Diffusional Kurtosis Imaging Detects Age-related Grey matter Changes in the Normal Mouse Brain

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INTRODUCTION: In a small number of disease-related rodent brain MRI studies, the brain aging process is briefly described based on changes in diffusion and other quantitative MR metrics[2-4], but only two papers[1,5] have quantified diffusion changes with age in the rodent brain, reporting no significant changes. Since the transition from young to aged adult during the normal aging process leads to changes in grey matter morphology[16], characterizing the age-related diffusion patterns in the rodent brain is important for interpreting and differentiating the changes associated with pathological process in rodents' models of neurodegenerative diseases. Diffusional Kurtosis Imaging (DKI) is a diffusion MRI technique that extends diffusion tensor imaging (DTI) by quantifying the non-Gaussian behavior of water diffusion, thereby contributing additional information beyond that provided by DTI [6-9]. Since non-Gaussian diffusion is believed to arise from the presence of diffusion barriers (cell membranes, organelles) and extracellular and intracellular water compartments, the additional measures provided by DKI can be considered natural indicators of tissue microstructural complexity in the grey matter as well as white matter structures. Indeed, several animal studies have shown that mean kurtosis (MK) and the directional diffusional kurtoses provide better differentiation of different brain tissues and are sensitive to changes in brain microstructural complexity associated with brain development[10] and in different diseases sets[11-13]. The main goal of this study was to quantitatively characterize the age-dependent DKI patterns of cortical and sub-cortical grey matter changes in the normal mouse brain.

METHODS: A total of 16 C57BL/6 mice were used in this study. Two age groups of mice were included in the study: 2-month old (n = 8) and 10-month old (n = 8) mice. The animals were held under standardized conditions with unrestricted access to food and water in the animal facility at NKI. All in vivo MRI experiments were performed on a 7T Agilent MR system. A respiration-gated 4-shot SE-EPI sequence was used for DKI acquisition. The sequence parameters were: TR/TE=3000/30 ms, δ/Δ=5/17 ms, slice thickness=1 mm, data matrix=128×128, image resolution=234×234 μm^2, 4 averages, 30 gradient directions[14] and five b-values for each gradient direction (0, 0.5, 1, 1.5, 2 and 2.5 ms/μm^2). All the standard diffusion tensor parameters (mean (MD), axial ($\lambda_{//}$) and radial ($\lambda_{\perp}$) diffusivity), as well as, the non-Gaussian diffusion metrics (mean kurtosis (MK), axial ($K_{//}$) and radial ($K_{\perp}$) kurtosis) were derived from the DKI data set[7] using an in-house software programmed in Matlab (The MathWorks, Inc., Natick, MA) called Diffusional Kurtosis Estimator (DKE))[15]. All parametric maps were masked (MD> 1.5 μm2/ms) to reduce partial volume effect. Brain regions of interest (ROIs) at the level of cortex (CT), thalamus (TH), hippocampus (dorsal (dHP) and ventral (vHP)) were manually drawn using ImageJ ((http://rsb.info.nih.gov/ij/). Two-sample-test was performed comparing the difference in the ROI measurements between the two age-groups, with $p < 0.05$ being considered as statistically significant.

RESULTS & DISCUSSION: Displayed in **Fig. 1** are the diffusion metrics measurements for different brain regions. The standard DTI metrics showed no significant difference between the two age groups for most of the ROIs. MD, $\lambda_{//}$ and $\lambda_{\perp}$ remained constant or showed a small but insignificant trend towards increase, except radial diffusivity, which was significantly increased in the cortex of the 10-month old mice, which may reflect some degree of myelin breakdown that occurs later in the old adult mouse brain. In contrast, all non-Gaussian diffusion metrics showed significant increase in all grey matter regions, with the exception of $K_{//}$ in the thalamus, which showed a trend for increase, but did not reach statistical significance. The increase of DKI metrics between the two age groups may reflect an overall increase of the degree of microstructural complexity during the transition from the young to the old adult group. The mouse brain age-related morphological changes are well established[16-17]. However, there are almost no reports showing the behavior of water diffusion, as measured by diffusion MRI, associated with the age-related morphological process. The majority of diffusion MRI studies in animals have reported changes in the developing brain[12,18]. Here we report that the non-Gaussian diffusion metrics can characterize the age-related microstructural changes in the cortex and sub-cortical regions of the mouse brain. In conclusion, our results support the concept that DKI metrics are useful for characterizing structural grey matter patterns of change, including those seen during the transition from young to the adult age.

