Comprehensive assessment of the regional microstructure of the preterm human brain cerebral cortex using DKI and DTI

Tina Jeon[1], Austin Ouyang[1], Virendra Mishra[1], Alejandra Perez[1], Lina Chalak[2], Jonathan Chia[3], Muraleedharan Sivarajan[2], Nancy Rollins[4], and Hao Huang[1]

[1]Advanced Imaging Research Center, UT Southwestern Medical Center, Dallas, Texas, United States, [2]Department of Pediatrics, UT Southwestern Medical Center, Dallas, Texas, United States, [3]Philips Medical Systems, Dallas, Texas, United States, [4]Department of Radiology, Children's Medical Center at Dallas, Dallas, Texas, United States

Target audience: Researchers interested in application of diffusion MRI to brain development, pediatric radiologists, neurologists and neonatologists

Introduction: From the early 3rd trimester to around birth, the cerebral cortex undergoes rapid microstructural changes. These changes reflect the underlying cellular and molecular processes including disruption of the radial glial scaffold, cell differentiation, dendritic growth and rapid synapse formation [1,2]. Decreases of fractional anisotropy (FA) derived from diffusion tensor imaging (DTI) in cerebral cortex during this developmental period have been well documented in the literature [e.g.1-3]. Diffusion kurtosis imaging (DKI) takes into account the non-Gaussian properties of water diffusion in complex media, and therefore offers complementary information on cortical microstructural development [4]. Specifically, mean kurtosis (MK), derived from DKI is capable of quantifying restricted water diffusion in the brain [5]. DKI has also been shown to be a more sensitive method than conventional DTI to quantify gray matter microstructural changes in adults [6]. In this study, we aim to gain more comprehensive insight into regional microstructural changes of cerebral cortex by combining DKI and conventional DTI of the preterm human brains.

Methods: *Subjects and data acquisition:* 60 normal preterm and term neonates (35 Male and 25 Female; gestational ages of 32 to 42 weeks; 37.0±2.7 wg) were recruited. For each subject, no evidence of bleeding or intracranial abnormality by serial sonography ultrasound was found. Diffusion weighted images (DWIs) were acquired from a 3T Philips Achieva system using a single-shot EPI sequence (SENSE factor = 2.5) without sedation. The imaging parameters were: FOV=168/168/96mm, imaging matrix = 112x112, axial slice thickness = 1.6mm without gap, 30 gradient directions; b values =1000 s/mm^2 and 1600 s/mm^2, repetitions=2, resulting in a total imaging time of 18 minutes for DWI acquisition. Of the 60 subjects, 22 (17 Male and 5 Female; 36.7±2.6 wks) were scanned with two b-values. *Kurtosis and tensor fitting:* The tensor fitting was conducted with DWI of b 1000s/mm^2 after motion and distortion correction to obtain FA and mean diffusivity (MD) map. After DWIs of b 1600 s/mm^2 were corrected for motion and distortion, kurtosis was fitted using in-house software in MATLAB to obtain MK map. *Extraction of cortical skeleton and parcellation of cortical skeleton into gyral level:* Based on the gestational age of the subjects, DTI and DKI of all subjects were categorized into 3 age groups at 33wg, 36wg and 39wg. With TBSS of FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS), cortical skeletons were extracted based either on averaged cortical FA map at 33wg and 36wg or averaged cortical tissue probability map at 39wg, as shown in Fig. 1a. The 56 gray matter regions of the JHU neonate atlas [7] were transformed to each brain, as shown in Fig. 1b. Combined with cortical skeleton, the gyral level cortical skeleton was obtained (Fig. 1c). *Measuring gyral level FA and MK at the cortical skeleton*: Cortical tissue probability map was created with segmentation based on the contrast of the mean diffusivity map [3] for all 33wg, 36wg and 39wg, as shown in Fig. 1d. Irregular small yet significant offsets between the cortical skeleton and subject's cerebral cortex were widespread, due to imperfect inter-subject registration for transforming cortical skeletons to individual brains. At a given cortical skeleton voxel, the offset was corrected by projecting the FA (or MK) from surrounding voxel of the highest gray matter probability [8], shown in Fig. 1e. In this way, FA and MK at center cortical regions were measured. *Correlation of cortical DKI metrics with age:* Pearson's correlation was conducted between cortical MK and FA with age. For FA, two correlations were conducted during 32-37wg and 37-42wg.

