Aging in Deep Gray Matter Revealed by Diffusional Kurtosis Imaging

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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. Compared to white matter, deep gray matter has received less attention from diffusion tensor imaging (DTI) studies and corresponding degenerative mechanism remains poorly understood. In addition, existing reports are inconsistent. For example, Wang's report of decreased MD with aging disagrees with Pfefferbaum's report of increased MD in the putamen [3, 4]. The objective of this study was to provide new insight into the current inconsistencies using exhaustive analyses of diffusivity and kurtosis metrics. Based on parametric correlations with age and differences between regions of interest (ROI), we also presented plausible interpretations for underlying neurobiological mechanisms.

METHODS: Subjects: Three Fifty-eight healthy subjects (age range 25 ~ 84 years) underwent 3T MRI scans (3T 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 directional metrics of axial diffusivity (DA), radial diffusivity (DR), axial kurtosis (KA) and radial kurtosis (KR) were derived using in-house MATLAB programs. **Image analysis:** We utilised the improved image registration algorithm of DARTEL contained in SPM8 to draw ROIs. First, 3D T1 weighted images were resliced and coregistered to b0 images. The resliced native space T1 weighted images were segmented and coregistered to generate a template. Custom b0 template was also generated using recorded transforming marix. ROIs of the globus pallidus, putamen, caudate nucleus and thalamus were then placed bilaterally on T1 weighted template by one radiologist using ImageJ. On the b0 template, ROIs of the substantia nigra and red nucleus were placed by the same radiologist. All ROIs were double checked by another radiologist. The ROI in template space were back projected into native space using the transforming matrix to calculate regional parametric values. **Statistics:** Comparisons were performed using Analysis of Covariance (ANCOVA) with general linear model, in which region was a within-subjects factor, and age and sex were covariates, correct for multiple comparisons. Associations between age and regional parametric values were investigated using multiple regressions with sex as a covariate. Standardized β values, as measurements of rates of age-related changes, were compared across regions, and between diffusivity and kurtosis metrics.

RESULRS and DISCUSSION: Regional comparisons (Fig. 1): All other pair-wise comparisons across deep gray matter structures were significant except for: the globus pallidus vs. substantia nigra in FA, substantia nigra vs. red nucleus vs. putamen for MD, globus pallidus vs. red nucleus, and caudate nucleus vs. thalamus for MK. Obeserved parametric ranking orders, especially from FA and MK, revealed distinct degrees of diffusional directionality and heterogeneity, in which the globus pallidus, substantia nigra and red nucleus were much higher than putamen, caudate nucleus and thalamus. These finding agreed well with histological reports [5, 6].

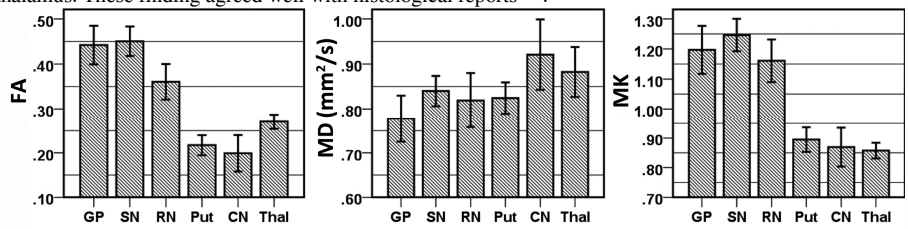

Fig. 1 *Bar charts of regional parametric values in deep gray matter. GP: globus pallidus, CN: caudate nucleus, Put: putamen, Thal: thalamus, SN: substantia nigra, RN: red nucleus*