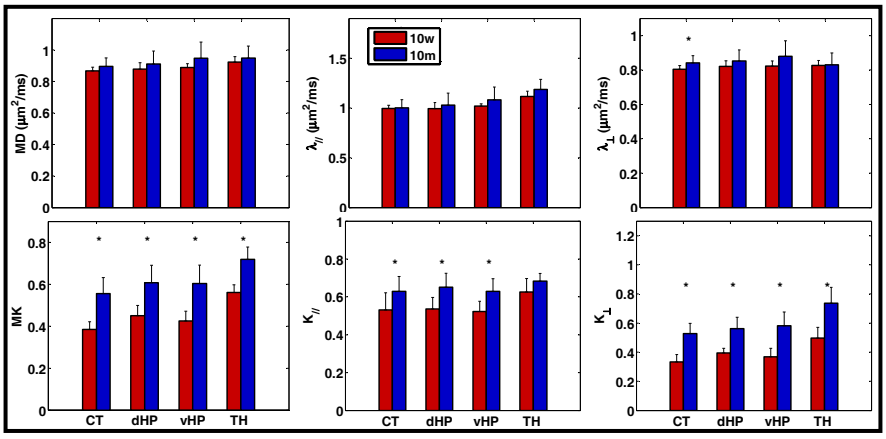

Figure 1. Mean diffusion metrics calculated using DKI for each group (10 weeks old in red) and (10 months old in blue). Brain regions: cortex (CT), hippocampus (dorsal (dHP) and ventral (vHP)); and thalamus (TH); * $p < 0.05$. Error bars are standard deviations.

REFERENCES: **1.** Heiland S, et al. (2002) Neurosci Lett. 334(3):157-60; **2.** Song SK , et al. (2004) Neurobiol Dis. 15(3):640-7; **3.** Falangola MF, et al. (2007) NMR Biomed. 20(3):343-51; 4. Maheswaran S, et al. (2009) Brain Res. 1270:19-32; **5.** Rau PR, et al. (2006) Life Sci. 78(11):1175-80; **6.** Jensen JH, et al. (2005) Magn Reson Med, 53(6):1432-40; **7.** Lu H, et al. (2006). NMR Biomed, 19(2):236-47; **8.** Jensen JH & Helpern JA. (2010) NMR Biomed, 23(7):698-710; **9.** Hui ES, et al. (2008) Neuroimage, 42(1):122-34; **10.** Hui ES, et al. (2008) Neuroimage, 42(1):122-34; **11.** Falangola MF, et al. (2007) Proc Intl Soc Mag Reson Med 15:310.; **12.** Cheung MM, et al. (2009) Neuroimage, 45(2):386-92; **13.** Cheung MM, et al. (2008) Proc Intl Soc Mag Reson Med, 16:3328. **14.** Jones DK, et al. (1999) Magn Reson Med, 42(3):515-525.; **15.** Tabesh A, et al. (2011) Magn Reson Med, 65(3):823-36; **16.** Jucker M, Ingram DK. (1997) Behav Brain Res. 85(1):1-26. **17.** Caviness Jr., VS. (1975) J. Comp. Neurol. 164, 247–263. **18**. Zhang J, et al. (2006) Conf Proc IEEE Eng Med Biol Soc. 1:2252-5. **ACKNOWLEDGMENTS:** This study was supported by NIH 5R03EB009711-2 (MFF) and 1S10RR023534-01.