

Accelerated human cortical microstructural changes from 35 to 40 weeks of gestation characterized with DTI

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Target Audience: The clinicians, MR physicists and neuroscientists interested in using high resolution DTI, specifically cortical fractional anisotropy derived from DTI, to understand the dynamics and mechanism of the cerebral cortex development of prenatal or perinatal brains.

Introduction

From middle 2nd trimester to term, different regions of human fetal brain cerebral cortex become the areas with distinct functions and cytoarchitectures. Characterizing the spatiotemporal microstructural changes of these different cortical regions provides insights on the formation of functional cortical areas. Diffusion tensor imaging (DTI) is useful to delineate the dynamics of microstructural changes of entire cortical plate noninvasively (e.g. 1-5). Specifically, DTI-derived metric, fractional anisotropy (FA), can be mapped to the cortical surface at different fetal developmental time points. High cortical FA in immature cortical plate is believed to be related to the organized radial glial scaffold (6-8) which is the pathway of neuronal migration from the ventricular and subventricular zone to cortical plate. Dendrite and axon growth and synapse formation in the cortical plate disrupt those organized radial glia, causing FA decrease. The spatio-temporal FA changes, therefore, could be used to suggest the dynamics of heterogeneous cortical development. In this study, we acquired high resolution and high SNR DTI data of human fetal brain at three landmark fetal developmental time points, middle second trimester (19 to 20 gestational week (wg)), middle third trimester (35wg) and term (40wg). FA of the complete cortical plate was mapped to the entire cortical surface to reveal the heterogeneous microstructural profile at these three time points. 12 regions of interests (ROIs) were placed on distinct functional regions to measure FA and FA change rates of these areas.

Methods

High resolution and high SNR DTI data acquisition of fetal brains at three time points: 10 postmortem fetal brain samples at 19-20 wg, 10 *in vivo* 35wg and 10 *in vivo* 40wg newborns were scanned with 4.7T Bruker (for *ex vivo*) and 3T Philips (for *in vivo*) scanner, respectively. The postmortem fetal brain samples were borrowed from the University of Maryland Brain and Tissue Bank for Developmental Disorders (NICHD contract no. N01-HD-4-3368 and N01-HD-4-3383). Multiple spin echo diffusion tensor imaging was performed in 4.7T Bruker scanner for DTI of 19-20wg fetal brains. Single-shot EPI with SENSE was used for DTI of 35wg and 40wg *in vivo* newborns. High resolution DTI images were acquired for cortical FA mapping. The DTI parameters are as follows, b=1000s/mm², DTI resolution of 19wg/35wg/40wg brain: 0.3x0.3x0.3mm /0.66x0.66x1.6mm /0.89x0.89x2mm.

Cortical FA mapping and ROI placement: After careful skull stripping, the cortical FA was mapped to the cortical surface rendered with the Amira software following the literature (4,5). ROIs were placed at distinct functional areas following the literature (9), shown in the right panel of Fig. 1.

Regional FA change rate: At each ROI, FA change rate was calculated by absolute values of FA differences across the two time points divided by the gestational age change of the same two time points. Data from 5 fetal brains at each time point were used for this abstract.

Fig. 1: High resolution color-encoded FA (upper left panel) and FA map (lower left panel) of an axial slice of a typical 19wg, 35wg and 40wg brain. A1C: auditory cortex; ALC: anterior limbic cortex; BA: Broca's area; DFC: dorolateral prefrontal cortex (PFC); IPC: inferior parietal cortex; M1C: motor cortex; OFC: Orbital PFC; MFC: medial PFC; S1C: somatosensory cortex; SOC: superior occipital cortex; STC: superior temporal cortex; VFC: ventral PFC.

