Framework for comparing mutant mice against a DTI-based normative atlas of mouse brain development

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INTRODUCTION. In this work we provide a framework for comparing differences between a knockout strain and a normative atlas of the developing mouse brain. We have used Diffusion Tensor Imaging (DTI) in a novel computational neuroanatomy approach to quantify postnatal developmental patterns of C57BL/6J mouse brain and have created a growth and maturation profile of the C57BL/6J mouse, which is used as a normative brain for several knock-out strains. This lays the foundation for a normative atlas for a developing brain against which brain anomalies can be quantified. In this work we provide a framework that facilitates such a comparison of neuropathology against the normative baseline. We show the application of this normative atlas in determining growth and maturation abnormalities in a hybrid mouse that has been genetically altered. The framework is general and can be applied to determining changes in mice that have been mutated, at any stage of their development.

METHOD. We have created a normative atlas of the developing mouse brain using mice of days 2, 3 , 5 , 7, 10, 15, 20 , 30 and 40 on the lines of [1] which includes several specimens for each day (33 specimens in all). We choose a particular day (day 10 in our case) as the template and spatially normalize the mice [1, 2] to this template using deformable registration. Figure 1 shows the averaged mouse brain FA and orientation map. Then by studying the Jacobian of the deformation fields and the change in the anisotropy maps, we form a growth and maturation profile for a normal developing mouse brain. Fig. 2 shows the changes in FA as a result of development. In order to create a developmental profile of a knock-out/ mutated mouse, we register the hybrid mice to the corresponding day in the normative atlas and then through to the template of the normative atlas. We are then in a position to compare the hybrid mouse brains to those of the corresponding day. This analysis is further enhanced by computing difference maps of the FA and voxel-wise z-scores of change.

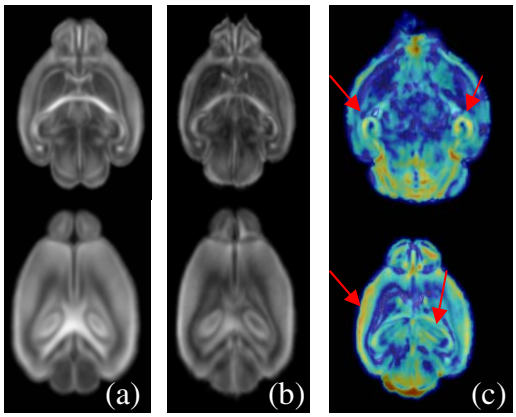

Figure 3. (a) Slices from average of day 5 images of the normative strain; (b) comparative slices from the knock-out mouse shows decreased FA in the WM tracts, changes in the cortex and ; (c) slices from the difference map between the hybrid mouse and the average of day 5 images from normative strain with red arrows indicating region with large changes.

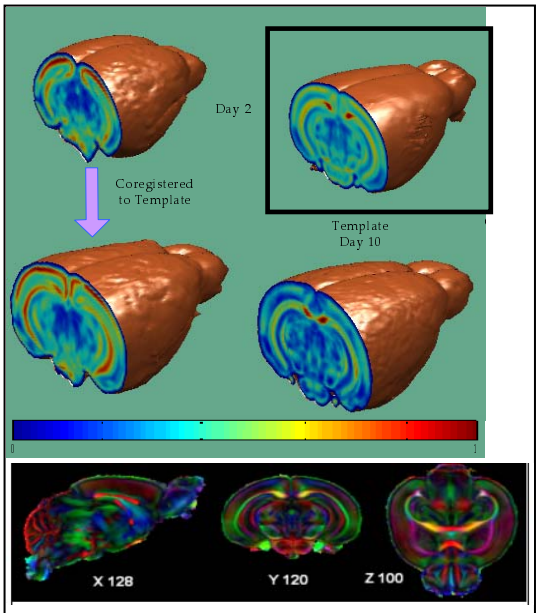

Figure 1: (Top) Spatial Normalization of day 2 brain to a common template of Day 10. (Inset) Mean normalized brain from mice of all days.(Bottom) Color map of the principal direction of the group-averaged mouse brain

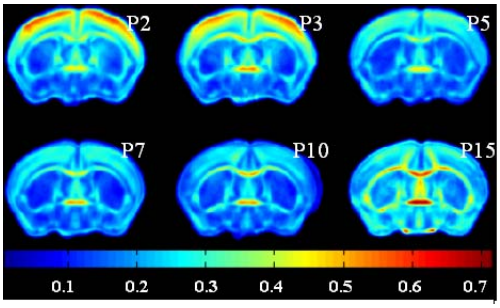

Figure 2: Average daily FA means of Day 2 to Day 15 (Axial view) indicate a gradual decline in FA values in GM structures such as cortex, and a steady increase in FA in GM structures.

RESULTS. We demonstrate the applicability of the normative atlas in studying differences in hybrid and mutant mice by analyzing a hybrid offspring (F2) of the B6EiC3SnF1/J hybrid mouse against the wild type mouse. The hybrid mouse is of day 5 and hence is compared against controls from the normative data of the same day. These hybrids are bred by crossing a male and female B6EiC3SnF1/J. As they are both hybrids, any offspring is expected to show some genetic defects, albeit subtle. Fig. 3 (c) shows decrease in anisotropy in the major white matter tracts (indicated by red arrows), anisotropy of the cortex, as well as growth related differences as in the hippocampus. The distance-score map (c) computed for the hybrid image against the day 5 images of the normative dataset, is able to identify these subtle differences as distances from the normative set. Regions marked by red arrows like the cortex and white matter tracts, demonstrate changes from the normative atlas. This demonstrates the ability of the normative atlas in identifying subtle changes in mice. Fig. 4 shows sample slices from the z-score maps indicating large changes in regions in yellow and red. The z-score maps show more diffuse changes owing to the variability in the day 5 specimens of the normative atlas. We expect the changes to be more specific as the normative atlas gets populated. This framework was applied to a single mouse brain, but it can be extended to a large sample size of mutant mice whose profile can be created independent of the normative atlas and then these can be compared on a daywise basis.

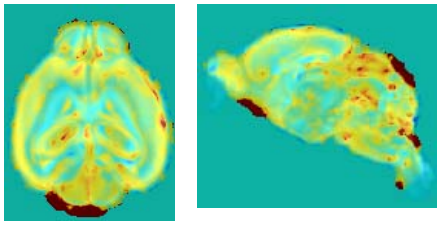

Figure 4. z-score map of the hybrid mouse. Yellow and red regions are regions of large changes

DISCUSSION. The results of these experimental studies will form the basis for further investigation of hybrid mouse model based on the difference in maturation patterns with the wild type mouse. They will also serve as normative data against which transgenic mouse models are compared. Although imaging and analysis cannot resolve micro-structural changes, it can provide a macro-structural characterization of underlying brain changes; it can also help guide more detailed histological studies, focused on the regions and mouse models that present interesting imaging findings. The morphological image analysis methodologies proposed herein will be able to quantify localized morphological characteristics of mutant mice, both in terms of gross morphology and in terms of fiber architecture, as compared to a normative baseline. This automated framework will help in high throughput studies of developmental changes in mutant mouse as compared to the normative atlas.

REFERENCES.

[1] PNAS, vol. 102, pp. 6978-6983, 2005.[2] D. Shen, MICCAI'04, pp. 582-590, 2004.