Detection of Microscopic Diffusion Anisotropy in the Living Human Brain

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Diffusion anisotropy measures derived from diffusion-tensor imaging (DTI) reflect a mixture of two tissue properties: (i) the eccentricity of the cells and (ii) their orientation distribution within the voxel. This ambiguity hampers the informative value of such measures. For instance, a vanishing fractional anisotropy (FA), e.g. in brain white matter, is consistent with the absence of eccentric cells like neurons but also with a uniform orientation distribution of eccentric cells, e.g. neuronal fibers. Double-wave-vector (DWV) diffusion-weighting experiments [1] where two diffusion weighting periods are applied successively with a long mixing time in-between (see Fig. 1), offer access to the diffusion anisotropy present on a microscopic, i.e. cellular, level [1-3]. This has been demonstrated for tissue samples (e.g. [4]) and various model systems (e.g. [5,6]) on small-bore systems and, recently, also on a whole-body MR system [7].

In this study, it is shown that the underlying signal difference between parallel and orthogonal wave vector orientations can be observed in the living human brain. In particular, it is shown that this signal difference in white matter is independent of the macroscopic FA value and is also present in a region-of-interest (ROI) with vanishing FA. Thus, the signal difference could lead towards a reliable measure of white matter or neuronal integrity without the disturbing influence of fiber orientations.

Methods

Experiments were performed on a 3T whole-body MR system (Siemens Magnetom Trio) with a 12 channel receive-only head coil. Healthy volunteers were investigated after their informed consent was obtained. Measurements were performed with echo-planar imaging with a single refocusing RF pulse (Fig. 1) and a resolution of 3.0×3.0×3.0 mm^3 (TE / TR = 155 ms / 6 s) covering 20 slices. The two diffusion-weighting periods were applied with a *b* value of 500 s mm^{-2} each, a diffusion time Δ of 31 ms, and a mixing time τ_m of 48 ms.

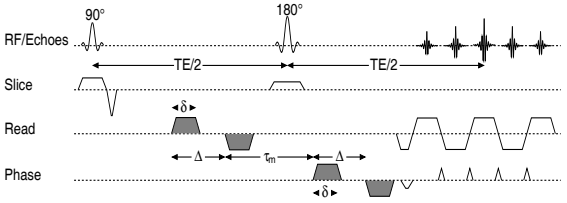

Fig. 1: Basic pulse sequence used in the present study.

Two different direction combination schemes for the first and second wave vector were used for the DWV experiments: (i) all 3×144 = 432 combinations of 12 equidistant directions (30° steps) in three orthogonal planes in order to investigate the signal modulation with the relative angle between the two wave vectors (one average, 32 min acquisition time) and (ii) 16 combinations in each of the three coordinate planes (48 combinations in total) that covered all combinations of the four planar diagonals, i.e. parallel (4 combinations in each plane/12 combinations in total), antiparallel (4/12 combinations) and orthogonal combinations (8/24 combinations) only (4 averages, 15 min). DTI acquisitions were performed with the 12 parallel combinations of the latter scheme (four averages, 4 min). For these acquisitions (color-coded) FA maps were calculated with an algorithm provided by the manufacturer.

400 voxels in the centrum semiovale were considered that were determined using a pixel intensity range defined of the non-diffusion-weighted images and a threshold FA value of 0.3 for the DTI acquisition. The signals of these voxel were accumulated with different weighting factors to obtain a mean signal that exhibits different anisotropy properties. Averaging all voxels with an identical weighting yielded a high FA value of 0.48 ("ROI I"). By modifying the weighting factors of the voxels, mean signals with lower FA values could be obtained. In particular, by solving a corresponding linear equation system, weighting factors could be determined for which the averaged signal has a vanishing FA ("ROI II") although all voxels contributing had a minimum FA of 0.3. Thus, ROI II can be considered to represent a (large) voxel that due to fiber orientation heterogeneity is macroscopically isotropic but on a sub-voxel level exhibits a pronounced anisotropy that is not reflected in the FA.

