Imaging the Progression of Brain Atrophy in a Mouse Model of the Huntington's Disease

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Introduction: Mouse models of Huntington's disease (HD) have been widely used in preclinical development and testing of potential therapeutic treatments. In vivo longitudinal monitoring and quantitative evaluation of the developing phenotype are especially important for the evaluation of treatment efficacy. In this study, we acquired longitudinal MR images from R6/2 and age matched control mice, and evaluated the dynamic process of brain atrophy using advanced computational techniques. R6/2 mouse is a commonly used mouse model of HD. The model has well documented behavioral symptoms and neuropathology up to 14 week [1], with atrophy in striatum and enlarged ventricles as its hallmarks.

Methods: In vivo longitudinal MRIs of R6/2 (n = 7) and age matched control (n = 8) were performed on a 9.4T MR system at 7 time points (3week (w), 4w, 5w, 6w, 8w, 10w and 12 w after birth). High resolution 3D T_2-weighted images (FSE, TE = 40 ms, TR = 700 ms, ETL = 4, NSA = 2, resolution = 0.1 x 0.1 x 0.25 mm^3, twin navigator echoes for motion correction, total imaging time of 40 minutes) were acquired and skull stripped. We selected one 3 week old mouse brain image as a template, and normalized other mouse brain images to the template using rigid transformation followed by Large Deformation Diffeomorphic Metric Mapping (LDDMM) [2]. The results were visually inspected for mapping accuracy, and Jacobian maps were calculated from the mappings. Volumes of several major brain structures were obtained via semi-automated segmentation based on the mapping results. Differences in local tissue volume (as Jacobian maps) between the R6/2 and control mice at different time points were calculated. Two way ANOVA and cluster analysis were used to locate regions with significant ($p < 0.05$) difference in volume between R6/2 and control mice and regions with significant ($p<0.05$) volume changes over time in the R6/2 mice. The rates of change in local tissue volumes over time in the R6/2 mice were also calculated based on the mapping results.

Results: Fig. 1 shows the volumetric growth of the brain, lateral ventricles, caudate putamen (part of the striatum) and hippocampus in the R6/2 and control mice. The volumes of the brain and caudate putamen in R6/2 mice had significant ($p < 0.05$) atrophy at 5 week, while the hippocampus had significant atrophy at 8 week. The lateral ventricles in the R6/2 mice were in general larger than those in the controls, and the difference became significant after the 8th week. In Fig. 2, MR images from selected R6/2 and control mice showed mild brain atrophy and enlargement of the lateral ventricles in R6/2 mice at 5 week and became more severe at 12 week. Comparison between R6/2 and control mice at different time points (Fig. 2, Jacobian R6/2 vs control) showed significant atrophy in the caudate putamen and hippocampus at 5 week. Atrophy in the motor cortex and piriform cortex (region 1 and 2 in Fig. 2, respectively) were also observed and later confirmed by silver staining histology. Atrophy in brain became more severe and widespread at 12 week than at 5 week. The calculated rates of atrophy in R6/2 mouse brains (Fig. 2, Jacobian, R6/2 vs Time) showed that atrophy was not uniform over time. The rate of atrophy were higher at early stages (around 5 week) than at late stage (8~12 week).

Discussions: This study demonstrates the feasibility of longitudinal MRI in study of brain atrophy in R6/2 mice. Longitudinal MRI can delineate fine morphological details and can follow the same animal over time and therefore is less sensitive to biological variations. Advanced techniques of computational anatomy further enhance our ability to quantitatively characterize brain atrophy and its time course. The atrophy detected by MRI and their timing reported in this study agree with existing behavioral and pathological evidences [1]. Our results revealed that brain atrophy in R6/2 mice were not uniform over time and atrophy was most active at early stage. The results can be used as baseline data in future studies involving R6/2 mice. The information on the time course of atrophy is important for development and testing of potential treatment.

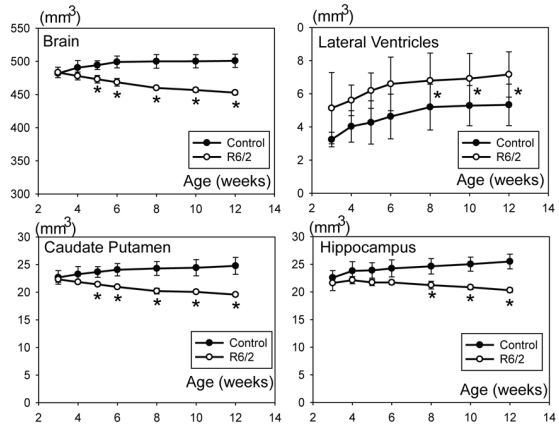

Fig. 1: Volumetric development of the whole brain, lateral ventricles, caudate putamen and hippocampus in R6/2 mice (white circles) and age matched controls (dark circles) from 3 week to 12 week. * = there is significant ($p < 0.05$, Student's *t* test) difference between R6/2 and control mice.

References:

1). E.C. Stack, et al. J. Comp. Neurology (2005) vol. 490, pp. 354-370 **2).** M.I. Miller, et al. Ann Rev Biomedical Engr (2002) Vol.4, pp.374-405

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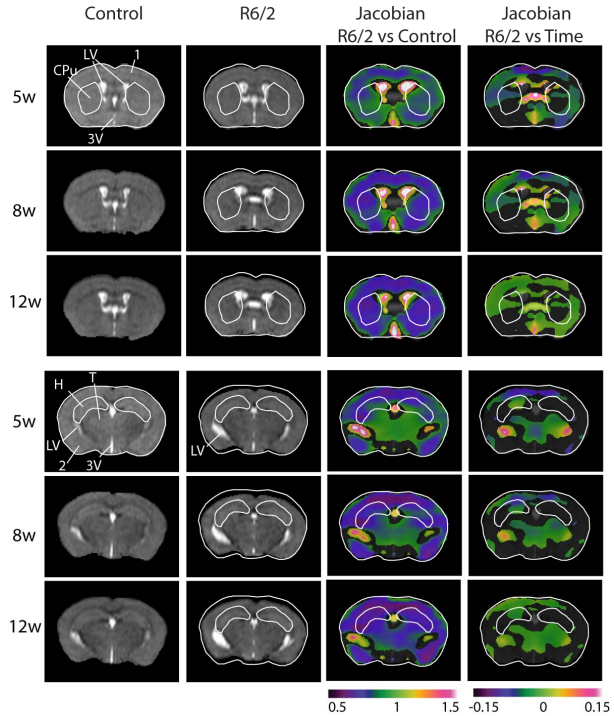

Fig. 2: Selected in vivo MR images of developing R6/2 and control mouse brains at two coronal levels (two left columns) and color-coded maps of relative tissue volume between R6/2 and control mice (the third column from left) and changes in volume over time in the R6/2 mice (the last column on the right). Only regions with significant difference/change are shown. Tissue boundaries defined in control mice are overlaid on the color-code maps as landmarks. Structural abbreviations are: CPu: caudate putamen; H: hippocampus; LV: lateral ventricles; T: thalamus; 3V: 3rd ventricle; 1: motor cortex; 2: piriform cortex.