Microstructural development of human brain cerebral cortex from early 3rd trimester to around the birth with diffusion kurtosis imaging

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Target audience: Clinicians and MR physicists interested in microstructural changes of cerebral cortex in the perinatal brain.

Introduction: From early 3rd trimester to around the birth, active cellular and molecular processes take place in the human brain cerebral cortex, resulting in dramatic microstructural changes. These complicated cytoarchitectural processes are featured with neuron migration along the radial scaffold composed by glial cells in a well-defined columnar organization and subsequent cell differentiation and synapse formation in the cortical plate. Decrease in cortical fractional anisotropy (FA) derived from DTI has been used to infer the disruption of columnar organization, dendrite growth and synapse formation during development [1,2]. Diffusion kurtosis imaging (DKI) [3] is capable of characterizing restricted water diffusion in the brain and has been applied in normal, developmental and pathological states [4-6]. In addition, DKI has been shown to be a more sensitive method than conventional DTI to quantify gray matter microstructural changes in adults [5]. In this investigation, we aim to characterize regional changes in the cortical microstructure from early 3rd trimester to around the birth, namely, 32 weeks of gestation (wg) to 40wg, with DKI.

Methods: *Subjects and data acquisition:* 12 normal preterm and term neonates (6 Male and 6 Female; age range 32 to 40 wg of age) with no evidence of bleeding or intracranial abnormality by serial sonography ultrasound 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, 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). Following the literature [7], cerebrospinal fluid (CSF) effects were suppressed by thresholding the MD map by <2μm^2 and applying the thresholded MD masks to all parametric maps derived from DKI. *Cortical parcellation on the gyral level:* FSL FAST was used for segmentation using the mean diffusivity (MD) map, providing better contrast than T2 or T1 weighted image. Segmentation was further fine-tuned using manual segmentation. The 56 regions of the JHU neonate atlas [8] were transformed into the native space to obtain the initial cortical parcellation of the subject brain. Irregular small yet significant offsets between the cortical labels and segmented gray matter were all over the cortex, due to imperfect inter-subject registration. This offset is corrected by fast marching with cortical segmentation of MD map as a template [9]. *Correlation of cortical DKI metrics with age:* Pearson's correlation was conducted between cortical DKI metrics (MK, RK and AK) and age.

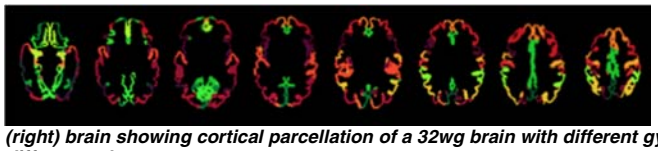
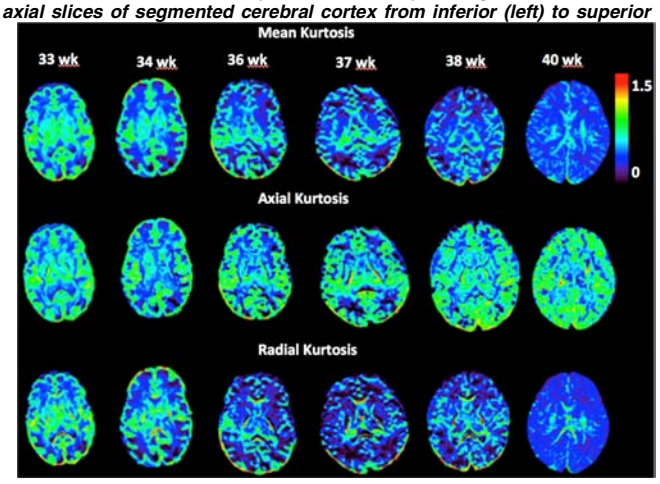
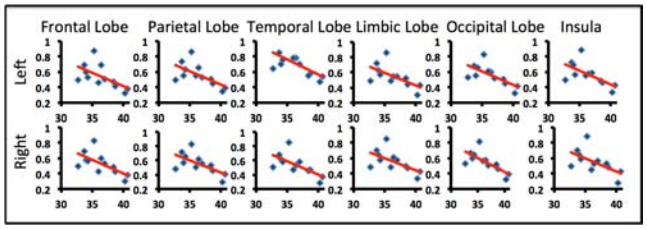


Figure 1: The axial slices of segmented cerebral cortex from inferior (left) to superior (right) brain showing cortical parcellation of a 32wg brain with different gyri labeled with different colors.

