Aging in White Matter Revealed by Diffusional Kurtosis Imaging

Nan-Jie Gong[1,2], Chun-Sing Wong[1], Chun-Chung Chan[3], Lam-Ming Leung[4], Yiu-Ching Chu[5], and Queenie Chan[6]

[1]*Diagnostic Radiology, The University of Hong Kong, Hong Kong, China,* [2]*Radiology, Stanford University, Stanford, CA, United States,* [3]*Geriatrics & Medicine, United Christian Hospital, Hong Kong, China,* [4]*Psychiatry, United Christian Hospital, Hong Kong, China,* [5]*Radiology, Kwong Wah Hospital, Hong Kong, China,* [6]*Philips Healthcare, Hong Kong, China*

PURPOSE: Diffusional kurtosis imaging (DKI) along with its three major metrics, namely fractional anisotropy (FA), mean diffusivity (MD) and mean kurtosis (MK), has already been shown promising in probing microstructural abnormalities in Alzheimer's disease and Parkinson's disease [1, 2]. An investigation of disease free normal subjects that will establish the baseline, against which patients' data should be compared, is urgently needed. Previous diffusion tensor imaging (DTI) studies of normal aging subjects reported controversial results in identifying the driving mechanism leading to white matter degeneration. Some findings supported the demyelination and retrogenesis theory, while others support axonal loss and Wallerian degeneration. Using DKI method and in accordance with a DKI-based white-matter-model [3,4], we additionally calculated two metrics, namely, the intra–axonal space axonal water fraction (AWF) and the extra–axonal space tortuosity. It has been shown that AWF, as a measurement of the fraction of intra–axonal water volume, is sensitive to axonal loss. Tortuosity, as an indirect measurement of the myelinated axonal fraction, is sensitive to demyelination. We sought to provide insight into the above inconsistencies in the literature using exhaustive analyses of diffusivity and kurtosis metrics. Based on parametric correlations with age and differences across regions of interest (ROI), we also present plausible interpretations for the underlying neurobiological mechanisms.

METHODS: Subjects: Fifty-eight healthy subjects (age range 25 ~ 84 years) underwent 3T MRI scans (Philips Achieva scanner with 8-channel head coil). **DKI imaging:** DKI data were acquired using a single shot EPI sequence with 32 gradient directions and two nonzero b values (1000 and 2000 s/mm^2). Other imaging parameters were: TR/TE = 2000/69 ms, reconstruction resolution = 2×2×3 mm^3, 33 axial slices with no interslice gap to cover the brain. **Post-processing:** The diffusion-weighted images were first corrected of eddy-current distortion and heads' motion using FSL, and then Gaussian smoothed. Summary metrics of FA, MD and MK and white-matter-model metrics of AWF and tortuosity were derived using in-house MATLAB programs. **Parametric analyses:** Following Tract-Based Spatial Statistics (TBSS) procedures, the effect of age on the parametric values was modelled using a general linear model and 'randomise tool' with 5000 permutations. Significance was tested at the cluster level using threshold-free cluster enhancement and family-wise error corrections at $p < 0.05$. The JHU DTI WM atlas was used to identify white matter tracts that exhibited significant correlations. For tract-based ROI analyses, the JHU DTI WM atlas was used to generate masks for the anterior and posterior limbs of the internal capsule (ALIC and PLIC), the cerebral peduncle (CP), the superior longitudinal fasciculus (SLF) and the splenium and genu of the corpus callosum (SCC and GCC). Regional values of all metrics were later calculated.

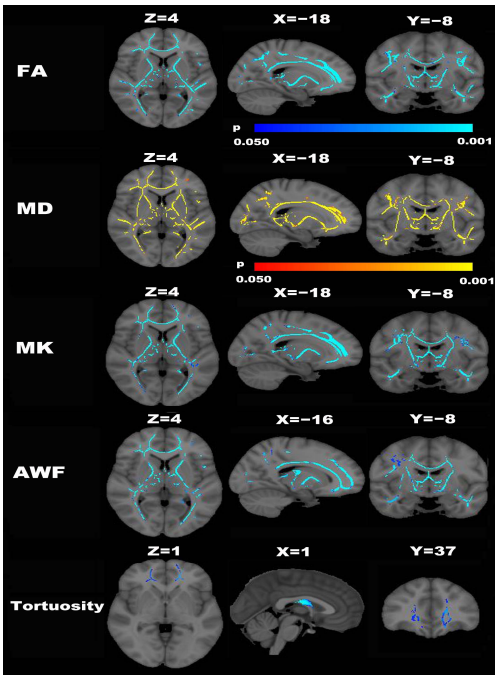

Fig. 1 *TBSS results over the whole brain. Tracts that exhibited significant parametric correlations with age are in blue (negative) or yellow (positive)*

