Longitudinal *in vivo* MRI based spatiotemporal mapping of brain atrophy in the R6/2 mouse model of Huntington's disease

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Introduction: Huntington's disease (HD) is a fatal neurodegenerative disorder with no known treatments. Progressive atrophy of the brain, particularly the striatum, is an important hallmark of HD and is known to begin long before the onset of motor symptoms. Longitudinal studies in mouse models are therefore important to understand the spatiotemporal progression of brain atrophy, in order to identify windows for therapeutic intervention. In this study, longitudinal analysis of deformation based morphometry (DBM) metrics was established to analyze 3D *in vivo* MR images of the R6/2 mouse model of HD. The aim is to understand the dynamic spatiotemporal patterns of brain atrophy, e.g. the spatially varying rate of atrophy, in this model. The combination of longitudinal DBM analysis with high resolution *in vivo* MRI allowed, for the first time, elucidation of the growth patterns of normal wild-type (WT) brain development, progressive atrophy in R6/2 HD brains, and longitudinal differences in structural shape deformation, especially of the striatum, between the WT and R6/2 brains.

Methods: R6/2 HD and WT control mice (n=8 each) were imaged *in vivo* weekly from 3 to 6 weeks of age, and thereafter biweekly upto 12 weeks of age on a 9.4 T spectrometer. A 3D T2-weighted fast spin echo (FSE) sequence with navigator-echo phase correction scheme [1] was used (ETL=4, TE/TR = 40/700 ms, flip angle = 40°, NEX=2). The spatial resolution was 0.1 x 0.1 x 0.25 mm^3 with an imaging time of 40 min per animal. The serial WT and R6/2 brain images were spatially normalized to an *in vivo* population-averaged mouse brain atlas previously developed by our group [2], using a nonlinear image transformation technique based on large deformation diffeomorphic metric mapping (LDDMM) [3]. For analysis of longitudinal morphological changes, a linear mixed effects (LME) model with linear splines and a node at 5 weeks of age was established for voxelwise modeling of the following DBM-derived metrics: i) log-transformed Jacobian maps of the LDDMM-based deformation fields, and ii) projection of the deformation vectors along the normal to the surface of the striatum. The resulting statistical maps were corrected for multiple comparisons using a false discovery rate of 0.05.

Results & Discussion: Longitudinal statistical analysis of voxelwise log-Jacobian maps revealed regions within the brain with significant age-related changes in the WT brains, significant progressive atrophy in the R6/2 HD brains, and regional differences in atrophy patterns between the 3 to 5 week period and the 5 to 12 week period. Fig. 1 (top panel) shows the growth patterns detected during normal WT mouse brain development. Brain development in the mouse is known to continue during the first few postnatal weeks. Several regions within the brain such as the cerebellum (cer), olfactory bulb (ob) and striatum (st) were found to undergo significant growth upto 5 weeks of age (Fig. 1 A), while the lateral ventricles (LV) showed significant enlargement throughout upto 12 weeks of age. Interestingly, progressive age-related atrophy within the cortex (Cx) was also detected in the WT mice (Fig. 1 A'). The bottom panel in Fig 1 shows the spatiotemporal mapping of progressive atrophy in the R6/2 HD brains compared to WT controls. From week 3 to week 5, significant atrophy primarily within the cortex could be detected in the R6/2 brains (Fig. 1 B). Between weeks 5 and 12, the atrophy was found to extend to regions within the striatum, superior colliculus and the hippocampal formation (Hi) (Fig. 1 B'). Fig. 2 shows the longitudinal differences in striatal shape deformation between R6/2 and WT mice. Compared to WT controls, significant inward deformation of the striatal surface could be detected in the R6/2 mice. The differences observed were bilateral, and detected primarily in the lateral and inferior regions of the striatum, suggesting gross progressive atrophy of the striatum in these regions in the R6/2 mice.

