# Advanced Diffusion Methods Proved More Robust Assessments of Microstructure than Standard DTI in Complex Human Brain Tissue

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**Target Audience:** Neuroimaging scientists and Diffusion imaging scientists.
**Purpose:** This study aimed to examine the robustness and sensitivity of non-mono exponential multi-tensor diffusion imaging derived parameters to microstructure of human autopsy tissue.
**Methods:** 1 x 2 x 3 $cm^3$ of human brain autopsy tissues were employed. Tissues were fixed in 10% neutral buffered formalin (Sigma-Aldrich, St. Louis, MO, USA). Prior to diffusion imaging all tissue were soaked in 1x PBS with 0.1% $NaN_3$ for two weeks at 4 °C. A lab house built RF coil, 4 cm length and 3 cm diameter, was employed as RF transmitter and receiver. Diffusion imaging was performed at 12 T magnet (Agilent Inc., Palo Alto, CA) with 120 G/cm gradient. All tissues were brought to room temperature for 12 hrs prior to MR measurement. Mono-exponential diffusion tensor imaging was conducted with b-value 4000 s/$mm^2$ and 30 non-collinear diffusion scheme[1]. Three spatial resolution diffusion maps were acquired, 0.4, 0.8, and 1.2 mm isotropic. For multi-tensor diffusion imaging generalized q-ball imaging (GQI) was conducted with maximum b-value 8000 s/$mm^2$ and 202 non-collinear diffusion scheme[2]. For non-mono exponential diffusion imaging diffusion kurtosis imaging (DKI)[3] was performed with 30 direction diffusion scheme[1] and 5 shells; b-value of 2000, 4000, 6000, 8000,and 10000 s/$mm^2$. Both GQI and DKI were acquired twice and the test-retest reproducibility was calculated as the mean of two measures divided by the difference of two measures, (Ave/Δ).

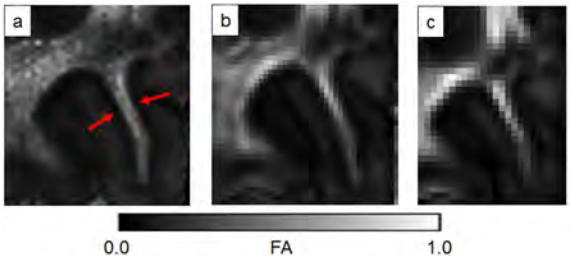


Figure 1. Fractional anisotropy map with three spatial resolutions: 0.4 (a), 0.8 (b), and 1.2 (c) mm isotropic. Diffusion weighted images were collected with b-value 4000 s/$mm^2$. and 30 non-collinear diffusion scheme known as Derek Jones 30. High spatial resolution diffusion map shows microstructure clearly like deep cortical layer axon shown dark in FA map, which is indicated by arrows.

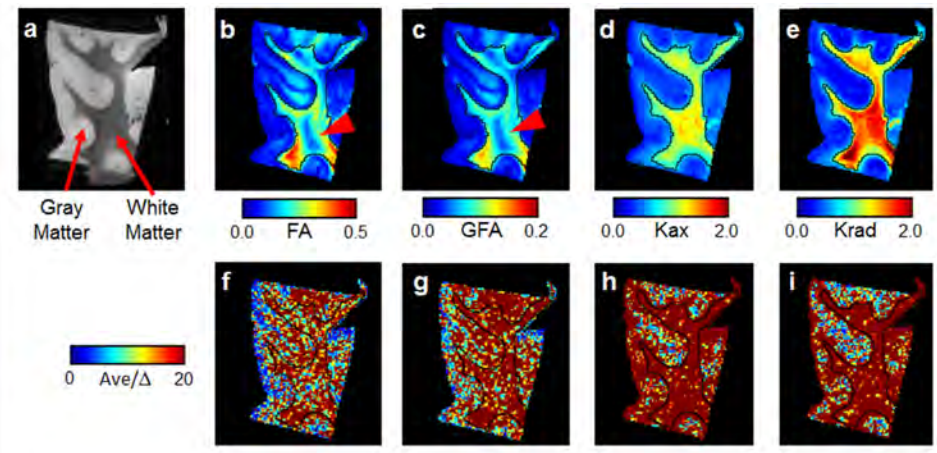


Figure 2. Diffusion parameter maps of fractional anisotropy (b, FA), generalized fractional anisotropy (c, GFA), axial kurtosis (d, Kax), and radial kurtosis (e, Krad). All maps have 0.31 x 0.31 x 0.5 $mm^3$ voxel size. The T2 weighted image is shown in panel a for anatomical reference. The black line delineates white matter. The reproducibility is quantified as mean of two measures (Ave) divided by the difference of two measures (Δ). The test-retest results are shown in panels f (FA), g (GFA), h (Kax), and i (Krad). Both non-mono exponential diffusion (Kurtosis) and non-single tensor (GFA) based diffusion parameters show better reproducibility than mono exponential single tensor based fractional anisotropy. The crossing fiber region indicated by arrow heads show low FA and GFA, which might be mistaken for axonal pathology. However, both kurtosis measures don't show this false positive signal.

**Results and Discussion:** Figure 1 shows Mono-exponential single tensor based diffusion tensor imaging derived fractional anisotropy with three spatial resolutions. It is apparent that the microstructure of complex brain tissue is better reflected with high spatial resolution. The GQI and DKI derived parameters and test-retest reproducibility maps having 0.31 x 0.31 x 0.5 $mm^3$ voxel size are shown in Fig. 2. The diffusion weighted images of GQI were also used to calculate fractional anisotropy. In general, the multi-tensor and non-mono exponential based diffusion parameters showed better reproducibility than mono-exponential single tensor based FA. In addition, GQI and DKI show highest reproducibility even at gray/white matter junction and gray matter region. Considering the frequently reported pathology at gray/white matter junction area, the GQI and DKI may provide sensitive examination on complex tissue pathology. Both FA and GFA show extremely low values in the centralwhite matter, which is a likely crossing fiber region. This could confound assessment of white matter injury, and it is a well known limitation of diffusion imaging. Interestingly, both axial and radial diffusion kurtosis maps do not have this limitation; central white matter kurtosis values are similar to those in other white matter regions.
**Conclusion:** The results clearly show that high spatial resolution diffusion image is beneficial for assessment of microstructure in anatomically complex brain tissue. Advanced diffusion imaging approaches such as non-mono exponential and multi-tensor diffusion imaging may provide biomarkersto detect subtle change in tissue that may not be apparent using standard diffusion tensor imaging. In addition, the test-rest based reproducibility provides an objective comparison of robustness among various diffusion imaging derived parameters. Kurtosis measures and GQI-based GFA appear more robust than DTI-based FA.

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