# Three Dimensional Atlas of Developing Mouse Brains Based on Diffusion Tensor Imaging

**N. Chuang[1], J. Zhang[1], J. Li[2], B. Xu[2], S. Senft[3], R. L. Sidman[2], and S. Mori[1,4]**

[1]Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2]Neurology, Beth Israel Medical Center, Harvard Medical School, Boston, MA, United States, [3]Krasnow Institute of Advanced Study, George Mason University, Washington, DC, United States, [4]Kennedy Krieger Institute, Baltimore, MD, United States

**Introduction:** The mouse has been the most commonly used model for studying mammalian brain development because advances in molecular biology allow observation of gene activation and protein distribution in the developing mouse brain. To examine anatomical phenotypes due to brain development or gene mutation, imaging and atlases are important tools for researchers. Because MRI is non-destructive, 3D morphological registration of complex brain structures in this database are well preserved compared to histology based atlases. Furthermore, the database contains rich information on developing axonal tracts, as diffusion tensor imaging (DTI) has been shown to provide superb, consistent tract contrasts in embryonic and neonatal brains[1],prior to myelin formation. which is often difficult to obtain with conventional $T_1$/$T_2$-weighted MRI. DTI thus enables us to study the development of axonal tracts in mouse brains[1,2], and provide a DTI based atlas that can help neuroscientists to study and characterize evolving neuroanatomy in either wild-type or mutant immature mouse brains,. We have begun developing a MRI database of developing mouse brains starting from embryonic day 13 (E13) to adult. The database contains a large number of high-resolution serial images with multiple image contrasts ($T_2$, diffusion-weighted, apparent diffusion coefficient, diffusion anisotropy, and orientation maps) at 24 hour intervals during embryonic stages E13-E18, and representative time points at postnatal (P) stages. Identifiable structures were labeled according to histology-based atlases. This database will serve as important resources for anatomical references, histology/MRI data registration, and studying developmental neuroanatomy.

**Methods:** Imaging of ex-vivo immersion- or perfusion-fixed mouse brain specimen was performed on an 11.7 Tesla NMR spectrometer. All postmortem brains were held within skull to preserve brain morphology. Diffusion weighted images were acquired with a 3D diffusion weighted multiple spin echo sequence. (TE/TR = 35/700 ms, ETL = 6, $b$=1000 s/mm$^2$, six diffusion directions: [0.707, 0.707, 0], [0.707, 0, 0.707], [0, 0.707, 0.707], [-0.707, 0.707, 0], [0.707, 0, -0.707], [0, -0.707, 0.707], NA = 2, resolution 0.08 mm x 0.08 mm x 0.08 mm for embryonic and neonatal specimen and 0.12 mm x 0.12 mm x 0.12 mm for juvenile and adult specimen,). $T_2$-weighted images (RARE, TE/TR = 50 / 900 ms, flip angle = 40$^o$, NA = 4) were acquired with the same or higher resolution than the diffusion weighted images. Diffusion tensor data were computed with a Log-linear algorithm. The adult mouse brain images were manually aligned to an orientation defined in the Paxinos Mouse Brain Atlas, and images from postnatal mouse brains were aligned to the adult brain image using rigid transformation. Reconstruction of major white matter tracts were performed with our fiber-tracking technique (DTIStudio), and manual segmentation of major gray matter structures was performed with Amira. The reconstructed white matter tracts and gray matter segmentation are organized in a convenient software package for ease of viewing and navigation. A 2D atlas was also created with structure labels as defined in histology-based mouse brain atlases.

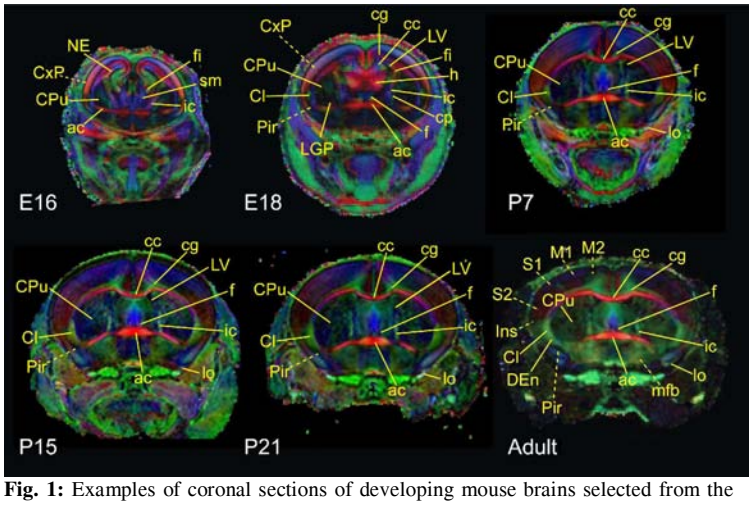


**Fig. 1:** Examples of coronal sections of developing mouse brains selected from the 2D atlas. Major structure abbreviations: ac: anterior commissure; cc: corpus callosum; cg: cingulum; CPu: caudate putamen; CxP: cortical plate; f: fornix; fi: fimbria; ic: internal capsule; lo: lateral olfactory tract; LV: lateral ventricle; M1/M2: motor cortex; S1/S2: sensory cortex; NE: neuroepithelium;

**Results & Discussion:** Fig. 1 shows coronal slice images from the 2D atlases at the level of the anterior commissure. Unlike conventional MR images, which often fail to generate satisfactory contrast in embryonic and neonatal brains due to lack of myelin, DTI provides sharp contrast between gray and white matter structures throughout development. This capability of DTI enables us to track the development of various axonal tracts from embryonic to adult stages. Fig. 2 shows 3D reconstruction of fiber tracts in developing mouse brains. Fiber tracts are color-coded and their spatial relationship e.g., the stria terminalis (st) arching over the internal capsule (cst), can be appreciated. The atlas is accompanied by software that can perform landmark based MRI-to-MRI and histology-to-MRI coregistration.

This database and atlas will help neuroscientists to read DTI results and appreciate the trajectories of developing fiber tracts. Furthermore, with today's advanced image registration techniques, it is possible to transform images from mutant mouse brains to the normal developmental atlas for easy comparison. This may greatly improve the efficiency and accuracy of phenotyping. It is also possible to coregister cellular or molecular information obtained from histology, such as gene expression, to this atlas, to study genetic controls of brain development. In summary, our DTI-based 3D atlas of developing mouse brains will prove useful for studying mice exhibiting genetic alterations.

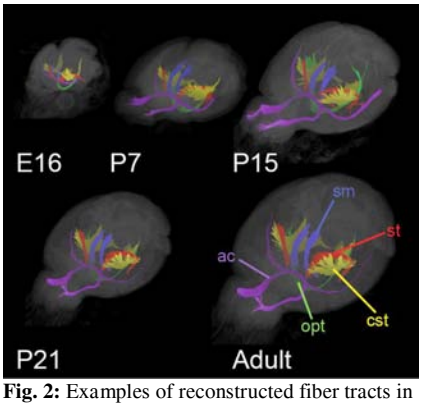


**Fig. 2:** Examples of reconstructed fiber tracts in developing mouse brains. Abbreviations: ac: anterior commissure; cst: cerebral peduncle and internal capsule (corticospinal tract); opt: optic tract; sm: stria medularis; st: stria terminalis

**References: 1).** Mori S. et al. MRM (2001) (46) 18-23. **2).** Zhang J. et al. Neuroimage (2003) (20) 1639-1648.