Demyelination versus increased free water in schizophrenia: A pilot study using q-space trajectory imaging

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Introduction – Higher order moments of the diffusion propagator contain important microstructure information. In this work, we estimate the second and fourth moments, i.e. the mean (2nd order tensor) and the covariance (4th order tensor) of a distribution of tensors [1]. Estimation of the covariance tensor was enabled by q-space trajectory imaging (QTI), but is impossible using conventional diffusion encoding [1]. We explore novel invariant scalar quantities of the 4th order tensor, and compare these between schizophrenia patients and healthy controls in order to investigate primary mechanism behind diffusion changes observed in schizophrenia [2].

Theory – Consider a collection of microenvironments, where the diffusion in each environment is described by a diffusion tensor. These microenvironments can be modeled with a distribution over tensors, where the tensor $\mathbf{D}$ is a stochastic variable with expectation $\langle\mathbf{D}\rangle$. The covariance of $\mathbf{D}$ is given by a 4th order tensor, $\underline{\mathbf{S}}$ [3]. The cumulant expansion of the MR signal in this scenario reveals a key relationship [1]

$$E(\mathbf{B}) \approx \exp\left(-<\mathbf{B},\langle\mathbf{D}\rangle>+\frac{1}{2}<\mathbf{B}\otimes\mathbf{B},\underline{\mathbf{S}}>\right) \qquad (1)$$

where $\mathbf{B}$ is the b-matrix, $\otimes$ denotes tensor outer product, and $<\cdot,\cdot>$ denotes the inner product. The tensor $\underline{\mathbf{S}}$ is superficially similar to that obtained in diffusional kurtosis imaging (DKI), however, estimating the full structure of $\underline{\mathbf{S}}$ requires data obtained using b-matrices of rank 2 or 3, which we achieve by performing diffusion encoding with complex gradient waveforms. By contrast, conventional pulsed field gradient encoding yields b-matrices of rank 1. Inspired by the definition of the bulk and shear modulus of the fourth-order stiffness tensor [1,4], we convert $\underline{\mathbf{S}}$ to scalars by taking the inner product with the corresponding isotropic 4th order tensor, according to

$$\text{BULK} = <\underline{\mathbf{S}}, \mathbf{E}_{\text{iso}}\otimes\mathbf{E}_{\text{iso}}> \qquad \text{SHEAR} = <\underline{\mathbf{S}}, \tfrac{1}{3}\underline{\mathbf{I}}-\mathbf{E}_{\text{iso}}\otimes\mathbf{E}_{\text{iso}}> \qquad (2)$$

where $\mathbf{E}_{\text{iso}} = \mathbf{I}/3$, and $\mathbf{I}$ and $\underline{\mathbf{I}}$ are the second and fourth order identity tensors, respectively. Since $\underline{\mathbf{S}}$ is a covariance tensor, the BULK and SHEAR parameters relate to variance in diffusivity of isotropic and anisotropic tissue components. Fractional anisotropy (FA) was obtained from $\langle\mathbf{D}\rangle$ in the usual way, and mean diffusivity by MD = $<\langle\mathbf{D}\rangle, \mathbf{E}_{\text{iso}}>$.

Methods – MRI was performed using a Philips Achieva 3T system, in 20 slices at a spatial resolution of 3×3×3 mm^3 with TE/TR = 160/6000 ms/ms, and with b-matrices of four different shapes: linear, prolate, spherical and oblate. Spherical b-matrices were obtained by spinning the q-vector at the magic angle (qMAS) [5]. The remaining shapes were obtained by modifying the qMAS gradient waveforms [1]. In total, 216 diffusion-weighted volumes were acquired, for b-values (i.e. trace of the b-matrix) of 50, 250, 500, 1000 and 2000 s/mm^2. The primary eigenvector of the b-matrix was rotated according to icosahedral, dodecahedral and truncated icosahedral directional schemes in varying combinations. Total acquisition time was 25 minutes. Estimates of $\langle\mathbf{D}\rangle$ and $\underline{\mathbf{S}}$ were obtained by linear regression.

Five schizophrenia patients and five age-matched healthy controls were investigated. Informed written consent was obtained. All patients met the DSM-V criteria for schizophrenia (295.90), disease duration between 5 and 12 years (median of 10 years), and median symptom severity score 55 according to the Positive and Negative Syndrome Scale, range 42–71, at the time of MRI. FA maps were registered to MNI space using FNIRT. ROIs for global white matter (WM) and cortical gray matter (GM) were defined in template space using the Harvard-Oxford atlas and projected to subject space to extract values for analysis.