Regional correlations with age (Fig. 2, Table 1): Strikingly, the putamen exhibited unique pattern distinctly different from the other regions in parametric associations with age. FA correlated negatively with age in the globus pallidus, while positively in putamen. MK correlated negatively with age in the caudate nucleus, thalamus and globus pallidus, while positively in putamen. Similarly negative regression with age in the putamen opposite to the other regions was also observed for KR. For diffusivities, all parametric correlations with age were positive. A previous DTI study that quantified iron content *in vivo* suggested an iron deposition induced increase in FA in the putamen [3]. Another recent DTI study validated this argument with an *in vitro* model and *in vivo* analyses [5]. We speculate that the age-related increasing MK, KR and FA in the putamen can also be attributed in part to its high level and fast iron deposition. More specifically, in contrast to the caudate nucleus and thalamus, a positive correlation with age was observed for MK in the putamen, indicating increasing diffusional heterogeneity and higher structural complexity. DR in the putamen increased with aging at a much slower rate compared to the thalamus (β_{stand} = 0.338 vs. 0.666). This may suggest that accumulated ferritin protein presented additional obstacles mainly along the 'radial' direction. The presence of more and more densely packed obstructions along the radial direction was corroborated by the increasing KR. It was also notable that the greatest age effect in globus pallidus was found in KR.

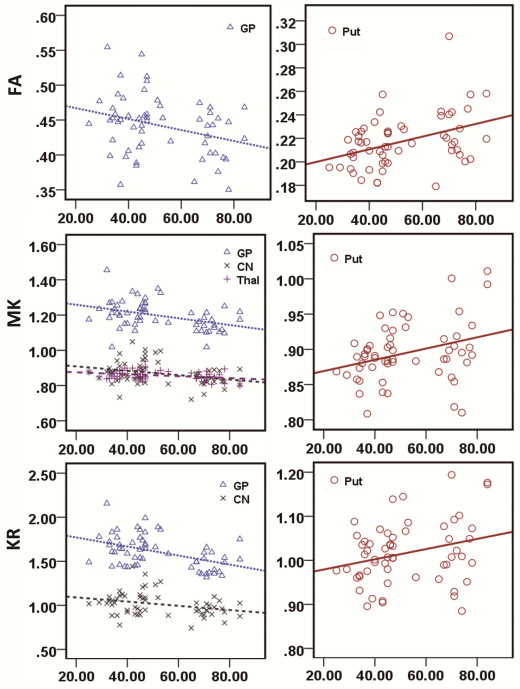

Fig. 2 *Regression lines between age and FA, MK and KR in deep gray matter. GP: globus pallidus, CN: caudate nucleus, Put: putamen, Thal: thalamus, SN: substantia nigra.*

	globus pallidus	substantia nigra	red nucleus	putamen	caudate nucleus	thalamus
FA	-0.301*	-0.089	0.232	0.405**	-0.248	-0.195
MD	0.289*	0.382**	0.331*	0.522***	0.497***	0.680***
MK	-0.399**	-0.051	0.054	0.316*	-0.307*	-0.338**
DA	0.069	0.186	0.473***	0.665***	0.372**	0.675***
KA	-0.051	-0.010	-0.265*	0.025	-0.136	-0.290*
DR	0.365**	0.397**	0.178	0.338**	0.247	0.666***
KR	-0.465***	-0.030	0.138	0.272**	-0.289*	-0.212

Table 1 *β_{stand} for age in regression between regional parametric values and age, covarying for sex. *: p< 0.05, **: p< 0.01, ***: p< 0.001*

CONCLUSION: In summary, we utilised DKI method in both deep gray and white matters of normal aging adults. The results suggested that diffusional kurtosis can provide measurements in a new dimension complementary to those of diffusivity metrics. Kurtosis together with diffusivity can more comprehensively characterize microstructural compositions and age-related changes than diffusivity alone. In terms of deep gray matter, higher MK and FA in the globus pallidus, substantia nigra and red nucleus mirrored the higher microstructural complexity and directionality compared to putamen, caudate nucleus and thalamus. In particular, we proposed that the unique age-related increasing of FA, MK and KR in the putamen may be resulted from iron deposition.

References: 1. Gong NJ, et al. Magn Reson Imaging. 2013. **2.** Wang JJ, et al. Radiology. 2011. **3.** Pfefferbaum A, et al. Neurobiol Aging 2010. **4.** Wang Q, et al. AJNR 2010. **5.** Percheron G, et al. J Comp Neurol. 1984. **6.** Kemp, JM, et al. Philos Trans R Soc Lond B Biol Sci. 1971. **7.** Ruiseh, AM, et al. J Magn Reson Imaging. 2013