MICROSTRUCTURAL CHANGES OF SHORT ASSOCIATION FIBERS IN PARKINSON'S DISEASE AND NORMAL AGING ASSESSED BY DIFFUSION TENSOR IMAGING.

Jan Sedlacik[1], Jan-Rüdiger Schüre[1,2], Kai Boelmans[3], and Jens Fiehler[1]

[1]*University Medical Center Hamburg-Eppendorf, Hamburg, Hamburg, Germany,* [2]*Technical University of Ilmenau, Thüringen, Germany,* [3]*University Hospital of Würzburg, Bayern, Germany*

TARGET AUDIENCE: DTI-researchers, structural neurobiologists, clinical neurologists.

PURPOSE: Short association fibers (U-fibers) connect neighboring cortical regions and continuously branch-off to the cortex [1] (Fig. 1). A study in autism spectrum disorder showed microstructural abnormalities of the U-fibers by increased mean diffusivity (MD) and decreased fractional anisotropy (FA) [2]. So far, only changes in large white matter tracts were reported for Parkinson's disease (PD) [3]. Due to the observed frontal dysfunction and motor symptoms in PD [4], increased micro-structural degeneration may be observed in frontal and central U-fibers of PD patients as compared to healthy age matched controls. Furthermore, we investigated micro-structural change over age in a larger healthy cohort.

METHODS: DTI with b=1000s/mm², 20 directions, 2 averages, 1.9x1.9mm² in-plane resolution, 27 slices, 4mm slice thickness, TE=83ms, TR=4500ms, acquisition time 3:33min and MPRAGE with TE=2.46ms, TR=1900ms, inversion time=900ms, 9° flip angle, 0.94mm³ isotropic voxels, acquisition time 3:42 min were acquired on a 3T MAGNETOM Skyra MRI system. 82 healthy subjects (18-85 years old, 45±20 years mean±SD age, 44 male, 38 female) were investigated for micro-structural changes during normal aging. 56 PD patients (40-70 years old, 65±9 years mean±SD age, 39 male, 17 female) were compared to 41 age-matched normal controls (41-85 years old, 63±11 years mean±SD age, 27 male, 14 female) which were selected from the first cohort. FMRIB's Software Library (FSL), Freesurfer and Matlab were used for data processing and analysis. b0 images of the DTI data were non-linearly registered to the corresponding MPRAGE data of each subject using FNIRT (FMRIB's Nonlinear Image Registration Tool). MPRAGE data was segmented for each subject using Freesurfer. The segment of the cortical gray matter (GM) was dilated using a 3x3x3 kernel in Matlab. The overlap of the dilated GM with the Freesurfer segments of sub-cortical white matter (WM) were obtained as new segments resembling U-fiber regions. Frontal and central U-fiber regions were realigned to DTI data by using the inverted transformation information from the previous DTI to MPRAGE registration. Due to local distortions of DTI, especially in the frontal regions, non-linear registration obtains higher congruency of the anatomical WM segments with DTI data as compared to linear registration (Fig. 2). Median DTI values of each individual U-fiber region were analyzed over age by linear regression and compared between PD and healthy controls by an ANOVA.

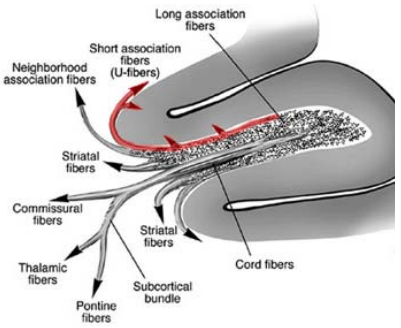

Figure 1: *Scheme of U-fibers (red) and their branches to the cortex [1].*

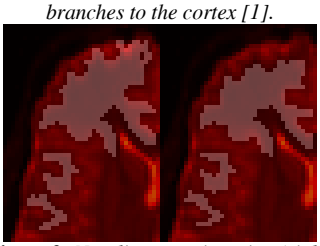

Figure 2: *Non-linear registration (right) results higher congruency of anatomical sub-cortical WM segments with DTI as compared to linear registration (left).*

RESULTS: Linear regression of DTI data showed highly significant increases of axial (AD), radial (RD) and MD over age for all investigated U-fiber regions (Tab. 1). However, changes of FA were ambiguous, showing a highly significant increases for the post central U-fiber region as well a highly significant decreases for the orbito frontal region (Fig. 3). About 2% average differences (ANOVA p<0.001) were found between PD and age-matched healthy controls in the DTI data for all regions. Diffusivity was higher and FA lower for PD as compared to normal controls (Fig. 4). No significant correlation was found between DTI data and the Unified Parkinson's Disease Rating Scale (UPDRS) score (data not shown).

