

Towards a tract-based atlas of mouse brain maturation and gender differences

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Background and Objective: Generation of a comprehensive DTI mouse atlas has become increasingly important for understanding the effect of genetic mutations on formation, myelination, or degeneration of axonal fibers. Earlier work in this area concentrated on creating a fractional anisotropy based normalized atlas of mouse maturation [1,2]. Our work aims at developing a normative atlas of changes in fiber tracts as a result of maturation, which can be applied to determine differences in knockout mice. Here we present a sample study where fiber tracking is employed to understand the spatio-temporal growth patterns and identify gender differences during maturation in fiber tracts in two regions: cortex and the corpus callosum (CC).

Methods: 57 inbred mice of C57BL/6J strain were used in this study. Brains of these mice were scanned ex-vivo on a 9.4 T scanner with TR/TE = 900/37 ms., with different b-values ranging from 150 -2000 s/mm² and at least 7 diffusion weighted images and a scan time of 24 h. The imaging resolution ranged from 93 μ m isotropic to 120 μ m isotropic. The DTI images were acquired on days 2, 3,5,7,10,15,20,30 and 40 after birth. Each age group contained between 4-7 subjects. Diffusion tensor fitting was performed using DTI-Studio [3]. The tensors were then spatially normalized to the day 10 template using intensity and orientation descriptors in DROID [4]. All the mice younger than age 7 were incrementally registered to the template to achieve higher accuracy. After registration, ROI's were located on the template image, which were then used for fiber tracking in each subject using DTI-Studio.

Results: Figure 1 shows the reduction in cortical fibers as the mice mature. It can be observed from Fig. 1 (a) that the fibers take a radial path which is formed by co-oriented neuronal cell bodies, axons and glia. As the mice mature, dendritic trees are formed and the synaptic density increases reducing the number of fibers (Fig1 (b-c)) in the cortex. The mean FA in the cortical fiber tracts drops more rapidly in females (in early stages, till age 7) than in males (Fig 3) suggesting higher synaptic density in females [5]. Although in adolescence (day 10-20), however, the cortical FA in males reduces rapidly while in females it reduces gradually (Fig.3). In the CC, the fiber density and the anisotropy increase with age. Fig 2 (a-c) shows a 3D rendering of the fibers in CC. It can be observed that fibers have faster growth during the early days (3-15) than in adolescent mice (15-40 days). The FA increase in the CC follows a similar path for males and females (Fig 4). Also, the maximum FA at each timepoint exhibited high heterogeneity (Fig.4). A logarithmic function is used as a fit since the growth in early days is rapid compared to the rate of development in adolescence.

Discussion: We lay the foundation of a tract based atlas, demonstrating feasibility in two regions. We have therefore demonstrated that tractography can be applied to quantify structural maturation patterns and gender differences during growth of a mouse brain in early postnatal period. Dynamic patterns of change were observed in the cortex reflecting elaboration of dendrites and rise in synaptic density. Females displayed rapid reduction in fibers in early days potentially due to higher synaptic density than males [5]. The CC showed an increase in fiber density and anisotropy as the mice matured, although no differences were observed between the two sexes.

In future we aim at generating a normative maturing mouse template using fiber tracts which will serve as reference for analyzing mice with gene manipulations, altered development, etc.

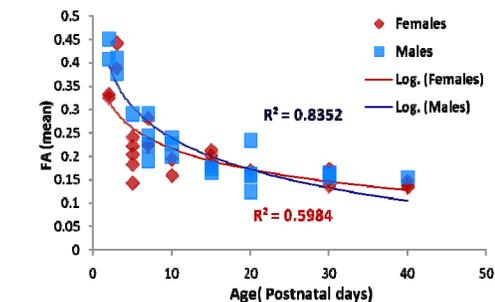


Fig.3: Plot of mean FA in cortex as the mice mature.

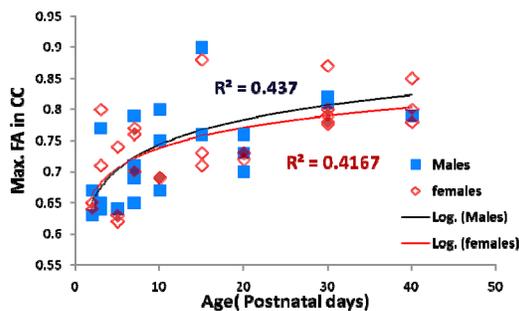


Fig. 4: Plot of FA in the CC as the mice mature.

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