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# Combined Diffusion Relaxometry: Phantom Validation and Ex Vivo Characterization of Alzheimer's Disease Lesions

Andrea Jacobson[1], Amaya Murguia [2], Scott D. Swanson[3], Ulrich Scheven[4], Jon-Fredrik Nielsen[1,3], Jeffery A. Fessler[2], and Navid Seraji-Bozorgzad[5]
*[1]Biomedical Engineering, University of Michigan, Ann Arbor, MI, United States, [2]Electrical Engineering and Computer Science, University of Michigan, Ann Arbor, MI, United States, [3]Radiology, University of Michigan, Ann Arbor, MI, United States, [4]Mechanical Engineering, University of Michigan, Ann Arbor, MI, United States, [5]Neurology, University of Michigan, Ann Arbor, MI, United States*

## Synopsis

**Keywords:** White Matter, Alzheimer's Disease, Combined Diffusion Relaxometry

**Motivation:** There is a need for better characterization of white matter lesions in Alzheimer's disease and related disorders (ADRD) to distinguish between benign lesions and destructive lesions.

**Goal(s):** Evaluate the utility of diffusion-$T_2$ (D-$T_2$) 2-dimensional MR in characterizing white matter abnormalities in post-mortem ADRD samples.

**Approach:** We scanned a D-$T_2$ phantom (spin-echo D-$T_2$) and post-mortem ADRC brain samples (EPI D-$T_2$), then we computed their 2D spectras.

**Results:** We successfully validated our D-$T_2$ protocol with the phantom. D-$T_2$ spectra resolved tissue components of varying $T_2$ and diffusion values in normal and abnormal white matter, revealing more information than 1D diffusion tensor imaging ADC outcomes.

**Impact:** The D-$T_2$ phantom can serve as a standard for validating D-$T_2$ imaging protocols. Applying D-$T_2$ to assess ADRD lesions could allow for more disease-specific diagnostics with MRI.

## Introduction

White matter hyperintense lesions in $T_2$ weighted images of patients with Alzheimer's disease and related disorders (ADRD) are sensitive measures of tissue pathology but lack specificity and do not always correlate with disease severity. Incorporating diffusion with $T_2$ scans through combined diffusion relaxometry (D-$T_2$) and evaluating compartments not resolvable in 1D ($T_2$ or D) spectra has the potential to increase the specificity of MR measures of white matter pathology in ADRD.

## Methods

Phantom Construction: D-$T_2$ is an emerging technique, and how to best process and reconstruct this data is an active area of research. Thus we validated our D-$T_2$ technique prior to applying it to ex vivo ADRD lesions. Inspired by [1], we constructed a polyethylene glycol 3350 (PEG) gadobenate dimeglumine (Gd, Bracco) phantom with 15 NMR tubes with varying concentrations of PEG (to slow diffusion) and Gd (to shorten $T_2$) (Fig. 2). The tubes were capped and stabilized within an agarose gel-filled cylinder.

Ex Vivo Brain Samples: Michigan Alzheimer's Disease Center (MADRC) Brain Bank samples stored at −80° C were transferred to −20° C. Seven samples (~33×33×9 mm) were cut from the thawed brain tissue in a region containing both lesions and normal-appearing white matter (NAWM) based on pre-mortem $T_2$ FLAIR MRI scans.

MRI Scanning Protocol: Using a 7T Varian/Agilent animal scanner, the phantom was scanned with a diffusion-weighted spin-echo acquisition (12 TEs: 23-133 ms, 11 b values: 4-1825 s/mm$^2$) with uniform directional diffusion-encoding gradients (x,y,z). Tissue samples were scanned with three different EPI D-$T_2$ protocols (12 TEs: 50-161 ms, 11 b values: 1.6-2434 s/mm$^2$) each with a different directional gradient. Samples were scanned (TE 50 ms, b 2.4k s/mm$^2$) with a DTI sequence to 1) compare FA/ADC outcomes with [2] to assess tissue preparation methods and 2) compare DTI ADC (one-compartment) with D-$T_2$ (multi-compartment) outcomes. For lesion visualization, a fast spin-echo sequence was acquired (TR=4000ms, TE=40ms, ESP=10ms, matrix size=256×256).

Data Analysis: From the three directional EPI acquisitions ($SI_x$,$SI_y$,$SI_z$) , we used MATLAB to compute an apparent diffusion coefficient (ADC)-$T_2$ dataset[3] as follows:

$$(1) SI_{ADC} = \sqrt[3]{SI_x \times SI_y \times SI_z}$$

To resolve D-$T_2$ spectra from the phantom, lesion, and NAWM regions without assuming number of components a priori, a non-negative least squares algorithm with Tikhonov regularization (MATLAB) (2D inverse Laplace transform) was used to fit the average signal intensity ($SI_{ADC}$) per ROI.

From the DTI datasets, a diffusion tensor matrix was resolved individually for six lesions and NAWM ROIs. The eigenvalues of the tensor matrix were used to calculate the ADC values[4] and the FA values[4]. The means between the two groups for these parameters were compared using an unpaired t-test in GraphPad Prism. Additionally, ADC and FA maps were generated on a voxel-wise basis.

## Results

Phantom: The phantom's expected $T_2$ range (10 - 100 ms) and diffusion values (slow: 1x10$^{-5}$, fast: 1x10$^{-3}$ ) were similar to peaks observed in the 15 derived D-$T_2$ spectras. Co-analyzing two phantom tubes resolved the components from the individual spectras, demonstrating the technique's ability to define compartments that otherwise may be averaged together or overlooked (Fig. 1).

