Reproducibility and Normal Values of Microscopic Diffusion Anisotropy Measures and Their Variation in Healthy Volunteers

Marco Lawrenz[1,2] and Juergen Finsterbusch[1,2]

[1]*Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Hamburg, Germany,* [2]*Neuroimage Nord, University Medical Centers Hamburg-Kiel-Luebeck, Hamburg-Kiel-Luebeck, Hamburg-Kiel-Luebeck, Germany*

Double-wave-vector diffusion-weighting (DWV) or double-PFG experiments [1] in which two diffusion weighting periods are applied successively in a single acquisition (Fig. 1), have been shown to offer access to tissue properties on a microscopic scale [1-3]. Of particular interest is the signal modulation that can occur when varying the angle between the two diffusion weightings [1]. With a short mixing time τ_m in-between it can be used to estimate cell or compartment sizes [1, 4], for a long τ_m it reflects diffusion anisotropy present on a microscopic scale [1]. The latter effect has been used to demonstrate the presence of anisotropic diffusion in vivo in a white matter region-of-interest that appeared isotropic in a DTI experiment, i.e. has a fractional anisotropy (FA) equal to 0 [5]. Thus, DWV experiments may help to unravel the microstructural background of FA differences or changes, e.g. by distinguishing a reduced axon density and a less coherent axon orientation distribution which both would result in a lowered FA.

For a reliable application of such DWV experiments, a rotationally invariant measure of the microscopic diffusion anisotropy, the MA index, has been proposed [6]. Recently, first measurements of the MA index in human brain white matter in vivo have been reported at a single subject level [7]. In this study, as a prerequisite for applications in clinical studies or neuroscientific research, normal values in typical WM structures and their variation in a group of healthy volunteers as well as the reproducibility of MA measurements within and between sessions are investigated.

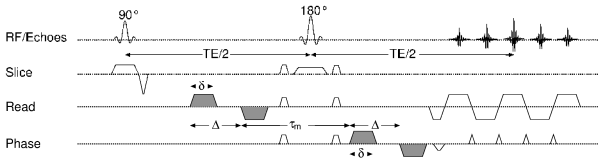

Fig. 1: Basic DWV pulse sequence with EPI readout used in the present study.

Methods

Experiments were performed on a 3T whole-body MR system (TIM Trio, Siemens Healthcare) with a 32-channel head coil. 18 young, healthy volunteers (18–32 y) were investigated after their informed consent was obtained. Measurements were performed with spin-echo echo-planar imaging (Fig. 1) using an isotropic resolution of 3.0 mm (TE/TR = 150 ms/6.5 s) and covering 35 slices (gap 0.5 mm). The two diffusion-weighting periods were applied with a *b* value of 500 s mm^{-2} each, a diffusion time Δ of 25 ms, a mixing time τ_m of 45 ms and a gradient pulse duration δ of 22 ms. 96 combinations of 18 directions of the diffusion weighting were performed [7]. With six images without diffusion weighting acquired in-between the total acquisition time was 11 min 10 s. Four MA measurements, a standard DTI experiment (60 directions, TE/TR = 100 ms/4.8 s), and a T1-weighted anatomical measurement (MPRAGE, voxel size 1x1x1mm^3) were performed in each session (≈1h). Two sessions on different days were performed for each volunteer. Data processing steps included motion-correction, coregistration and DARTEL [8] normalization performed with SPM08.

Results and Discussion

Results for the reproducibility between sessions for a single subject are shown in Fig. 2. Within a session, the reproducibility of the MA is very high, only in the lower temporal lobe where EPI suffers from susceptibility artifacts, some significant deviations are present. Between sessions, more variations are observed, in particular for the MA maps. This not only affects the lower temporal lobe but the MA seems to be more variable in general. However, with absolute values of 0.048 +/- 0.028 for a single and 0.016 +/- 0.001 for the average over all volunteers, respectively, there is only a minor systematic offset from zero for a typical WM region-of-interest. Normalized MA and FA maps averaged over all 18 volunteers are presented in Fig. 3. While FA values vary significantly in white matter depending on the actual fiber orientation distribution, MA values appear to be more homogenous (see also Table 1). MA values are generally larger. Even in regions known to have a significant amount of crossing fibers, the MA values are very similar to those found, e.g., in corpus callosum (see Table 1). This is consistent with the expectation that the MA, in contrast to the FA, is independent of the actual fiber orientation in a voxel. The variation of the MA values between volunteers is not very pronounced, the typical standard deviation for a white matter voxel was about 5-7%.

Conclusion

DWV experiments offer a reliable access to the diffusion anisotropy on a cellular or microscopic scale in human brain white matter in vivo. The information obtained is complementary to that of DTI and could help to characterize white matter tissue microstructure and integrity in the healthy and pathologic brain.

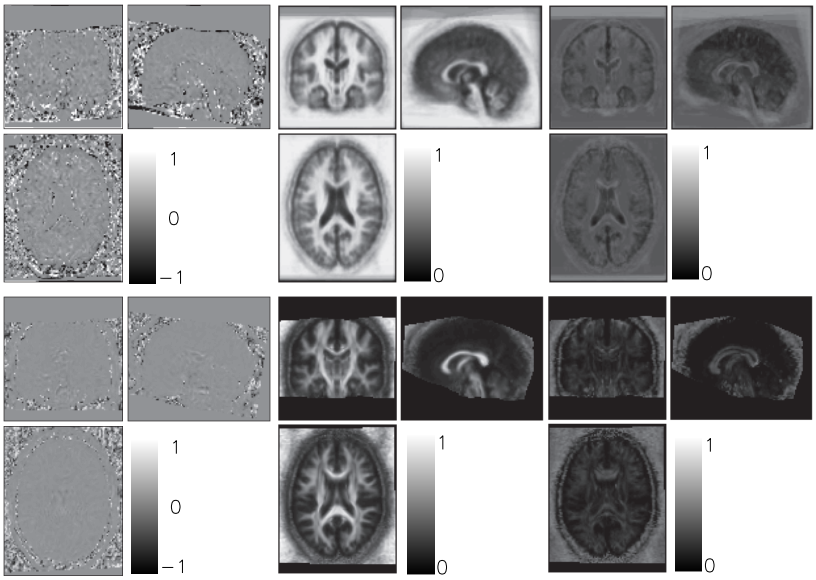

Fig. 2: Cross sections (cor, sag, tra) of the difference of MA maps (day 1 –day 2) for one volunteer (upper) and averaged over 18 volunteers (lower).

Fig. 3: **A**verage (left) and standard deviation (right) of MA (upper) and FA maps (lower) in 18 healthy volunteers. While the FA map exhibits low values in regions with fibre crossings, the MA map overall appears smoother. See text for details.

	FM	PLIC	SCC	P	GP	CR
FA [9]	0.500 ±0.047	0.714 ±0.049	0.775 ±0.052	0.121 ±0.028	0.233 ±0.046	0.53 ±0.069
FA	0.478 ±0.057	0.644 ±0.049	0.882 ±0.046	0.140 ±0.047	0.227 ±0.028	0.530 ±0.101
MA	0.740 ±0.049	0.997 ±0.017	0.804 ±0.127	0.588 ±0.074	0.789 ±0.172	0.841 ±0.081

Tab. 1 FA and MA values in several anatomical regions-of-interest obtained from ref. [9] (upper) and this study (F=forceps minor, PLIC=posterior limb of internal capsule, SCC=splenium of corpus callosum, P= putamen, GP=globus pallidus, CR= corona radiata)

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