RESULTS and DISCUSSION: Whole brain correlations (Fig. 1): FA exhibited significant age-related decreases in widespread tracts including the GCC and SCC, ALIC and PLIC, CP, uncinate fasciculus, anterior corona radiate and fornix and hippocampal cingulum. MK exhibited negative correlations that were distributed similarly to those of FA, with additional correlations observed in the SLF and superior and posterior corona radiate. MD exhibited negative correlations with age in more tracts than MK, including the cingulated gyrus and external capsule. Interestingly, age-related decreases of AWF were observed in tracts such as the GCC and SCC, fornix, ALIC and PLIC, CP, anterior, superior and posterior corona radiate, external capsule, SLF and uncinate fasciculus. These age-related decreases suggested a decrease in axonal density with aging in most of the white matter tracts. Noteworthy results were observed in tortuosity, which exhibited negative correlations with age only in the anterior corona radiate and fornix. **Regional correlations (Table 1):** Significant negative correlations for MK and positive correlations for MD were observed in all six ROIs. Except for the SLF, all other regions exhibited significant negative correlations with FA. For AWF, correlations in the ALIC, PLIC, and GCC, SCC were significant. In contrast, negative correlations for tortuosity were only observed in the anterior parts of corpus callosum (genu) and internal capsule, rather than the posterior parts. We didn't observe consistent higher aging effects in late-myelinated tracts as compared to the early-myelinated. It was notable that the greatest age effect in PLIC and GCC were found in MK. **Regional comparisons (Fig. 2)**: Group comparisons revealed distinct differences in microstructural compositions between anterior and posterior parts of the tracts. FA, MK, AWF and tortuosity were significantly lower and MD was higher in genu of the corpus callosum and anterior limb of internal capsule than their posterior counterparts. We didn't observe consistent greater overall integrity and complexity in the early-myelinated tracts as compared to the late-myelinated.

		Early-myelinated		Late-myelinated		
	ALIC	PLIC	CP	SLF	SCC	GCC
FA	r = − 0.656 p < 0.001	r = − 0.573 p < 0.001	r = − 0.321 p = 0.014	NS	r = − 0.466 p < 0.001	r = − 0.490 p < 0.001
MD	r = 0.630 p < 0.001	r = 0.441 p = 0.001	r = 0.566 p < 0.001	r = 0.447 p < 0.001	r = 0.670 p < 0.001	r = 0.632 p < 0.001
MK	r = − 0.634 p < 0.001	r = − 0.614 p < 0.001	r = − 0.321 p = 0.014	r = − 0.297 p = 0.024	r = − 0.447 p < 0.001	r = − 0.671 p < 0.001
AWF	r = − 0.627 p < 0.001	r = − 0.610 p < 0.001	NS	NS	r = − 0.386 p = 0.003	r = − 0.628 p < 0.001
Tort-uosity	r = − 0.385 p = 0.003	NS	NS	NS	NS	r = − 0.259 p = 0.050

Table 1 *Pearson's correlations between regional metrics and age NS: correlation not significant*

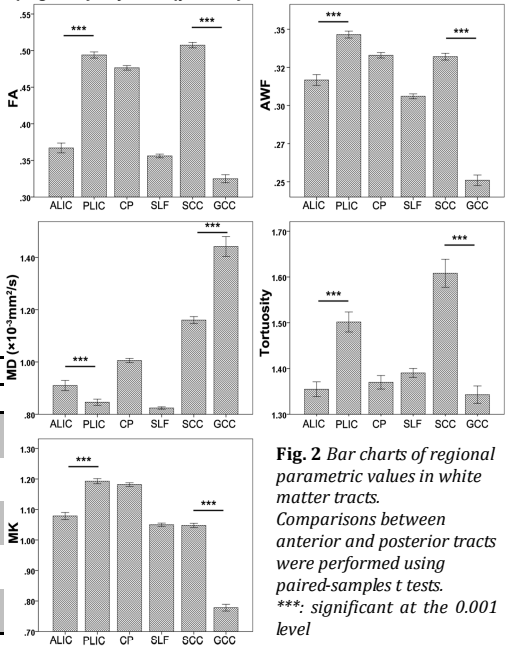

Fig. 2 *Bar charts of regional parametric values in white matter tracts. Comparisons between anterior and posterior tracts were performed using paired-samples t tests. ***: significant at the 0.001 level*

CONCLUSION: We utilized DKI, and for the first time a white-matter-model that provided metrics of explicit neurobiological interpretations in cognitive aging adults.Briefly, current results suggested that age-related white matter degenerations were broadly driven by axonal loss. In the anterior brain which is mostly composed of the late-myelinated fibre tracts, demyelination was also a major mechanism contributing to disintegration. Such probable coexistence of both mechanisms was in line with the Wallerian degeneration theory and is more supportive of the anterior-posterior gradient degeneration than the retrogenesis theory.

References: 1. Gong NJ, et al. Magn Reson Imaging 2013. **2.** Wang JJ, et al. Radiology. 2011. **3.** Jensen JH, et al. NMR Biomed 2010. **4.** Fieremans E, et al. Neuroimage 2011.