Investigating white matter degeneration in healthy aging by combining diffusion-tensor imaging and diffusion-weighted spectroscopy in the human corpus callosum at 7 T

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Target audience: Clinicians and researchers interested in aging processes and in a new method for investigating axonal damage.

Purpose: By providing interhemispheric communication, the corpus callosum (CC) integrity plays a crucial role in the cognitive decline of elderly[1]. Previous diffusion tensor imaging (DTI) studies *in vivo*[2,3] and histological analysis[4,5] in monkeys revealed age-related declines in white matter (WM) fractional anisotropy (FA), enhancements in water mean diffusivity (MD), and structural alterations in myelin sheaths, suggesting degeneration of WM microstructure in normal aging. Unlike water, N-acetylaspartate (NAA) is known to be present almost exclusively inside neurons, thus providing a specific marker to WM degeneration. NAA diffusivity within axonal fibers is solely influenced by the integrity of intra-axonal components, and it has been proposed as potential marker for intra-axonal degeneration processes[6]. Here, we compare the diffusion properties of water and NAA in the CC of elderly and young subjects, measured at 7T by using DTI and diffusion-weighted spectroscopy (DWS), respectively, in order to discriminate between myelin alterations and possible axonal structural damage in elderly.

Methods: 11 young volunteers (27 ± 3yrs) and 13 elderly subjects (64 ± 3yrs) were scanned on a 7T Philips scanner equipped with a 32-channel receive coil and a quadrature transmit head coil. DTI data were acquired using a multi-slice single shot 2D spin-echo echo planar imaging sequence, resolution of 2x2x2 mm^3, 16 diffusion-weighting directions with b = 1000s/mm^2. A single VOI diffusion-weighted PRESS sequence was employed to measure diffusion of NAA. A VOI of dimensions 30(AP)x15(RL)x8(FH)mm^3 was located in the anterior body of the CC (Fig.1) for the DWS acquisition (diffusion time 52 ms, gradient pulse duration 34 ms, repetition time 3 cardiac cycles - triggering using PPU - spectral width 3kHz, sample points 1024). Diffusion gradients were applied in two directions parallel and perpendicular to the CC fibers (directions (0,0,1) and (1,1,0) respectively, in the VOI reference frame, see Fig.1), in an interleaved way, with 4 increasing gradient strength corresponding to b values in the range 300-6300 s/mm^2. For each direction and b value 32 spectra were acquired. Residual water peak was used to perform phase and frequency corrections on individual scans before summation. Non-water suppressed spectra were acquired under similar conditions for eddy current corrections. The spectra were quantified using LCModel. Water average MD, FA, axial and parallel diffusivities ($D_{(0,0,1)}$(water) and $D_{(1,1,0)}$(water), respectively) and tensor main eigenvectors were derived in the VOI using standard procedures and in-house developed Matlab codes (Fig.2). NAA axial and parallel diffusion coefficients $D_{(0,0,1)}$(NAA) and $D_{(1,1,0)}$(NAA) were estimated by fitting to single exponential functions the signal decays induced by diffusion weighting applied in the directions parallel and perpendicular to the CC fibers, separately (Fig.4). In addition, the NAA "free" diffusion coefficient D(NAA) was estimated from fits of the signal decays to a standard model of diffusion in parallel cilinders[7], corrected for the macroscopic curvature of the CC as derived from DTI data, and including a microscopic axonal dispersion φ, as described in[5].

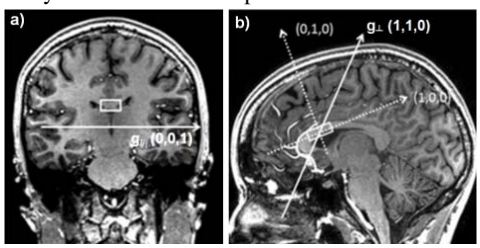

Fig.1: VOI and diffusion-weighted directions on a coronal (a) and sagittal (b) view.

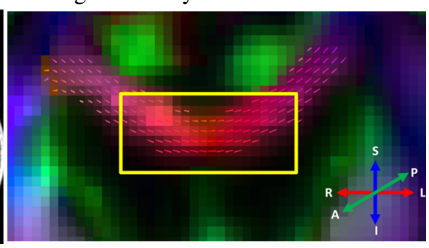

Fig.2:FA map of a coronal section of the CC overlaid with the main eigenvectors projections.

