Study the cerebral wall of the fetal brain with DTI and histology

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Introduction

The cerebral wall, which is the major component of the fetal brain, contains multiple layers [1] and undergoes active structural changes during fetal development. DTI imaging can clearly identify three layers in the cerebral wall, which are cortical plate, subplate and inner layer from outer to inner direction [2,3]. Among these layers, the outmost cortical plate has been found to have radial microstructures [4], which has been confirmed by several studies using *in vivo* DTI imaging of preterm newborn babies [2,5]. It has also been reported that inner layer has relatively higher fractional anisotropy than the middle subplate [2]. However, the detailed characterization of this inner layer is rare in the literatures. In this study, we used both DTI and histology to qualitatively and quantitatively characterize the cerebral wall, especially inner layer. DTI data and histology of postmortem human fetal brain tissue from 13 to 22 gestational weeks which cover most of the second trimester were acquired. The fractional anisotropy (FA) of the inner layer during the second trimester is less than that of the cortical plate, but higher than that of the subplate. Our primary finding in this study is that radial structure, rather than the tangential structure of fetal white matter (or intermediate zone) parallel to the ventricular surface and also residing in this layer, is dominant in the inner layer during second trimester. The interference of these radial and parallel structures may cause the lower FA values than those of the cortical plate where uniform radial structures were found.

Methods

Postmortem sample and data acquisition: Three samples at each week from 13 to 22 gestational weeks were obtained from a tissue bank. For diffusion tensor imaging, a set of DWIs were acquired in 7 linearly independent directions with 3D multiple spin echo diffusion tensor sequence. For 13 to 17 gestational week fetal brains, 11.7 T Bruker system was used. Diffusion weighed imaging (DWI) parameters were: TE=35ms, TR=0.8s, FOV=37mm/28mm/28mm, imaging matrix=128×80×80. For fetal brains older than 17 gestational weeks, 4.7 T Bruker system was used. DWI parameters were: TE=32.5ms, TR=0.8s, FOV=54mm/53mm/37mm, imaging matrix=128×72×72. *FA measurement and histology preparation:* As FA of fixed tissue is well preserved [6], we measured FA of three layers in the left frontal and occipital lobe. FA maps of all fetal brains were carefully examined and only those with sharp contrast and high SNR were used for the measurements. Regions of interests (ROI) were carefully drawn in each layer as shown in Fig.1 and averaged FA values were calculated for each ROI. Details of histology preparation can be found in the literature [7].

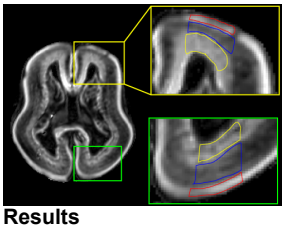


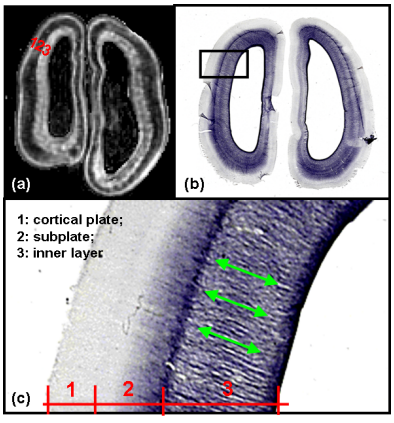
Fig. 1: ROI selection of the cortical plate (red), subplate zone (blue) and inner layer (yellow) in an axial image of FA map of a 20 week fetal brain.

