INTRODUCTION: Diffusion tensor imaging (DTI) is sensitive to WM degeneration caused by demyelination and axonal loss, hallmarks of both multiple sclerosis (MS) and Alzheimer’s Disease (AD). However, distinguishing demyelination from axonal loss with DTI is challenging, because they have similar effects on conventional DTI metrics such as the fractional anisotropy. Since demyelination, unlike axonal loss, may be reversible, a diffusion MRI method that differentiates between the two would be of potential clinical value. Recently, studies have shown that the non-Gaussian diffusion kurtosis imaging metrics to the characteristics of the WM microstructural integrity, including the axonal water fraction (AWF) and the tortuosity of the extra-axonal space (EAS). In this work, we establish for the first time that the AWF is most sensitive to axonal loss, while the EAS tortuosity is most sensitive to demyelination. For that, we performed Monte Carlo (MC) simulations in a realistic geometry for the corpus callosum.

METHODS: MC simulations: We generated an axonal geometry of parallel tubes with a mean diameter of 1 μm and diameter distribution similar to the human corpus callosum, Fig. 1(a). The so-called g-ratio of the inner to the outer axonal diameter (including the myelin sheath) was initialized at g=0.5. Neurodegeneration was modeled by either taking out axons (the mean axonal density from 0.44 axons/µm² to 0.27 axons/µm²), or by uniformly shrinking of the outer tube radius (demyelination) by increasing the g-ratio from 0.5 to 0.7. The AWF is defined as the volume ratio between the intra-axonal (red in Fig. 1(a)) and EAS (blue in Fig. 1(a)). The time-dependent diffusion coefficient \(D_g\) in the EAS was simulated for each geometry in \(C^+\) based on the dynamics of \(10^6\) random walkers. The tortuosity \(\alpha = D_g/D_{\perp}\) was defined as the ratio of the free diffusivity \(D_g(= 2 \text{ µm}^2/\text{ms})\) over the diffusivity perpendicular to the axons, \(D_{\perp}\), at 50 ms.

Clinical applications: Data from two clinical studies performed on a Siemens Tim Trio MRI scanner were selected for comparison with the numerical simulations: (1) 51 young subjects consisting of 32 patients with RR MS (8 male; mean age 29 ± 9 yrs, mean disease duration 3.6 ± 4.0; median expanded disability status scale (EDSS): 2.0) and 19 matched normal controls (NC) (6 male, mean age 36 ± 11.4); (2) 43 elderly subjects consisting of 14 patients diagnosed with probable AD (7 male; mean age 78±3; global deterioration scale (GDS) 4.2±0.4, mini-mental state exam (MMSE) = 22±3; education level 15±3), 15 subjects with mild cognitive impairment (MCI) (6 male; mean age 79±9; GDS 3±0.3; MMSE = 27±7; education level 15±3) and 14 NC (5 male; mean age 78±3; GDS 2±0; MMSE = 29±1; education level 16±3). Diffusion imaging was performed with 3 b-values (0, 1000 and 2000 s/mm²) along 30 diffusion encoding directions. WM parametric maps were derived as described in ref. 6 yielding maps for the AWF and tortuosity \(\alpha\). The MS analysis is restricted to normal appearing WM by removing all voxels in lesions. All parametric maps were transformed to a standard space using TBSS and average values of the AWF and tortuosity in the corpus callosum genu and splenium were derived based on the Johns Hopkins University WM label atlas for group comparisons.

RESULTS & DISCUSSION: Numerical simulations of the tortuosity as a function of the AWF are shown in Fig. 1(b) for varying axon number and g-ratio, revealing that the tortuosity decreases rapidly for increasing demyelination, while it is relatively unaffected by axonal loss. In fact, the tortuosity even increases initially when taking out fibers randomly, which can be explained qualitatively by the creation of lakes in which spins get locally trapped. On the other hand, the AWF decreases rapidly with axonal loss, but relatively slowly with demyelination. Hence, the AWF and tortuosity can be used to distinguish between axonal loss and demyelination, demonstrating the advantage of non-Gaussian diffusion metrics.

The distinction between axonal loss and demyelination is illustrated in Fig. 1(c) for the genu in MS patients compared to age-matched NC, and for the splenium in AD patients compared to MCI subjects and aged matched NC. As expected, a strong dependence of the AWF and tortuosity with age is observed (not shown), and the tortuosity and AWF are consistently higher in MS than in the genu, which is explained by the varying degree of myelination and axonal density across the corpus callosum. The change between the young NC and MS in both the AWF and tortuosity (Fig. 1(c) left) indicates that RR MS pathology is characterized by both axonal loss and demyelination, which agrees with postmortem histological studies. The change between elderly NC and MCI (Fig. 1(c) right) is larger in the tortuosity than in the AWF, suggestive of demyelination, while the change between MCI and AD is larger in the AWF than in tortuosity, suggestive of axonal loss as the more important neurodegenerative process for conversion from MCI into AD.

In conclusion, the MRI-measured EAS tortuosity and AWF are proposed as new biomarkers for demyelination and axonal loss respectively.