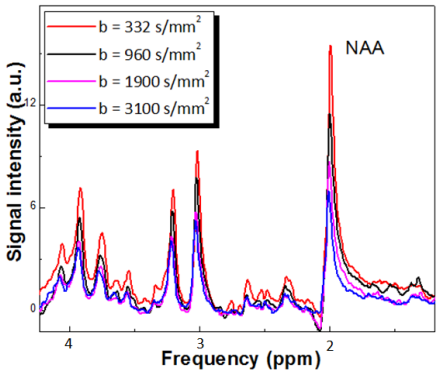

Fig.3: Examples of spectra acquired at different b values for direction (0,0,1). Note the sharp decrease in the NAA peak.

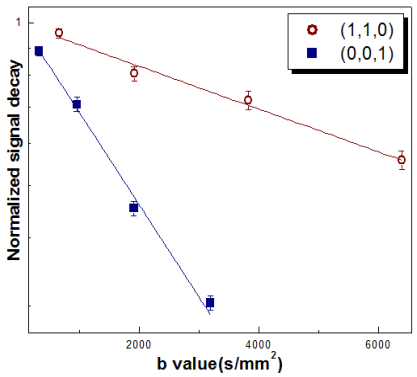

Fig.4: NAA signal decay vs b value measured for a single subject at directions (0,0,1) and (1,1,0). Solid lines represent fits to the model.

Results: The main results are summarized in Table 1. An *increase* in water MD and axial diffusivity $D_{(0,0,1)}$(water) close to statistical significance (p=0.07 and 0.08, respectively) were observed in elderly subjects compared to young volunteers, while a trend towards a *decrease* of D(NAA) and $D_{(0,0,1)}$(NAA) in elderly was detected (p=0.11 and 0.10, respectively).

Table 1	*Young*	*Elderly*	*p value*
MD(water) (μm²/ms)	0.77±0.04	0.80±0.04	0.07
FA(water)	0.76±0.02	0.75±0.04	0.32
$D_{(0,0,1)}$ (water)(μm²/ms)	1.62±0.01	1.67±0.01	0.08
$D_{(1,1,0)}$(water) (μm²/ms)	0.34±0.03	0.36±0.04	0.17
D(NAA) (μm²/ms)	0.64±0.06	0.59±0.08	0.11
$D_{(0,0,1)}$ (NAA) (μm²/ms)	0.41±0.04	0.39±0.03	0.10
$D_{(1,1,0)}$(NAA) (μm²/ms)	0.08±0.01	0.08±0.02	0.79
φ (deg)	8±5	11±5	0.09

Discussion and conclusion: The observed increase in water MD is consistent with the hypothesis of demyelination processes occurring in healthy elderly. The combination of *increase* in water axial diffusivity and *decrease* in NAA axial diffusivity (already observed in MS patients by Wood *et al.* [8]) suggests that axial diffusivity of water alone cannot be interpreted as purely reflecting intra-axonal changes. This point is further emphasized by the confirmation of the existence of significant axonal misalignment (φ) by DWS and histology[6], which makes the axial diffusivity of water in the extracellular space susceptible to demyelination. The results reported here corroborate the uniqueness of NAA diffusion as a marker for intracellular/intra-axonal changes. In addition, the *decrease* in $D_{(0,0,1)}$(NAA), as well as the *decrease* in D(NAA), observed in elderly for the first time in this study are likely to be related to the presence of structural disruptions associated with axonal degeneration, or pruning of thinner axons, and the very slight effect is in line with the fact that our group included healthy aging subjects. Neuropsychological cognitive tests performed on all subjects still need to be incorporated in the study, and the statistical significance of the results needs corroboration from more subjects.

References: [1] PA Reuter-Lorentz and L Stanczak, Dev Neuropsychol, **18**, 113 (2000). [2] ED Sullivan and A Pfefferbaum, Neurosci Biobehav Rev., **30**, 749 (2006). [3] DH Salat *et al*, Neurobiol Aging, **26**,1215 (2005). [4] A Peters and C Sethares, J Comp Neurol, **442**, 277 (2002). [5] A Peters and T Kemper, Neurobiol Aging, **33**, 2357, (2012). [6] I Ronen *et al*, Brain Struct Funct, Epub ahead of print (2013). [7] P van Gelderen *et al*, J Magn Reson B, **103**, 255, (1994). [8] ET Wood *et al*, J. Neurosci, **32**,6665 (2012).