Ex Vivo Brain Samples: Figure 3 shows representative FA/ADC maps and a fast-spin echo image, illustrating changes between NAWM and lesions. DTI results (n=6, 1 lesion/NAWM ROI each) show trends similar to [2], suggesting high quality tissue preparation. Figure 4 displays ADC-$T_2$ plots for a representative sample, and Fig. 5 shows spectral trends across 15 ROIs. D-$T_2$ spectra plots were consistent with [2] (increased ADC and longer $T_2$ in lesions), and additionally revealed main spectral component shapes differed between lesions and NAWM. Restricted diffusing sub-compartments were observed.

## Discussion

The multi-compartment D-$T_2$ spectra help differentiate healthy and damaged white matter by 1) preserving ADC and $T_2$ trends observable with one-compartment analysis and 2) adding specificity through main spectral component analysis. In both the NAWM and lesions, a restricted diffusion component (hidden with just DTI ADC, which assumes one-compartment) appeared, possibly due to diffusion within the cells or outside/between myelin sheets perpendicular to fibers.

## Conclusion

The D-$T_2$ spectra accurately described compartments in phantom. In lesion and NAWM tissue, the spectra not only preserves expected outcomes, but may have potential to differentiate between destructive and benign ADRD lesions.

## Acknowledgements

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## References

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## Figures

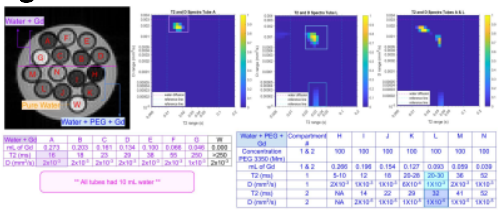

Figure 1. The D-$T_2$ phantom tubes A-G contained water, while tubes H-O had a mix of water and 100 mM PEG 3350 (for slower diffusion). The tubes were filled with varying concentrations of Gd, as detailed in the purple and blue tables. The same tables detail approximately measured $T_2$ and D values. The D-$T_2$ spectras of tubes A (Water + Gd) and L (PEG + Water + Gd) are shown. Assessing tubes A and L together (averaging signal intensities) reveals compartments overlooked in 1D.

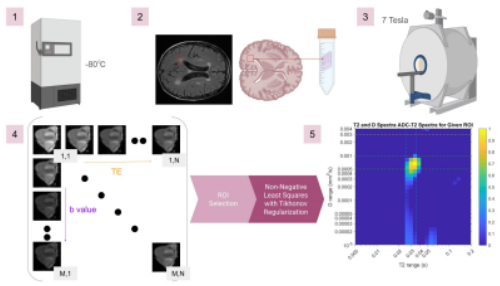


Figure 2. Ex vivo brain tissue workflow. 1) Three brain sections stored at -80°C were thawed to -20°C . 2) From each, 1-4 samples with lesions were cut (~ 33×33×9 mm). They were placed in histology cassettes and submerged in Fluorinert FC-770 (3M, St. Paul, MN). 3) The samples were scanned with the D-T2 protocol at 7T (Varian/Agilent). 4) An ADC-T2 SI dataset was derived. 5) We averaged signal intensity in an ROI, and applied the NNLS algorithm to obtain D-T2 spectra.

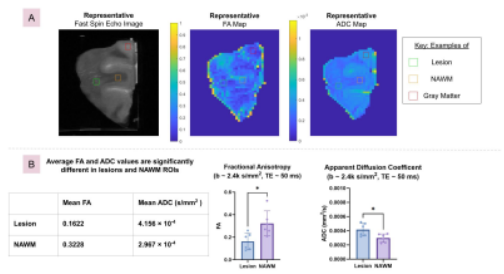


Figure 3. A conventional single-compartment DTI protocol[3] was used to assess tissue preparation quality and compare it with multi-compartment D-$T_2$ spectra. A) FA and ADC maps aligned with literature (lesions decreased FA and increased ADC)[2]. B) Average FA and ADC from six lesions and NAWM ROIs are summarized to compare with ADC-$T_2$ trends. An unpaired t-test showed statistically significant differences ($p < 0.05$) in mean FA/ADC between the groups.

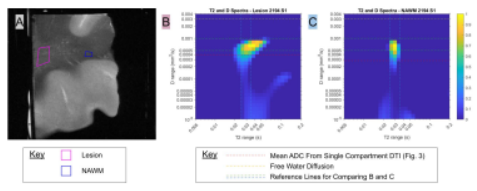


Figure 4. Representative lesion and NAWM spectra: A) Fast spin echo image used for lesion identification. B) Compared to NAWM, the lesion's main spectral component has longer T2, faster ADC, and is elongated and slanted. C) The NAWM main spectral component is condensed and circular. B&C) Similar to the PEG's slow diffusing component, these samples appear to have restricted diffusion. The DTI ADC values obtained were lower on average than the ADC value of the main spectral component.

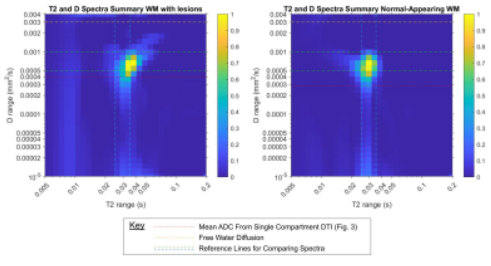


Figure 5. Summary ADC-$T_2$ spectra from averaging together the individually normalized spectra from 15 NAWM and 15 lesion ROIs. These summary spectra have similar trends as DTI and $T_2$ FLAIR analysis (lesions with increased ADC and $T_2$). In addition to presenting characteristics shared with one compartment DTI models, the differing main spectral component shape and sub-component locations may help distinguish between different populations of white matter.

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