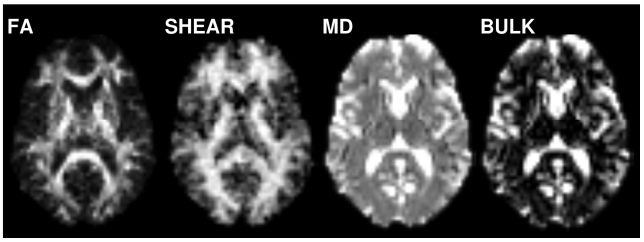

Figure 1. QTI-maps. Notice the high values of shear in regions of crossing fibers, and the correspondence between MD and BULK.

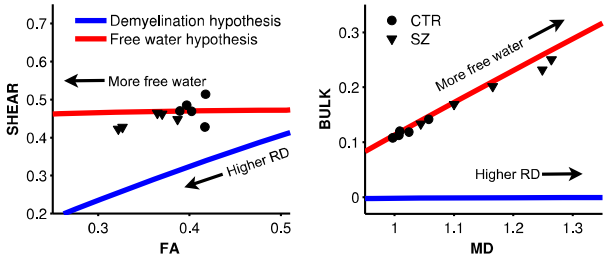

Figure 2. Scatter plots of SHEAR vs. FA and BULK vs. MD. Data points obtained by averaging across cerebral white matter. FA and SHEAR were weakly correlated, but MD and BULK were strongly correlated. Solid line shows results from analysis of data simulated to represent a demyelination hypothesis, i.e. increasing radial diffusivity (blue), a free-water hypothesis, i.e. replacing WM with isotropic freely diffusing water (red).

Table 1. QTI parameter mean (SD), in controls (CTR, n = 5) and schizophrenia patients (SZ, n = 5), in white and grey matter (WM/GM).

	CTR (WM)	SZ (WM)	CTR (GM)	SZ (GM)
FA	0.41 (0.01)	0.35 (0.03)*	0.15 (0.01)	0.15 (0.01)
SHEAR	0.47 (0.03)	0.45 (0.02)†	0.22 (0.01)	0.22 (0.01)
MD	1.02 (0.02)	1.17 (0.09)*	1.06 (0.02)	1.10 (0.03)
BULK	0.12 (0.01)	0.20 (0.05)*	0.16 (0.01)	0.18 (0.02) †

* $p < 0.05$ † $p < 0.1$ (U-test)

Previous studies suggest that two separate pathologies dominate changes seen in schizophrenia by diffusion MRI [2]: cellular pathology (likely demyelination) and increased levels of extracellular free water (attributed to atrophy or to neuroinflammation). We test these hypotheses by comparing analysis of simulated data with average WM data. For demyelination, we simulated measurements on a group of dispersed fibers with varying radial diffusivity (RD) while keeping the axial diffusivity (AD) fixed (AD = 2.1 μm^2/ms, RD = 0.2 → 1.6 μm^2/ms), inspired by [6]. For the free water hypothesis, we simulated measurements on fibers with AD = 2.1 μm^2/ms and RD = 0.2 μm^2/ms being gradually replaced with isotropic water with MD = 2.8 μm^2/ms.

Results and discussion – Figure 1 shows the two anisotropy-related FA and SHEAR maps, and the two mean-diffusivity maps MD and BULK. The SHEAR map exhibited high values in white matter, also in regions where FA was reduced due to crossing fibers; SHEAR appears sensitive to fiber anisotropy while FA is sensitive to voxel-level anisotropy. Across subjects, FA and SHEAR covaried weakly, whereas MD and BULK correlated strongly (Fig. 2). The data from average white matter did not agree well with the predictions of the demyelination hypothesis (blue lines), here modeled by a coherent increase in the radial diffusivity of fibers. For the free water hypothesis, however, here modeled by replacing fibers with an isotropic diffusion component, the agreement was good (red lines). Finally, Table 1 shows a comparison of parameters between controls and patients with schizophrenia. In the patients, lower FA and higher MD were observed in the white matter. A similar effect was observed in SHEAR and BULK, although only borderline significant for SHEAR. No significant differences were found in the GM on the 0.05 level.

Conclusions – To our knowledge, this is the first application of QTI in a pilot study on patients, which demonstrates that the approach is feasible in a clinical in-vivo setup and can generate new observations. By comparing QTI and DTI measures from the subjects with those obtained from simulations of two different pathologies, we were able to show that diffusion changes occurring in schizophrenia are best explained by an increasing fraction of free water. This suggests that increased levels of extracellular water, e.g. due to chronic neuroinflammatory processes or atrophy, is the primary mechanism explaining white matter diffusion changes in our cohort of patients with chronic schizophrenia. However, further studies with larger sample sizes are needed to validate this finding.

References – [1] Westin., et al. MICCAI. 2014, 209-16. [2] Pasternak et al., Neurosci. 2012, 32, 17365–17372 [3] Basser and Pajevic, Sig Proc 2007, 87:220-236 [4] Moakher, J Mech App Math 2008, 61:181-203 [5] Topgaard. Microporous Mesoporous Mater 2013, 178:60-63 [6] Song et al NeuroImage 2002, 17:1429–1436