Dynamics of tract level diffusion kurtosis metrics of perinatal brain white matter from 32 to 40 gestational weeks

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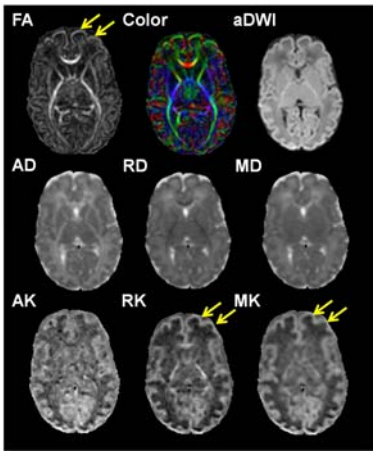
Target Audience: Clinicians, neuroscientists and MR physicists interested in perinatal brain development.

Purpose: From early 3rd trimester to around the birth, increased myelination and axonal density take place in brain white matter (WM), resulting in dramatic microstructural changes. Diffusion kurtosis imaging (DKI) measures non-Gaussian diffusion properties [1]. DKI-derived metrics, such as mean kurtosis (MK), reflect microstructural complexity and may provide complimentary microstructural information to that from conventional diffusion tensor imaging (DTI). Enhanced myelination and axonal density during the developmental stage from 32 weeks of gestation (wg) to 40wg is associated with increased microstructural complexity. WM tracts can be categorized into functionally heterogeneous tract groups, namely limbic, commissural, association and projection tract groups. We hypothesized that such WM enhancement is not homogeneous across different WM tracts or WM tract groups. DKI metrics can be measured at the tract level based on parcellated WM. However, partial volume effects have to be alleviated through measuring DKI metrics at the core of WM tracts to increase accuracy. In this study, we aimed to characterize the dynamics of the DKI properties at the tract level and at the core of WM tracts during the vital brain developmental stage from 32wg to 40wg, with high resolution DKI data.

Methods: *Subjects and data acquisition:* 12 normal preterm and term neonates (6 Male and 6 Female; age range 32 to 40 wg of age) were recruited. Written consents from parents were obtained before scan. Diffusion weighted image (DWI) was acquired from 3T clinical scanner (Philips, Best, The Netherland) using a single-shot EPI sequence (SENSE factor = 2.5) without sedation. The imaging parameters were: FOV=168/168/96mm, imaging matrix = 112x112 with 1.5x1.5mm in-plane imaging resolution, 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. *Kurtosis and tensor fitting:* The tensor fitting was conducted with DWI of b=1000s/mm^2 after motion and distortion correction. For kurtosis fitting, all DWI of b=1000s/mm^2 and 1600 s/mm^2 data was coregistered to the b=0 image after motion and distortion correction. DKI data was processed using in-house software in MATLAB with spatial smoothing Gaussian filter (2 mm fwhm). Fractional anisotropy (FA), mean, axial and radial diffusivity (MD, AD and RD) derived from DTI and axial, radial and mean kurtosis (AK, RK and MK) derived from DKI were obtained. Cerebrospinal fluid (CSF) effects were suppressed by thresholding the MD map by <2μm^2 [2] and applying the thresholded MD masks to all parametric maps derived from DKI. *Tract level MK measurement at the core of the WM tracts:* The FA maps of individual subjects were nonlinearly transformed to a JHU neonate atlas [3]. The averaged FA at the template space was used to generate a skeleton in TBSS/FSL representing core of WM tracts. MK maps were then projected onto the FA skeleton by applying each subject's nonlinear transformation. Both the WM skeleton and tract labels from JHU neonatal WM parcellation were used as the binary masks to obtain the tract level MK values at the core of the WM tracts. Such measurements were conducted on all WM tracts labeled in JHU neonate atlas. The tracts of interest were grouped based on their functional categories: projection, association, limbic, and commissural fibers [4]. These measured MK values were plotted against their gestational ages to observe tract level MK dynamics.