Results

The three layers are well identifiable for the fetal brains from 15 to 22 gestational weeks of age, but not in 13 to 14 weeks of brains. In Fig. 2, axial image of FA map and correspondent histological slide at the upper cerebrum of a 17 week fetal brain are shown. Both layered and radial structures can be clearly demonstrated with FA map and the correspondent histological slide. Three layers can be identified in the FA image with one layer of low FA nested in two layers of high FA. By enlarging part of the cerebral wall in the histological slide, it can be clearly observed that very organized radial structures are dominant in the inner layer surrounding the ventricle. The inner layer contains several zones, namely ventricular, periventricular, subventricular and intermediate zone from inner to outer direction [1]. The histological slide in Fig. 2 matches the visualization of primary eigenvectors in Fig. 3c where the radial structures in the cerebral wall of a 22 week fetal brain are evident in layers 1 and 3 and absent in layer 2. Fig. 4 shows the FA measurements at frontal and occipital lobe. The subplate has the smallest FA for all ages in the second trimester. FA of the cortical plate is higher than that in the inner layer. There is an overall pattern of FA increase for the cortical plate during the second trimester.

Conclusion and discussion

The major finding of this study is that well-organized radial structures are also dominant in inner layer of the fetal brain during second trimester. These radial structures might be part of the neuron migration pathway. The neurons are generated from close to the ventricle and migrate in the inner layer to the low-FA subplate zone where growing major afferent systems temporarily reside in this zone, establish synapses and take part in cellular interactions that are crucial in subsequent cortical development. Our study indicates these well-ordered radial structures in the inner layer exist from 15 to at least 22 weeks. Cortical plate has been the research focus in the cerebral wall and its radial organization has been well delineated first by McKinstry et al [4] and further confirmed by other researchers [2,3,5]. From the literatures [4], the radial organization in the cortical plate disappears in 36 gestational weeks of age. Our study finds it becomes apparent from 15 weeks, suggesting the radial organization of cortical plate exists from 15 to 36 weeks. Therefore, neuronal migration follows the radial direction from inside to outside across the cerebral wall in the second trimester and it seems there is a break of the cell migration at the subplate. The lower FA in the inner layer may be due to the interference of the radial pathway of cell migration and tangential fetal brain white matter. In the future, higher resolution DTI data and more histological slides will be acquired for the fetal brains spanning more weeks to examine the details in the cerebral wall.



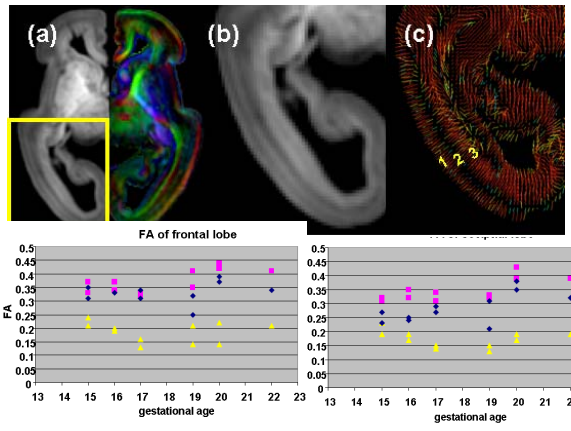


Fig. 2 (left): Axial image of FA map (a) and correspondent histological slide (b) of a 17 week fetal brain. The enlarged box in histology slide (b) is shown in (c) where three layers are labeled. Green arrows indicate the orientations of the radial structures in the inner layer.

Fig. 3 (upper right): The averaged diffusion weighted image on the left and DTI colormap on the right of a 22 week brain are shown in (a). (b) is the enlarged yellow box in (a), showing the laminated layers in the cerebral wall and (c) is the visualization of the primary eigenvectors in the yellow box of (a). Three layers are labeled in (c).

Fig. 4 (lower right): FA measurement of the frontal and occipital lobe of fetal brains from 15 to 22 gestational weeks of age.

References: [1] Kostovic (2002) Cereb Cortex 12, 536. [2] Maas (2004) Neuroimage 22, 1134. [3] Huang (2009) J Neurosci 29, 4263. [4] McKinstry, RC. (2002) Cereb Cortex 12, 1237. [5] deIpolyi (2005) Neuroimage 27, 579. [6] Sun (2003) MRM 50, 743. [7] Ren (2005) Anat Rec 288, 191. **Acknowledgment:** NIH R01AG20012.