Results: Fig. 1 shows the parcellated cortex. Crisp boundary of different cortical gyri is clear. From Fig. 2, the colors from the cortex change from green to blue and purple in mean kurtosis (MK) and radial kurtosis (RK) maps during the age range from 32wg to 40wg, indicating general significant decrease of the MK and RK all over the cerebral cortex. Axial kurtosis (AK) showed no significant changes with age. Regression analysis showed a significant decrease in MK on a lobe level, as demonstrated in Fig. 3. The significant decreases of MK at gyral level can be also observed in Table 1. The Pearson's correlational coefficients are significant on the gyral level. Correlation coefficient r values and p values of the correlations at some characteristic gyri across all major lobes are shown in Table 1.

Discussion and conclusion: In this study, we found significant decreases of MK and RK across the cerebral cortex at the lobe and gyral level from 32wg to 40 wg. Such decreases suggest the disruption of the microstructures supporting the restricted water diffusion. Based on previous DTI findings [1,2], the disruption of the radial glial scaffold is likely to be the major factor causing less restricted water diffusion with age increase during this period. The statistically significant decrease of MK (Fig. 2, Fig. 3 and Table 1) across the cerebral cortex demonstrates the high sensitivity of DKI-derived metrics. It is noteworthy that cortical labeling transformed into the native subject space is perfectly aligned to the cerebral cortex of DKI metric maps in the native space with the additional fast marching procedure after nonlinear transformation. Such procedures make the measurements of DKI metrics at different cortical regions more accurate. To the best of our knowledge, this study may be the first comprehensive kurtosis measurement of cerebral cortex from early 3rd trimester to around the birth. Application of DKI to measuring the restricted water diffusion properties of cerebral cortex provides us refreshing insight of active cortical microstructural changes during this critical developing stage.





lobe	Gyrus	r value	p value
Frontal	Middle frontal gyrus lh	-0.58	< 0.001
	Middle frontal gyrus rh	-0.67	< 0.001
Temporal	Superior temporal gyrus lh	-0.66	< 0.001
	Superior temporal gyrus rh	-0.67	< 0.001
	Inferior temporal gyrus lh	-0.63	< 0.001
	Inferior temporal gyrus rh	-0.71	< 0.001
Parietal	Angular gyrus lh	-0.65	< 0.001
	Angular gyrus rh	-0.67	< 0.001
	Lyngual gyrus lh	-0.67	< 0.001
	Lyngual gyrus rh	-0.68	< 0.001
Occipital	Inferior occipital gyrus lh	-0.62	< 0.001
	Inferior occipital gyrus rh	-0.62	< 0.001

Figure 2 (upper right): The MK, AK, and RK of the whole brain from ages 33 week (wk) to 40wk GA at scan time. The MK and RK show a decrease in the cortex and the AK shows a moderate increase.

Figure 3 (right): The significant MK decreases with age for the different lobes of the perinatal brains.

Table 1 (left): The r and p values showing the significant correlation between MK and age for various cortical gyri. Abbreviations: lh/rh: left/right hemisphere.

References: [1] McKinstry et al (2002) Cereb Cortex 12:1237. [2] Huang et al (2013) Cereb Cortex 23: 2620. [3] Jensen et al (2005) MRM 53: 1432. [4] Cheung et al (2009) Neuroimage 45:386. [5] Falangola et al (2008) J MRI 28:1345. [6] Helpern et al (2011) J MRI 33:17. [7] Yang et al (2013) J MRI 37: 365. [8] Oishi et al (2011) Neuroimage 56:8. [9] Jeon et al (2012) Neuroimage 62: 1705. **Acknowledgement:** This study is sponsored by NIH MH092535 and NIH MH092535-S1.