Results: Fig. 1 shows the high resolution DKI and DTI metric maps of a typical neonate brain at 35 wg with 1.5x1.5x1.6mm imaging resolution. At the stage of 35wg, the high FA, RK and MK at the cortical plate is clear, as indicated by yellow arrows. Using the forceps major and forceps minor of corpus callosum as the example, Fig. 2 shows the process of measuring tract level MK at the core with skeletonized MK map and WM tract labels. From Fig. 3, general trend of MK increases can be observed in a majority of the WM tracts. Tract level MK values at 3 tracts, namely the cingulum bundle at cingulate cortex, posterior corona radiata, and superior longitudinal fasciculus, demonstrate significant increase in MK with age ($p<0.05$).

Discussion /Conclusion: With high resolution DKI, these preliminary results from tract level MK measurements demonstrate the feasibility of characterizing the WM DKI properties from early 3rd trimester to birth. Measuring MK at the core or skeleton of the WM tracts effectively alleviated the partial volume effects and thus increased the accuracy of the measurements. General increases of microstructural complexity reflected by MK at the tract level suggest enhanced myelination and axonal density. Relatively a small number of tracts were observed to have significant increase of MK changes during this period, partly due to a small sample size. The heterogeneity of MK increases across different tracts and across different tract groups can be observed from Fig. 3.The more prominent trend of MK increases in limbic and association tract groups can be appreciated. More subjects during this age range will be recruited in the future. We will also explore the sensitivity differences of MK or RK from their DTI counterparts such as MD or RD for characterizing the microstructural dynamics of WM tracts during this developmental stage.



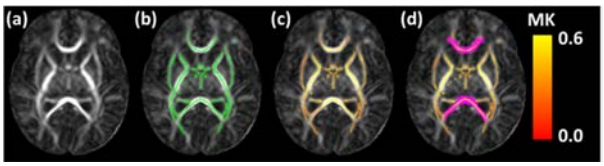


Figure 1 (left): DTI and DKI metric maps from a 35wg neonate brain. aDWI: averaged diffusion weighted image. Yellow arrows indicate high FA, RK and MK at the cortical plate.

Figure 2 (upper): (a) FA map of JHU neonate atlas; (b) WM skeleton obtained from averaged FA transformed to JHU single subject FA map; (c) Single subject MK projected to FA skeleton and overlaid on FA map of JHU neonate atlas; (d) WM tract segmentation (Fmajor and Fminor) overlaid on skeletonized MK map with underlying image from FA map of JHU neonate atlas.

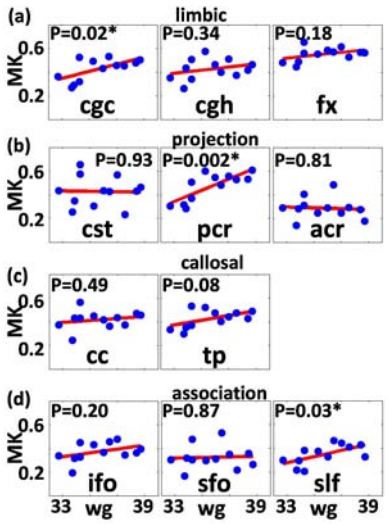


Figure 3 (right): Tract level MK dynamics for limbic (a), projection (b), commissural (c), and association (d) tract groups. Abbreviations: acr: anterior corona radiata; cc: corpus callosum; cgc/cgh: cingulum bundle in cingulate gyrus/hippocampal area; cst: corticospinal tract; fx: fornix; Fmajor/Fminor: forceps major/minor of cc; ifo/sfo: inferior/superior fronto-occipital fasciculus; slf: superior longitudinal fasciculus; tp: tapetum of cc.

References: [1] Jensen, et al. (2005) MRM 53:1432-1440. [2] Yang et al (2013) J MRI 37: 365. [3] Oishi K, et al. (2011) Neuroimage 56(1):8-20. [4] Wakana S, et al. (2004) Radiology 230(1):77-87. **Acknowledgement:** This study is sponsored by NIH MH092535, NIH MH092535-S1, MOST grant (2012CB825500), NSFC grant (91132302), and CAS grant (XDB02010001,XDB02050001).