Voxel-Based Correlation Analysis between Diffusion Anisotropy Measures and Myelin Content in Human Brain

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Introduction: An important objective in current MRI research of white matter degenerative diseases with deterioration of myelin structure and function is to find more sensitive and specific markers of the biological effects of the disease as well as to better monitor disease progression and response to treatment with improved differentiation of specific tissue pathologies. Despite much recent effort in imaging technology, there is currently no non-invasive modality capable of assessing myelin and its integral components explicitly. However, a number of MR techniques are available that attempt to study myelin by indirect methods, e.g. diffusion, magnetization transfer, ultra-short echo imaging, multi-component relaxation measurements, and spectroscopy. While a number of these techniques claim to be sensitive to myelin it is not clear how they compare in their capability to characterize changes in the microstructure and integrity of myelin. Our aim in this study was to investigate the correspondence of two of those proposed techniques: multi-component T_2-relaxation and diffusion tensor imaging (DTI) in normal volunteers. We present a novel voxel-based analysis (VBA) method of correlating myelin-water fraction (MWF) with diffusion anisotropy measures.

Methods and Analysis: Measurements were performed on a Philips Achieva 3.0T using a phased-array eight-element, six channel receive head coil and gradients with 66 mT/m amplitude, maximum slew rate of 200 T/m/s on a group of 6 (2 men and 4 women, mean age 25.7 years, ranging from 21 to 30 years) healthy volunteers. The multi-echo 3D-T2-sequence (3D-ME-TSE) was based on work recently published [1]. It uses tailored RF-refocusing pulses with a variable refocusing angle sweep to reduce the effects of stimulated echo while maintaining good slab-excitation profile and low SAR. The start angle of the refocusing pulse train was optimized on a large spherical phantom prior to the in-vivo measurements. The rest of the imaging parameters were as follow: acquisition matrix 256x128, 32 echoes at TE=10ms spacing, TR=1200 ms, receiver bandwidth=89 kHz, NSA=1, k-space under-sampling=0.75, 7 slices at 5 mm thickness. The deconvolution of the multi-echo decay curve into multiple T2-components was achieved by using a regularized NNLS-algorithm with the maximum χ^2 misfit between 1.010 and 1.02. The myelin-water fraction (MWF) was determined from the entire T2-distribution as the T2-distribution integral between 12 and 40ms divided by the entire integral [2].
Diffusion measurements were carried out by means of a single shot pulsed-field gradient Spin Echo EPI sequence with a phased-array coil that allowed the use of parallel imaging technology (SENSE-factor=2.0) to reduce the echo train length and therefore keep the susceptibility artefact level moderate in spite of the high static magnetic field. The scan parameters were: FOV=240mm at an acquisition matrix of 128 x 96 and a slice thickness of 5mm. TE=53ms resulting in a gradient duration of δ=14 ms with a resulting observation time of Δ=24.5 ms. No cardiac or peripheral gating was necessary to obtain high SNR diffusion weighted data sets. 13 slices were acquired for DTI with 2 b-values (0, 800 s/mm^2) and position matched to the T_2 experiment's slice location. 16 non-colinear gradient directions including one b=0 image (Philips proprietary implementation) with 2 averages were performed resulting in a scan time of 2min. Fractional anisotropy (FA), linear diffusivity, parallel and perpendicular diffusivity (ADC||, ADC$\perp$) were used as representations of invariant diffusion anisotropy.

Results: Some degree of correlation between MWF and specifically FA as well as the perpendicular diffusivity ADC$\perp$ could be verified, but some structures did not exhibit a significant linear correlation between MWF and DTI quantities. Fig.1 summarizes the ROI-based correlation between FA and MWF for all 11 investigated brain structures. The graph in Fig.2 shows one example of voxel-based correlation between FA and MWF from an entire slice (same position as for the ROI-based analysis) which confirms the findings of the ROI-approach but exhibits a much stronger linear correlation coefficient. This significant correlation changes and under certain conditions completely vanishes when the VBA is restricted to only certain WM- or GM-structures. Fig.3 shows an example of a qualitative comparison between FA (left) and MWF (right) for the same slice location in the brain indicating local correspondence as well as differences between myelin content and diffusion anisotropy.

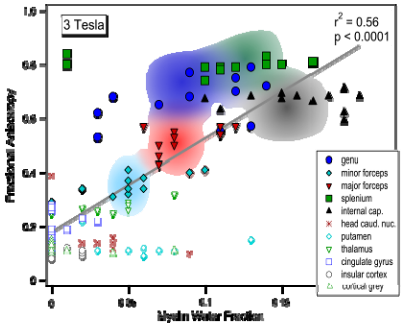

Fig.1: DTI-based fractional anisotropy (FA) versus myelin water fraction of the eleven investigated white and grey matter structures and their individual ROI-measures (6 subjects, left and right hemisphere).

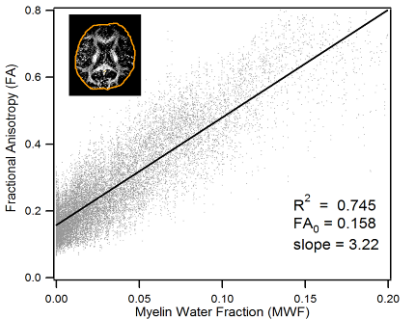

Fig.2: Voxel-based correlation of FA and MWF for an entire slice of the axial midbrain area through genu and splenium of the corpus callosum. All pixels inside the orange ROI (inset) were included in the analysis. All pixels outside the ROI were discarded.

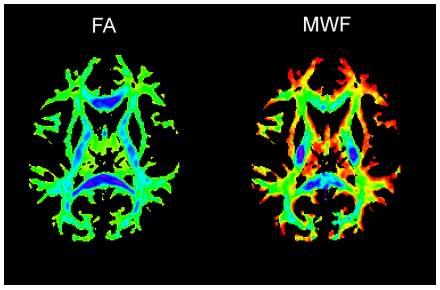

Fig.3: False colour representations of FA-map (left) and myelin-water map (right) from the same subject and location in the midbrain to resemble the similarities and differences between both analytical quantities. The FA-map was thresholded between 0.2 – 1.0 to produce an image mask which was consequently applied to both data sets.

Conclusion: The results confirm that while myelin may certainly contribute to diffusion anisotropy, it is not a necessary factor for it to exist. These findings however demonstrate that myelin can modulate the degree of diffusion anisotropy in white matter to an extensive degree. The placement and organization of axonal membranes, however, appear to play the major role in the determination of diffusion anisotropy. Hence, while we tend to see an increase in the FA value with an increase in MWF, other factors also affect the DTI measures, such as fibre density, fibre diameter, fibre organization, as well as the structural integrity of myelin. Therefore diffusion anisotropy seemed to be significantly influenced by factors other than myelin content.
Our findings suggest that in the highly organized fibre arrangement of compact white matter structures such as the genu of the corpus callosum, high diffusional anisotropies are measured which do not necessarily correspond to a high degree of myelin content but more likely reflect the highly organized directionality of fibre bundles in these areas (low microscopic and macroscopic tortuosity) as well as highly restricted diffusion in the interstitial space between the myelinated axons. Conversely, in structures with disorganized fibre bundles and multiple fibre crossings, such as the minor and major forceps, low FA values were measured, which did not correspond to lower myelin water content.

References: [1] Mädler B., MacKay AL. Proc. ISMRM 2006, 2112; [2] Whittall KP, et al, MRM 37:34-43 (1997)