Table 1: *Linear regression: Change of parameters over age in years. Asterisks denote p-values < 0.001.*

U-fiber region	MD 10^{-5} mm²/s	AD 10^{-5} mm²/s	RD 10^{-5} mm²/s	FA 10^{-3}
Post central	0.11*	0.19*	0.07*	0.56*
Pre central	0.09*	0.13*	0.06*	0.22 (p=0.03)
Para central	0.19*	0.22*	0.17*	0.10 (p=0.76)
Superior frontal	0.14*	0.16*	0.13*	-0.23 (p=0.03)
Orbito frontal	0.14*	0.13*	0.14*	-0.54*
Pars orbitalis	0.13*	0.16*	0.11*	-0.02 (p=0.60)
Rost.mid.front.	0.14*	0.17*	0.13*	-0.13 (p=0.08)

DISCUSSION: The ambiguity of FA changes over age may be caused by divergent changes of AD and RD. A very low change of RD as compared to AD causes increased FA, whereas similar changes in AD and RD as well as larger RD changes as compared to AD cause decreased FA values. The interpretation of these changes in AD and RD as changes in axonal density or myelination are hampered due to the continuous branches along the U-fibers into the cortex. Nevertheless, the highly significant increases of MD, AD and RD over age in all regions clearly demonstrate an age-related (e.g. physiological) degeneration of U-fibers in healthy aging. The very low difference and high variability of DTI data between PD and healthy controls as well as the missing correlation to the UPDRS-score suggest only a marginal increased U-fiber degeneration in PD patients which may be clinically of negligible relevance.

CONCLUSION: The significant increase of diffusivity over age in all investigated U-fiber regions clearly demonstrates an age-related degeneration of U-fibers in healthy aging. The ambiguity of the FA and the continuous branches along the U-fibers into the cortex do not allow any further interpretation in terms of axonal density or myelination. No relevant increased degeneration of U-fibers was found in PD patients as compared to age-matched normal controls.

REFERENCES: **[1]** Schmahmann JD, Pandya DN. Disconnection syndromes of basal ganglia, thalamus, and cerebrocerebellar systems. Cortex. 2008 Sep;44(8):1037-66, **[2]** Shukla DK, Keehn B, Smylie DM, Müller RA. Microstructural abnormalities of short-distance white matter tracts in autism spectrum disorder. Neuropsychologia. 2011 Apr;49(5):1378-82. **[3]** Zhan W1, Kang GA, Glass GA, Zhang Y, Shirley C, Millin R, Possin KL, Nezamzadeh M, Weiner MW, Marks WJ Jr, Schuff N. Regional alterations of brain microstructure in Parkinson's disease using diffusion tensor imaging. Mov Disord. 2012 Jan;27(1):90-7. **[4]** Teramoto H, Morita A, Ninomiya S, Shiota H, Kamei S. Relation between freezing of gait and frontal function in Parkinson's disease. Parkinsonism Relat Disord. 2014 Oct;20(10):1046-9.

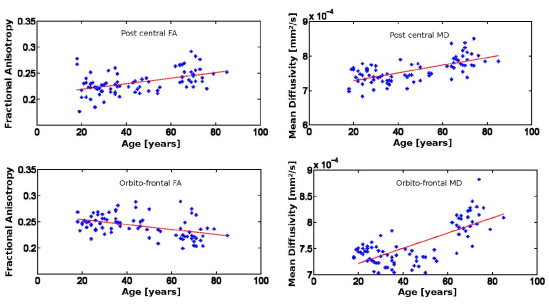

Figure 3: *Microstructural changes over age exemplarily shown for FA and MD of the orbito-frontal and post central regions. Interestingly FA increases over age in the post central region.*

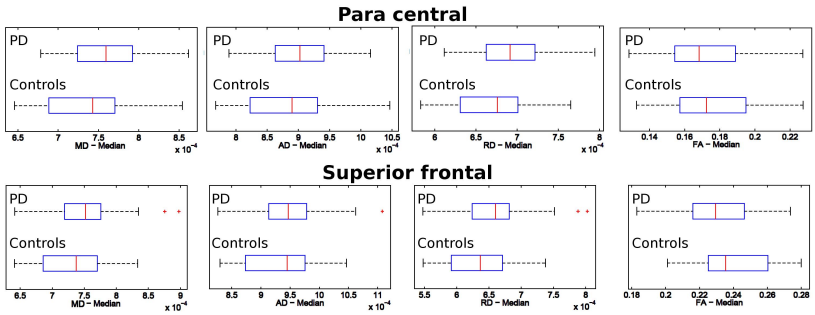

Figure 4: *Microstructural differences between PD and age-matched normal controls exemplarily shown for the superior frontal and para central regions. All regions showed about 2% average difference (ANOVA p<0.001) with higher diffusivity and lower FA for PD as compared to normal controls.*