Quantitative Analysis of Brain Morphology in a Mouse Model of the Huntington's Disease

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Introduction: Mouse models of Huntington's disease (HD) have been used widely in preclinical development and testing of potential therapeutic treatments. In vivo monitoring of the mutant phenotype, for which MRI is well suited, is especially important. However, investigation of surrogate markers and quantitative measurements of such markers are still in the early stages. Previous studies in patients[1] with HD and mouse models[2] suggest that enlargement in the ventricles and atrophy in the caudate putamen are hallmarks of HD. In this study, we acquired in vivo MR images from HD mice, age matched control mice, and wild-type mice, and used techniques from computational anatomy to quantitatively characterize the difference in brain morphology between HD and control mice caused by gene mutation.

Methods: In vivo MRI of R6/2 (HD mutant, n = 6), control (n = 6) and wild-type mice (n = 8) was performed on a 9.4T MR system at the 12th week after birth. High resolution T_2-weighted images (RARE, TE = 40 ms, TR = 6 s, ETL = 4, NA = 8, 64 slices, resolution = 0.08 x 0.08 x 0.3 mm^3), which provide good contrast between brain and CSF and between gray and white matter, were acquired for each mouse. Skull stripping was performed to remove non-brain tissues. Image intensity was carefully adjusted so that the intensity values of the CSF, white matter, gray matter and background among different subjects were comparable. We manually segmented the whole brain, lateral ventricles, cortex, hippocampus and caudate putamen for volumetric measurements. We selected one wild-type mouse brain image as an initial template, and normalized other wild-type mouse brain images to the initial template using affine transformation. We then averaged the affine normalized images. This population averaged image served as our template for further normalization and analysis. Images from the R6/2 and control mice were first normalized to the common template using affine transformations and then using intensity based Large Deformation Diffeomorphic Metric Mapping (LDDMM)[3] with optimized parameters. The results were visually inspected for accuracy. From the transformations, changes in local tissue volume (as Jacobian maps) and tissue displacement were computed and visualized. Pixel-wise Student *t* tests were performed to detect brain regions with significant changes in tissue volumes.

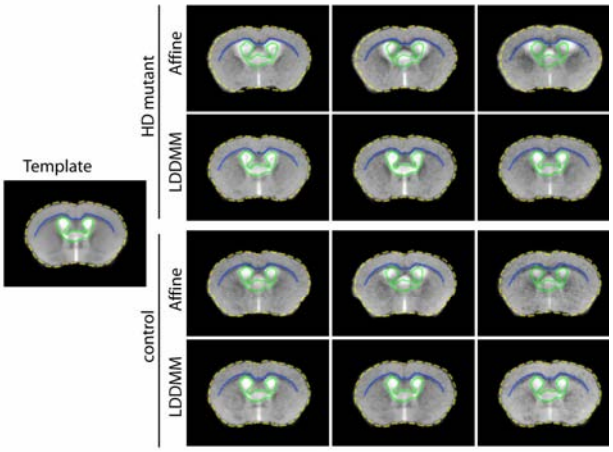

Fig. 1: Affine and LDDMM based normalization of three HD mutant and three control mice to a population averaged template (left). The boundaries of the whole brain, lateral ventricle and the corpus callosum and external capsule were defined in the template image and overlaid on the results to visualize the accuracy of normalization.

Results: Volumetric measurements from manual segmentation showed that the HD mutant mice have significantly enlarged lateral ventricles as well as atrophy in the caudate putamen ($p < 0.05$). The population average template images (Fig. 1 and Fig. 2, left column) show well defined lateral ventricles (bright) and white matter structures (dark). After affine transformation, images of HD mutant and control brains had similar overall shapes but still differed in detailed anatomical structures, e.g. the shape of lateral ventricles as shown by the overlaid boundaries defined in the template (Fig. 1). After LDDMM, differences in the shapes of the lateral ventricles between the subjects and the template were minimized. This result suggests that the nonlinear transformation obtained using LDDMM can capture the small difference in regional anatomy between mutant and control mouse brains. Differences in the LDDMM derived transformation then reliably reflected the shape differences between HD mutant mice and control mice. Fig. 2 shows the average local volume change as measured by the average Jacobian maps[3]. In the color-coded Jacobian maps, which show the local tissue volume changes between the HD mutant and control mouse brains, blue indicates possible atrophy in the HD mutant brains, while red and orange colors indicate possible structural expansion. By comparing the maps of local volume change with the template image and a histology based atlas, we could identify several regions with possible atrophy. These include regions in the caudate putamen, thalamus, frontal cortex, superior colliculus and part of the hippocampus (Fig. 2, blue regions). We also found significant expansion in the lateral ventricles and the 3rd ventricle (Fig. 2, red or orange regions). The results agree with previous descriptions of the phenotype based on histology[2].

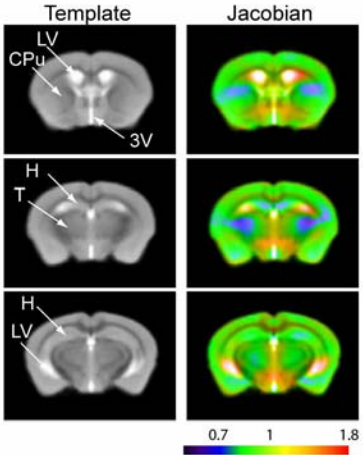

Fig. 2: The population averaged template (left) and Jacobian maps (right) showing regions of tissue expansion and shrinkage at three coronal sections. In the Jacobian map, red and orange color indicate local tissue expansion, blue color indicates local tissue shrinkage and green color indicates no change. Structural abbreviations are: CPu: caudate putamen; H: hippocampus; LV: lateral ventricles; T: thalamus; 3V: 3rd ventricle.

Discussion & Conclusion: Our results provide a quantitative characterization of the difference in brain morphology between HD mutant and control mice by combining in vivo MRI and techniques of computational neuroanatomy. Compared to the manual segmentation based approach, this approach has several advantages: first, it doesn't require manual delineation of anatomical boundaries, which is known to be susceptible to subjective errors; second, it allows analysis of the entire brains and is not based on prior assumptions about affected brain regions, which is required for manual delineation-based analysis. We believe that this type of approach will be an effective method to characterize the anatomical phenotype and monitor disease progression.

References: 1). H.D. Rosas, et al. NeuroRx (2004) Vol. 1, pp.263-272 **2).** E.C. Stack, et al. J. Comp. Neurology (2005) vol. 490, pp. 354-370 **3).** M.I. Miller, et al. Ann Rev Biomedical Engr (2002) Vol.4, pp.374-405