High resolution HARDI of early embryonic mouse brain development

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Target audience: Researchers who are interested in high-resolution diffusion MRI acquisition, and analysis of embryonic brain development.

Purpose: The laboratory mouse is an important model system to study the genetic control of brain development and diseases. MRI has been increasingly used to characterize anatomical phenotypes of the mouse brain. Compared to conventional T1- and T2-weighted MRI, diffusion MRI (dMRI) can generate superb tissue contrasts for structure delineation in the embryonic brain [1], but often lacks in term of spatial resolution due to the SNR limits and the lengthy scan time. In this study, we developed a fast 3D imaging sequence to acquire high resolution (30 -45 μm isotropic) HARDI data of the embryonic mouse brains to characterize embryonic mouse brain development.

Methods: CD1 mouse embryos (E10.5 to E15.5, n=5 per stage) were immersion fixed with 4% PFA and then transferred to PBS with 1mM Gd-DTPA before imaging. All experiments were performed on an 11.7T spectrometer (Bruker Biospin). The E10.5 embryos, the E11.5-E14.5 embryo brains and E15.5 embryo brains were imaged at 30 μm, 35 μm and 45 μm isotropic resolutions, respectively. We used a modified 3D diffusion-weighted gradient spin echo (GRASE) sequence [2], which acquired 40 echoes in each repetition. Double sampled EPI readout were incorporated to enhance SNR, and to reduce artifacts from imbalanced readout gradients. Twin navigators were implemented for phase error correction. Point spread function (PSF) was measured along the y and z phase encoding directions. The average full width half maximum (FWHM) of PSF for the E12.5 brain was 35.2 μm and 24.6 μm along y and z, respectively. Imaging parameters were: TE/TR = 30/700ms, 2 signal average, δ/Δ=4/12ms. Compared to T2-weighted images, there was no noticeable distortion in the diffusion-weighted images. High angular resolution diffusion imaging (HARDI) data was acquired at 30 diffusion directions at b-values of 1300-1500 s/mm^2 in approximately 32 hrs. Co-registered T2-weighted images were acquired at the same resolution. HARDI data was reconstructed using constraint spherical deconvolution with an order of 6 in MRtrix [3], and track-density images (TDI) [4] were generated based on probabilistic fiber tracks that are shorter than 1mm, and then re-gridded to 10 μm isotropic resolution.

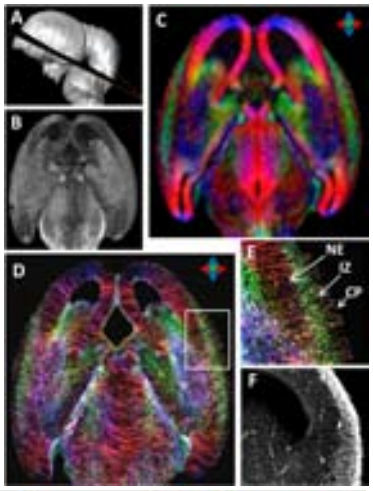

Fig. 1: (A): 3D rendering of an E12.5 mouse brain. (B-D): T_2-weighted image, DTI colormap, and TDI map at 35 μm isotropic resolution. (E): the three layer organization (NE, CP, IZ) in the embryonic cortex. (F): A Nestin stained section for radial glial fibers in the embryonic cortex.

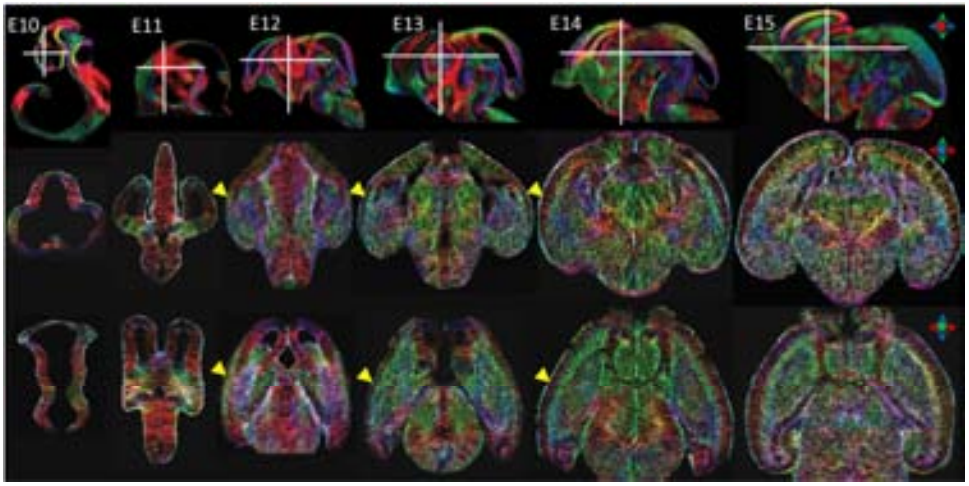

Fig. 2: Top row: mid-sagittal DTI colormaps of embryonic mouse brain from E10.5 to E15.5. Middle and bottom rows: TDI maps of the embryonic brains at each stage (the locations are indicate by the lines in top row). The yellow arrows indicate the location of the cortical plate. Note that the images are scaled differently for displaying purpose.

Results: Fig.1 shows images of an E12.5 mouse brain at a 35 μm isotropic resolution. Compared to the T_2-weighted image (Fig. 1B), which provides limited tissue contrasts within the brain, the DTI colormap image (Fig. 1C) and TDI map (Fig. 1D) allow delineation of the early gray and white matter structures based on their unique microstructural organization. For example, the well-organized radial glial fibers in the neuroepithelim (NE) (Fig. 1F) can be appreciated in the colormap and TDI map. TDI maps from E10.5 to E15.5 (Fig. 2) demonstrate spatiotemporal evolution of key structures. For example, the cortical plate, first detected at E12.5 (indicated by the yellow arrows), gradually expanded and covered the entire hemispheres at E15.5. During the same period, the intermediate zone (IZ) could be located between the NE and CP layers, resulting in a three-layer structure [5].

Discussion and conclusion: High resolution HARDI data has unique advantages for delineating fine structures in the embryonic brain. Emerging structures, such as the cortical plate at E12 could be well delineated at high resolution, and high angular resolution allowed us to resolve crossing fibers, such as radial glial fibers and axons in the intermediate zone. The 3D DW-GRASE sequence described in this study improved imaging speed and kept high data fidelity compared to spin-echo type of sequences in previous studies [5,6], so that both high spatial and angular resolutions are achievable within a reasonable scan time. The proposed acquisition scheme could be useful for developmental studies of various mouse phenotypes.

References: 1) Neuron 2006 51(5): 527-539. 2) MRM 2010 64(1): 249-61. 3) Neuroimage 2007 35(4): 1495-72. 4) Neuroimage 2012 59(1): 286-96. 5) Neuroimage 2003 20(3): 1639-48. 6) Comput Med Imaging Graph 1999 23(1): 15-24.