmer[4], Richard Buist[5], Xin-Min Li[6], Jonathan D Thiessen[7,8], and Melanie Martin[9,10]

[1]Physics & Astronomy, University of Mantioba, Winnipeg, Manitoba, Canada, [2]Biopsychology program, University of Winnipeg, Winnipeg, Manitoba, Canada, [3]Pharmacology & Therapeutics, University of Mantioba, Winnipeg, Manitoba, Canada, [4]Biomedical Engineering, University of Mantioba, Winnipeg, Manitoba, Canada, [5]Radiology, University of Mantioba, Winnipeg, Manitoba, Canada, [6]Psychiatry, University of Alberta, Edmonton, Alberta, Canada, [7]Imaging Program, Lawson Health Research Institute, London, Ontario, Canada, [8]Medical Biophysics, Western University, London, Ontario, Canada, [9]Physics, University of Winnipeg, Winnipeg, Manitoba, Canada, [10]Biomedical Engineering, Physics &Astronomy, Pharmacology &Therapeutics, Radiology, University of Mantioba, Winnipeg, Manitoba, Canada

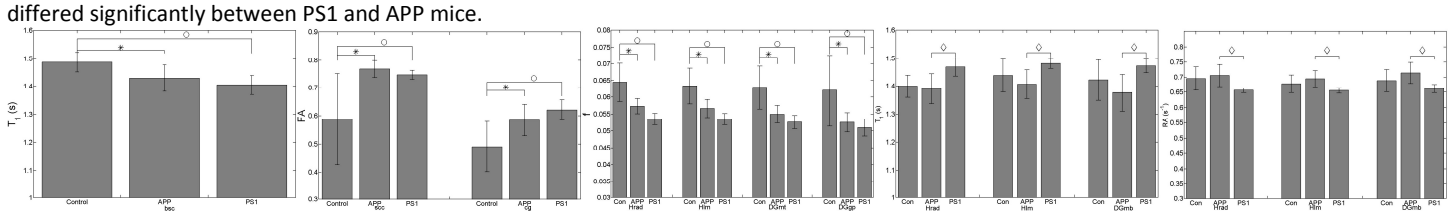
Introduction Alzheimer's disease (AD) results in atrophy and microstructural changes in the hippocampus with peripheral damage to various white matter (WM) structures[1,2]. Quantifying structural changes in the hippocampal formation (HF) and surrounding WM with MRI can improve both the diagnosis and understanding of AD. Although several studies have looked at quantitative MTI (qMTI)[3-5] and DTI[2,6-8] in and around the HF, studies focused on different structures within the hippocampus itself have been limited primarily to DTI[9-10]. The qMTI-derived bound pool fraction (f) might show changes in tissue content beyond just the myelin content with which it is often associated. In this study, T_1 relaxation, DTI, and qMTI were used to analyze the HF and surrounding WM structures in *ex vivo* transgenic mouse brains that were either wild type controls (n=7), or had overexpression of the presenilin-1 (PS1) protein (n=6) or the amyloid precursor protein (APP) (n=7).

Methods **Mouse Brains:** Mice were perfused with PBS followed by 4% PFA at 7.5 months of age. Brains (in skull) were transferred to a PBS solution 48 hours prior to imaging to leach out any remaining PFA. All experiments were approved by the universities' Animal Care Committee. **MRI:** Using a 7 T Bruker Avance III NMR system with PV 5.0, 3 coronal slices (0.5 mm SLTH, 1 mm interslice distance, (2 cm)^2 FOV, (256)^2 matrix size) were selected in each mouse to span the HF. **Relaxation Imaging:** T_1 maps were determined by fitting a saturation recovery curve to 5 RARE images (effective TE 11 ms; TR = 4895.5, 2895.5, 1395.5, 695.5, 295.5, 95.5 ms; RARE factor 2; NA 4; 71 minutes). **qMTI:** qMT maps were determined using an approximation of the two-pool model of MT[11] fit to 1 non-saturated and 18 RF-saturated FLASH images (10.25 ms Gaussian saturation pulse with saturation powers of 5, 10, and 20μT and frequency offsets at each power of 1000, 2000, 4000, 6000, 10000, and 30000 Hz, NA 32, T_E 6 ms, T_R 70 ms, 10° flip angle, 9.5 minutes/image) **DTI:** DTI maps were determined using a non-linear least squares fit and a modified Cholesky decomposition to ensure positive definiteness[12] fit to a PGSE acquisition (7-direction tetra-orthogonal gradient-encoding scheme, b-value = 1000 s/mm^2, δ = 6 ms, Δ = 14 ms, TE 26ms, TR 5000ms, NA 6, 8.5 h). **Image Analysis:** Prior to fitting, all images were aligned to the b=0 DWIs using a rigid affine transformation matrix determined automatically by maximizing the 2D correlation coefficient. An anisotropic diffusion filter was applied with 5 iterations and a gradient modulus threshold equal to 3 times the standard deviation of noise in each image[13]. White and gray matter ROIs were selected in the directionally encoded color map (DEC) with reference to a mouse atlas[14] and applied to analysis of all quantitative MR maps. Statistics were performed using SAS ® 9.3 software. One-way ANOVA was used to measure the significance in the effect of the MRI metrics based on mouse types. If statistical significance exists (p-values < 0.05), then Duncan's multiple range post-hoc test was used to test for significance.



ROIs **HF:** radiatum (Hrad) and lacunosum-moleculare (Hlm) layers of the hippocampus; top/bottom molecular (DGmt/DGmb) and granular/polymorph (DGgp) layers of the dentate gyrus. **WM:** corpus callosum (cc), cingulum (cg), fimbria of the hippocampus (fi), internal capsule (ic), splenium of cc (scc), external capsule (ec), brachium of the superior colliculus (bsc), cerebral peduncle (cp), optic tract (opt), and dorsal hippocampal commissure (dhc).

Results and Discussion Anatomical details visible only in DTI anisotropy maps allowed ROIs to be defined and applied to all quantitative MRI maps. FA and the FA-weighted DEC maps had much better contrast within the HF when compared to other quantitative MR methods. Many significant differences were found in MRI metrics between the transgenic mice when compared with controls (see bar graphs). For instance, in white matter structures, the T_1 of bsc, and the FA of the scc, and cg, all differ significantly between transgenic and control mice. For the gray matter the f of the Hrad, Hlm, DGmt, DGgp differed significantly between transgenic and control mice. Interestingly, the T_1 and the RA of the Hrad, Hlm and DGmb differed significantly between PS1 and APP mice.



Conclusion Quantitative MRI methods such as DTI and qMTI are useful for determining changes in tissue structure and content within the HF and surrounding WM tracts of APP and PS1 mouse models of AD. This work lays the foundation for future studies, which will incorporate *in vivo* and longitudinal measurements in transgenic mouse models of AD alongside age-matched controls and correlation with histopathology.

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Acknowledgments Natural Sciences and Engineering Research Council of Canada, Manitoba Health Research Council, Canada Foundation for Innovation and the Manitoba Research and Infrastructure Fund.