Results

High resolution FA map: Right panel of Fig. 1 shows the color-encoded FA map and FA map of a typical 19wg, 35wg and 40wg fetal brain. Bright band at cortical plate is clear in FA map of 19wg and 35wg fetal brain, but becomes much darker in 40wg fetal brain, as indicated by the white arrows. **Cortical FA profile at 19, 35 and 40wg:** As shown from Fig. 2, during the fetal developmental period from 19 to 35wg, significant decrease of FA occurs at motor and somatosensory cortex while FA of most other regions remains relatively high. On the contrary, during period from 35wg to 40wg, a large amount of FA decrease happens in most of the cortical areas, although the time interval is only 5 weeks, much less than the 16 weeks from 19 to 35wg. It should be noted that Broca's area does not demonstrate big FA drop from 35 to 40wg.

Accelerated FA change from middle 2nd to middle 3rd trimester: The accelerated FA drops for cortical areas other than Broca's area (BA) or motor/somatosensory cortex (S1C/M1C) from 35 to 40wg are clear in Fig. 3a. Consistently, as shown in Fig. 3b, the FA change rates from 35 to 40wg are much higher than those from 19-20 to 35wg in all cortical ROIs except BA or S1C/M1C. However, FA change rates in S1C/M1C are higher from 19-20wg to 35wg than those from 35wg to 40wg. FA change rates at BA are low in both periods (Fig. 3b).

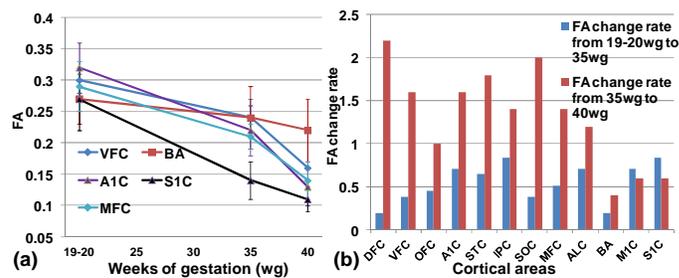
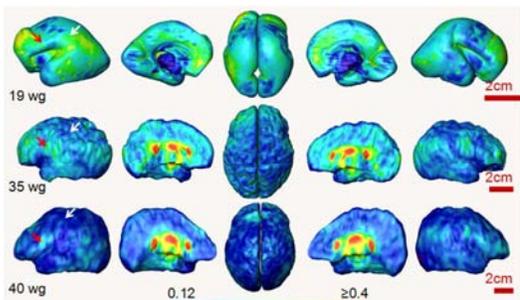


Fig. 3 (right): Averaged FA at different ROIs across the three time points (a) and FA change rate of all ROIs (b). See legend of Fig. 1 for abbreviation of cortical ROIs.

Discussion and conclusion

In this study, we used three landmark fetal developmental time points and revealed accelerated cortical development in most cortical areas except BA or M1C/S1C from 35 to 40wg. These results may represent the first record of comprehensive FA profile of the entire cortical surface at the three time points and suggest a heterogeneous yet organized spatiotemporal pattern of cortical development. These findings are consistent to the knowledge of distinctive function formation of fetal brain at different developmental stage. Specifically, except that primary motor and somatosensory functions develop to a great extent in late 2nd trimester and early 3rd trimester and language function related to BA develops after birth, most other cortical areas have experienced an accelerated development from 35wg to 40wg. More time points and more samples of fetal brain DTI datasets will be added to validate our conclusion.

References: [1] Mori, S et al (2001) MRM 46, 18. [2] McKinstry, RC et al (2002) Cereb Cortex 12:1237. [3] delpolyi, AR et al (2005) Neuroimage 27, 579. [4] Kroenke, CD et al (2007) J Neurosci 27, 12506. [5] Huang, H et al (2008) J Neurosci 28: 1427. [6] Rakic, P (1972) J Comp Neurol 145, 61. [7] Sidman, RL and Rakic, P (1973) Brain Res 62, 1. [8] Rakic P (1995) Trends Neurosci 18, 383. [9] Kang, HJ et al (2011) Nature 478, 483. **Acknowledgement:** This study is sponsored by NIH MH092535 and NIH EB009545.