Diffusion MRI with q-vector magic angle spinning (qMAS) disentangles effects of micro-anisotropy and orientation dispersion

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Introduction: The fractional anisotropy (FA) obtained from diffusion tensor imaging (DTI) has become a valuable bio-marker in neuroscience and neuroradiology. However, the use of FA as an indicator of tissue damage, or integrity, is impeded by its low specificity. Although a lower FA in white matter (WM) can be attributed to demyelination, FA is also reduced with increasing amounts of fiber orientation dispersion [1]. The low FA resulting from high orientation dispersion is evident in regions of crossing fibers, and at the interface between major WM tracts, but substantial dispersion is present in at least 90% of the WM [2]. Therefore, a metric of diffusion anisotropy that is unaffected by orientation dispersion would be a valuable addition to the FA.

The purpose of this study was to establish and measure such a metric, here called the microscopic fractional anisotropy (μFA), and to investigate its relation to DTI-FA.

Theory: Recently, Eriksson et al. [3] showed that spinning the q-vector at the magic angle (qMAS) allows time-efficient isotropic diffusion encoding. By combining conventional single-pulsed-field-gradient (sPFG) diffusion encoding with qMAS, the microscopic anisotropy of tissue can be probed. For example, a measurement on a system with isotropic cells will yield identical signal curves for sPFG and qMAS, while a system containing anisotropic micro-domains will yield a signal curve with a higher degree of non-Gaussianity (kurtosity) for the sPFG compared to the qMAS encoding. We suggest that the μFA can be calculated by using the following equations:

$$E(b) = \left(1 + b\frac{\mu_2}{\overline{D}}\right)^{-\frac{\overline{D}^2}{\mu_2}} \quad (1) \qquad \mu\text{FA} = \sqrt{\frac{3}{2}}\sqrt{\frac{\mu_{2,\text{sPFG}} - \mu_{2,\text{qMAS}}}{\mu_{2,\text{sPFG}} - \mu_{2,\text{qMAS}} + 2/5 \cdot \overline{D}^2}} \quad (2)$$

Equation 1 is the Laplace transform of the gamma distribution function, where $\overline{D}$ is the mean diffusivity and μ_2 is the second moment of the underlying distribution of diffusion coefficients, denoted as $\mu_{2,\text{sPFG}}$ and $\mu_{2,\text{qMAS}}$ when fitted to signal measured with sPFG and qMAS techniques, respectively. The μFA is then calculated according to Eq. 2. Under the assumption that the anisotropy in tissue is caused by cylindrically symmetric micro-domains with Gaussian diffusion [1], μFA describes the average FA of all these micro-domains. Thus, μFA is a close analogue to FA but is unaffected by the orientation dispersion of the WM. This means that the μFA in unidirectional and crossing WM is expected to exhibit high values, unlike the FA which is expected to be lower in the crossing WM due to the lower coherence of the fibers.

Methods: Scanning was performed using a Philips Achieva 3T system equipped with an 80 mT/m gradient system. Two sets of data were acquired, using first the sPFG sequence employing trapezoidal encoding blocks, and second, using isotropic encoding achieved by qMAS [3, 4]. The sPFG was acquired in six directions while the qMAS was repeated six times. Five axial slices were acquired, centered on the corpus callosum, at a spatial resolution of 3×3×3 mm^3, and sixteen *b*-values, between 50 and 2800 s/mm^2. The echo time was 160 ms, and the repetition time was 2000 ms. Total acquisition time was 6:40 min. Quantification of μFA was performed using Eq. 1 and 2. Standard DTI analysis was also performed on the sPFG data in order to generate FA maps. Three ROIs were defined in regions of unidirectional WM, crossing WM, and peripheral GM, in order to show the distribution of parameters in regions with varying levels of orientation dispersion and different types of micro-domains.

Results: The qMAS technique was successfully implemented on a clinical scanner and the FA and μFA maps were calculated. The μFA map corresponds well to known WM morphology. In contrast to FA, μFA exhibits high values in all WM regions, including crossing WM and interfaces between major tracts (Fig. 1). The mean values and standard deviations of FA and μFA in the three ROIs are detailed in Table 1.

