Characterizing Human Fetal Brain Development with Diffusion Tensor MR Microimaging

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Introduction

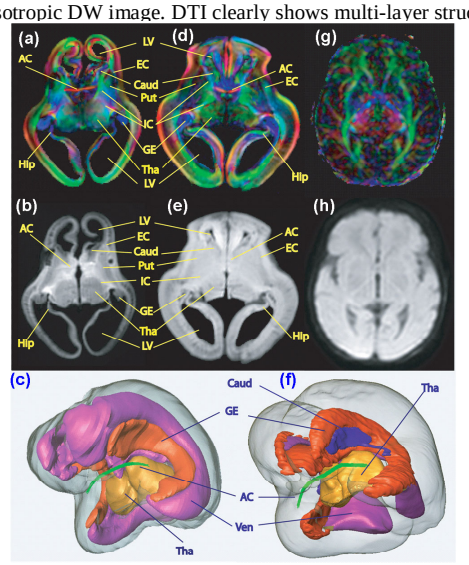
Neuroanatomical study of human fetal brain is of great importance to understand not only the normal brain development process, but also the mechanisms of the developmental disorders. Currently, only few histology-based atlases are available for human fetal brain anatomy [1,2]. Without 3D atlas, it is often difficult to comprehend complex sequences of bran development processes. With recent advances of MR microimaging technologies, especially diffusion tensor microimaging (microDTI), there is a great potential to precisely delineate the development process of neural structures of the human brain three-dimensionally. Such study may also serve as precious references for MR studies of premature babies, which is increasingly becoming an important application field of DTI [3-5]. In this study, we acquired high resolution MR and DT images of fixed brain tissues from post-ovulatory weeks 13 to 20 using 11.7 T and 4.7 T scanners. The MR results were compared with histology for structural assignments. Assigned structures were then segmented three-dimensionally to create a preliminary version of human fetal 3D atlases.

Methods

(1) Fixed brain tissue: Fixed human fetal brain samples were borrowed from Brain and Tissue Bank for Developmental Disorders (University of Maryland). The fixation solution (10% formalin) was replaced with buffer at least 24 hours before the scan. The brain was placed in a custom-made chamber. A set of DWIs were acquired in 7 linearly independent directions with a 3D multiple spin echo sequence. For 13, 14, 15, 16 post-ovulatory week 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 (zero filled to data matrix=128×128×128 with voxel size = 0.219×0.219×0.219mm after rotation and zero padding). For 17, 18, 19, 20 post-ovulatory week brains, 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 (zero filled to data matrix=128×128×128 with voxel size = 0.289×0.289×0.289mm after rotation and zero padding). Co-registered T_1-weighted images were also acquired for both scanner systems. **(2) In vivo neonatal brain:** Newborn volunteers were scanned in a 1.5T Philips Gyroscan NT. A single-shot echo-planar imaging (EPI) sequence with SENSE parallel imaging scheme was used. DWI parameters were: FOV=150/150/86.48mm, in plane imaging matrix=80×80 (zero filled to 256×256 with in plane pixel size=0.586×0.586mm), slice thickness=1.88mm. Co-registered magnetization-prepared rapid gradient-echo (MPRAGE) image was also acquired. All studies were approved by IRB of Johns Hopkins University.

Results

Fig. 1 shows 2D DTI images and 3D reconstruction of the fixed fetal brains at 15 and 20 post-ovulatory weeks and 2D in vivo DT images of a neonatal brain. As shown in Fig. 1, DTI provides contrasts to clearly identify various gray and white matter structures. The early fetal brain at 15 week is mainly composed of the ventricles. The prominent structure at 20 week fetal brain is ganglionic eminence, the transient structure which will become the future basal ganglion and the cortex. The volume of cortex increases considerably during this period. Fig. 2 shows the image of 17 week fetal brain histology slide with HE staining compared with DT color map and isotropic DW image. DTI clearly shows multi-layer structure of the cortex. Further structural assignment and 3D segmentation are under way.



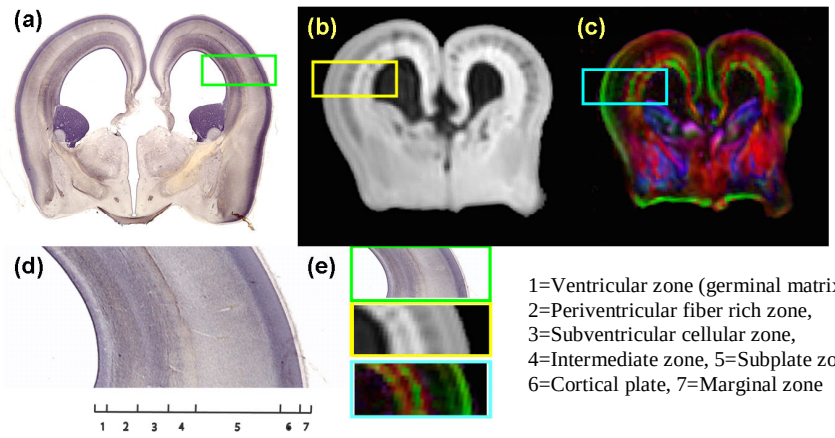


Fig. 2. Histology slide (a), ISO image (b) and colormap (c) of 17 week fetal brain. (d) and (e) are enlarged cortical layers.

Fig. 1(a-c) DT colormap, isotropic DW (ISO) image and 3D visualization of 15 week fetal brain; (d-f) colormap, ISO image and 3D visualization of 15 week fetal brain; (g-h) colormap and ISO image of in vivo neonatal brain. AC: anterior commissure, IC: internal commissure, EC: external commissure, Put: putamen, Caud: caudate, Tha: thalamus, Hip: hippocampus, LV: lateral ventricle, Ven: ventricle, GE: ganglionic eminence.

Discussion

Our study shows feasibility and usefulness of MR microimaging to create 3D atlas of developing human brains. DTI is especially an effective method to reveal anatomy of premyelinated brains. Because of the advent of recent gene engineering technologies, it is now possible to study molecular mechanisms of mammalian brain development using mouse models. However, scarcity of human fetal brain anatomic information makes it difficult to extrapolate such findings to human diseases. We believe that this effort will fill in the gap between the mouse models and human clinical studies. Recent clinical studies have shown that DTI is an important tool to study premature newborns [3,4,5] and this atlas may serve as a high quality reference for such studies.

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Reference: [1] O'Rahilly, R. and Muller, F. (1999). The embryonic human brain: an atlas of developmental stages, John Wiley & Sons, Inc, [2] Bayer, S.A. and Altman J. (2004) The human brain during the third trimester, CRC Press, [3] McKinstry, R.C. et al (2002), Cereb Cortex, 12, 1237, [4] Neil, J. et al, (2002) NRM Biomed, 15, 543, (5) Partridge, S.C. et al (2004) NeuroImage, 22, 1302