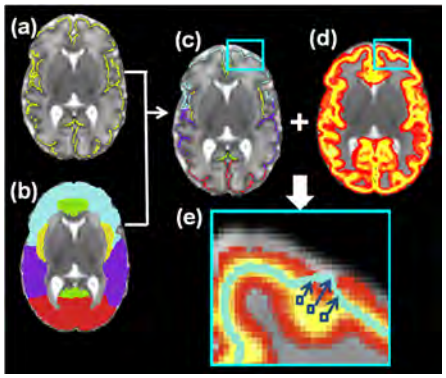

Figure 1: The pipeline to measure the cortical FA or MK at the cortical skeleton voxels of each gyrus. (a) Yellow cortical skeleton overlaid on MD map of a 34wg brain; (b) the gyral labels transformed from JHU neonate atlas with different colors denoting different gyri labeling; (c) the labeled cortical skeleton; (d) the cortical tissue probability map; (e) Enlarged map showing measurement of the metric at the cortical skeleton (cyan line) projected from nearby voxels with maximum gray matter probability (dark blue boxes).

Results: As shown in Figure 2, the age-dependent FA demonstrates a biphasic piecewise linear change with the significant FA decrease from 32wg to 37wg and the FA almost flat from 37wg to 42 wg; monotonically and significantly age-dependent decreases of cortical MK from 32wg to 42wg were observed at a representative gyrus of each lobe. The age-dependent FA change was most significant in the frontal gyri such as superior, middle and inferior frontal gyrus. Fig. 3 shows the different decrease patterns of FA and MK for certain gyri. In Fig. 3, significant age-dependent MK decreases were found at precentral and postcentral gyrus, the primary motor and somatosensory cortical areas, while there was no significant change in FA for these cortical areas.

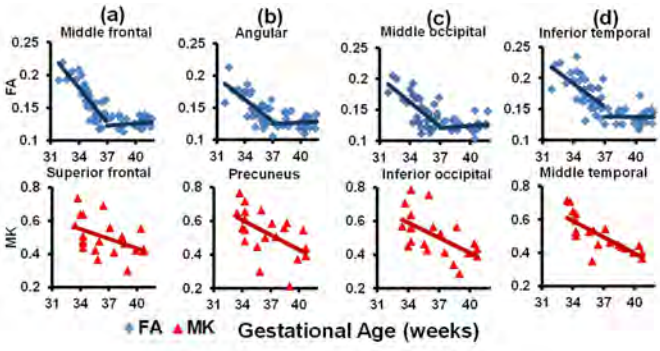

Figure 3 (right): Significant (p<0.05) MK decreases and nonsignificant FA changes with gestational ages in the pre- and post-central gyrus. MK is shown on the right y-axis and FA displayed on the left y-axis.

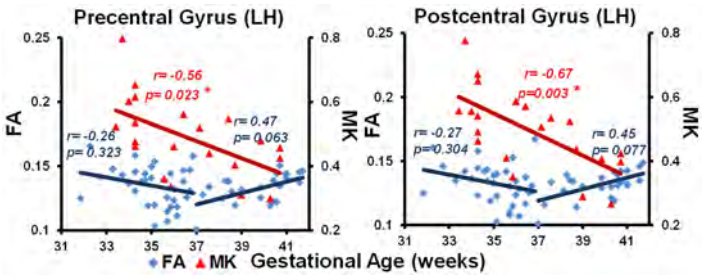

Figure 2 (left): The regional changes in FA (top row) and MK (bottom row) at a reprehensive gyrus in frontal (a), parietal (b), occipital (c) and temporal (d) lobe.

Discussion and conclusion: To our knowledge, this study represents the first comprehensive characterization of cortical microstructural changes in the preterm brains at gyral level with DKI and DTI. We found significant decreases of MK from 32wg to 42wg and significant decreases of FA from 32wg to 37wg all over the cerebral cortex. Cortical FA and cortical MK offer complementary microstructural information. Flattening FA changes are clear from 37 to 32wg in most cortical regions, while MK keeps decreasing (Fig. 2). Fig. 3 further demonstrated that MK provides extra information in addition to FA. Cortical FA is sensitive to cellular processes such as dendritic arborization and disruption of radial glial scaffold [e.g. 1-3] which take place early in primary motor and somatosensory regions, resulting in lower FA values in these regions as early as around 32wg and later nonsignificant FA changes from 32wg to 42wg. However, cortical MK shows microstructural developmental information that cannot be offered by FA. Specifically, the significant MK decreases in these regions indicate continuous decrease of diffusion barriers possibly associated with continuous decrease of neuronal density from 32wg to 42wg [8].

References: [1] McKinstry et al (2002) Cereb Cortex 12:1237. [2] Huang et al (2013) Cereb Cortex 23: 2620. [3] Ball et al (2013) PNAS 110: 9541. [4] Jensen et al (2005) MRM 53: 1432. [5] Cheung et al (2009) Neuroimage 45:386. [6] Falangola et al (2008) J MRI 28:1345. [7] Oishi et al (2011) Neuroimage 56:8. [8] Huttenlocher (1990) Neuropsychologia 28: 517. **Acknowledgement:** This study is sponsored by NIH MH092535 and NIH MH092535-S1.