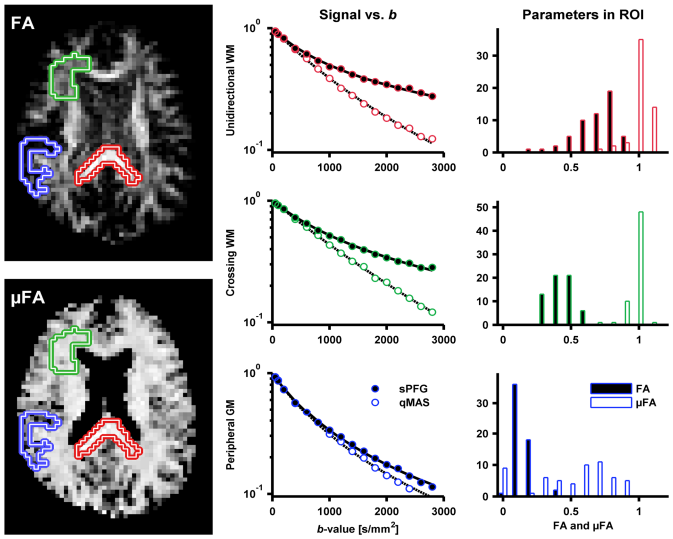

Figure 1. The figure depicts FA (top left) and μFA (bottom left) maps. Three ROIs were defined; unidirectional WM (red), crossing WM (green), and peripheral GM (blue). The central column features the mean signal from all voxels in each ROI, and the corresponding model fit. The initial slope is equivalent to $\overline{D}$, and the curvature (kurtosity) is parameterized as μ_2. The right column shows the distribution of the parameters in the ROIs. The FA is the highest in the unidirectional WM, and lower in regions of crossing WM. The μFA in WM is consistently high, while it is lower in the GM. As expected, the FA in the peripheral GM is close to zero, while the μFA is non-zero, indicating that there are anisotropic micro-domains in the GM tissue.

Table 1. The table contains the values for μFA and FA, quantified in three ROIs in the brain (see Fig. 1), represented as mean values and one standard deviation from the mean (for each ROI).

	Unidirectional WM	Crossing WM	Peripheral GM
FA	0.69 ± 0.15	0.44 ± 0.09	0.14 ± 0.06
μFA	1.01 ± 0.08	0.97 ± 0.06	0.51 ± 0.28

Discussion: In this work we present a novel measure of microscopic anisotropy that is based on sPFG and qMAS diffusion encoding, and its application in one healthy volunteer. The resulting μFA map is homogeneous and exhibits high values of microscopic anisotropy in regions of WM (Fig. 1 and Table 1). This result is in accordance with the findings of Lawrenz and Finsterbush, who also mapped microscopic anisotropy using a double-PFG sequence [5]. As expected, the contrast found in the FA map is substantially different, exemplified by lower values of FA in regions of crossing WM compared to unidirectional WM. Taken together, these results suggest that the micro-domains in various WM regions are similar with respect to their anisotropic micro-domains. More strikingly, this also raises the question whether or not the contrast in FA is mainly driven by the coherence of the WM fibers? Since μFA is not zero in peripheral GM, this parameter also holds promise as a bio-marker in tissues that are isotropic on the voxel scale. However, examination of the GM demands that the spatial resolution is improved in order to avoid strong partial volume effects.

In conclusion, this work presents the first implementation of qMAS in vivo. The results indicate that variations in the FA map mainly reflect variable degrees of orientation dispersion rather than differences in the underlying anisotropy of the microstructure. Mapping the μFA disentangles the effects of orientation dispersion and microstructure, possibly rendering a bio-marker with superior specificity compared to conventional FA.

References: **[1]** Zhang, H. et al. (2012) *NeuroImage: 61.* **[2]** Jeurissen, B. et al. (2013) *Hum Brain Mapp*: 34. **[3]** Eriksson S. et al. (2013) *J Magn Reson: 226.* **[4]** Topgaard D. (2013) *Micropor Mesopor Mat: 178.* **[5]** Lawrenz M. and Finsterbusch J. (2013) *Magn Reson Med: 69.*