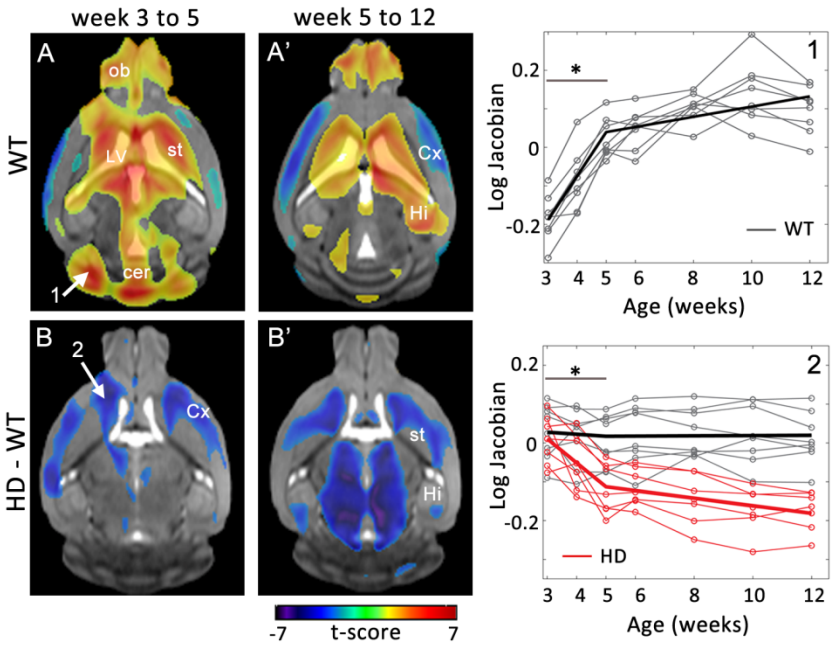

Fig. 1: Spatiotemporal mapping of local volumetric changes in HD and WT mouse brains. **A,A'**) Growth curves of the WT brains, showing significant growth in the cerebellum and ventricles (week 3 to 5) as well as age-related cortical atrophy from weeks 5 to 12. **B,B'**) Progressive atrophy in the R6/2 brains compared to WT controls. Gross atrophy in the cortex (week 3 to 5), striatum and hippocampus (week 5 to 12) can be seen. Log Jacobian plots show the individual trajectories and overall growth curve predicted by the LME model (bold line) for locations *1*, *2*.

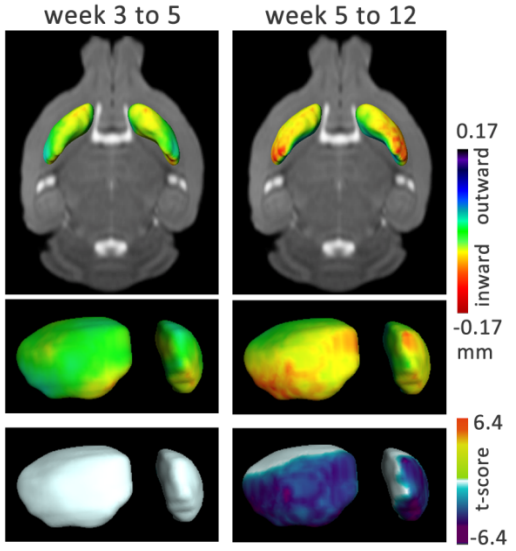

Fig. 2: Longitudinal differences in striatal shape deformation in R6/2 mice compared to WT controls. Color-code represents the net longitudinal inward or outward deformation of the striatal surface in R6/2 mice compared to WT. Significant inward deformation of the lateral and inferior striatal surfaces in R6/2 brains can be seen between weeks 5 and 12, suggesting gross atrophy of the striatum in these regions..

The findings in the current study indicate that longitudinal *in vivo* MRI and DBM-based analysis could sensitively detect progressive atrophy in the R6/2 mouse model of HD. Atrophy of the cortex and striatum detected in the current study is consistent with the known pathology of disease in the R6/2 model based on conventional histology. We also detected progressive atrophy within the R6/2 hippocampus, that has been implicated in the cognitive deficits known to occur in this model [5]. These results demonstrate the potential of longitudinal analysis of DBM-derived metrics for mapping the rate of brain atrophy and its spatiotemporal progression in the R6/2 HD mouse model, and can be used for assessment of the effects of potential therapeutic treatments in this model.

References: [**1**] Mori & van Zijl, *Mag Res Med* 40, 1998 [**2**] Miller *et al.*, *Ann Rev Biomed Eng* 4, 2002 [**3**] Aggarwal *et al.*, *Neurosc* 162, 2009 [**4**] Lerch *et al.*, *NeuroImage* 39, 2008 [**5**] Murphy *et al.*, *J Neurosc* 20, 2000