Results and Discussion

Figure 2 demonstrates that the signal difference between parallel/antiparallel and orthogonal wave vectors can be detected in white matter of the living human brain. The signal modulation with the angle θ between the two wave vectors is consistent with the cos2θ dependency expected from the theory [1,3] and observed in previous phantom studies [4,6,7]. In Fig. 3, the weighting factors for the two determined ROIs are presented together with a color-coded FA map derived from a DTI acquisition. The signal intensities of the two ROIs in the DTI and the DWV experiment (48 combinations) are presented in Fig. 4. In ROI I, there is a pronounced dependency of the signal amplitude on the actual orientation(s) of the wave vector(s) which reflect the high macroscopic anisotropy (FA 0.48). For ROI II, only noise-like signal variations are observed in the DTI experiment because its FA is 0.0. In the DWV experiments there is a significant difference between parallel/antiparallel and orthogonal wave vectors in both ROIs which demonstrates the presence of diffusion anisotropy on a microscopic level. In particular, this signal difference can also be observed in ROI II which is macroscopic isotropic, and is almost identical to that of ROI I.

Thus, DWV experiments may provide a reliable access to the diffusion anisotropy on a microscopic level that is independent of the orientation distribution of the cells and could be used to characterize white matter or neuronal integrity without the disturbing influence of fiber orientations.

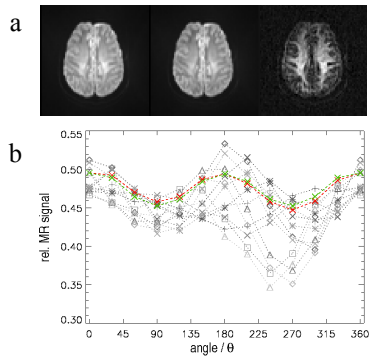

Fig. 2: Results of the DWV experiment with the 12×12 combination scheme. (a) Averages of all parallel/antiparallel, all orthogonal directions, and the difference image (from left to right). (b) MR signal vs. the angle between the two wave vectors.

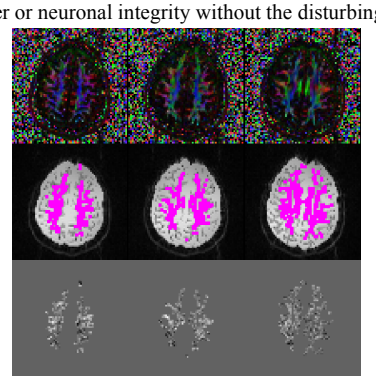

Fig. 3: Color-coded FA maps determined from the DTI acquisition (upper), voxels included in the ROIs overlaid on a non-diffusion-weighted image (middle), and relative weighting factors used for ROI II which has a vanishing FA value.

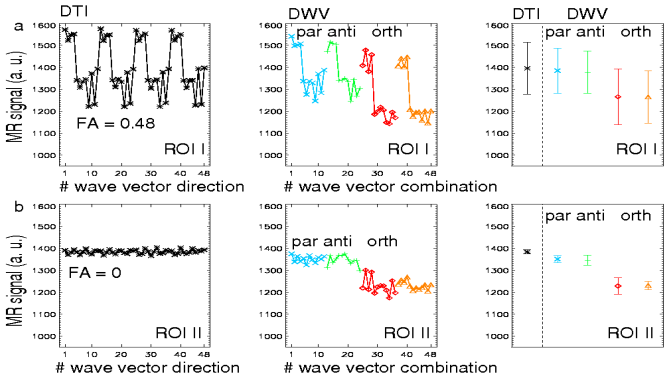

Fig. 4: Mean MR signals in ROI I (upper) and ROI II (lower) in DTI (black) and DWV experiments (colors, 48 combinations) vs. the wave vector orientations (left/middle) and averaged over all orientations (right, with standard deviation). The 48 samples of the DTI experiment reflect four averages of the 12 directions. The colors for the DWV experiment encode for parallel (blue), antiparallel (green), and orthogonal wave vectors (red, orange), respectively.

References

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