Characterization of age-dependent brain atrophy in presymptomatic YAC128 Huntington disease mice

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Introduction

Huntington disease (HD) is a neurodegenerative disorder characterized by decline of motor and cognitive abilities[1]. Magnetic resonance imaging (MRI) in human HD patients has revealed striatal, white matter and cortical atrophy[2-4]. Identification of brain regions that exhibit the earliest signs of atrophy by MR imaging could highlight areas for therapeutic targeting and may provide non-invasive endpoints for early intervention. The YAC128 mouse model of HD expresses the full human *HTT* gene[5] and mimics many features of the human condition. This model is therefore useful for understanding the progression of HD and evaluation of treatment trials. Ex-vivo cross-sectional studies of the YAC128 mice showed progressive decrease in total brain, striatal, white matter and cortical volume starting at 3 month old[6]. However, detailed in vivo longitudinal regional analysis is lacking and whether structural atrophy can be detected earlier is not clear. In this study we conducted longitudinal structural imaging to characterize the progression of brain morphological changes in the YAC128 HD mice.

Methods

8 wild-type (WT, 4 males) and 8 YAC128 (4 males) mice of the FVB strain were scanned at 1.5, 3 and 6 months old, on a 7T MRI (ClinScan, Bruker BioSpin, Germany) using 4 channel array coils. The structural image was acquired by fast-spin-echo T2-weighted MRI with TR=2760ms, TE=43ms and 0.1x0.1x0.3mm voxel resolution with coil inhomogeneity normalization. The brain was extracted using 3D-PCNN[7] with manual editing. Images were linearly registered to a mouse brain template[8] and then averaged to create time-point specific templates. Data of each subject were then non-linearly registered to their corresponding time-point templates using FSL. Tensor-based morphometry (TBM), based on the Jacobian determinant (a measure of volume changes from non-linear registration), was conducted to compare the tissue volume differences between WT and YAC128 mice. Total brain volumes were quantified based on the extracted brain. To track volume changes, a region of interest (ROI) was drawn in the caudate putamen (CPu) based on the results of the TBM at 6 months, and was transformed accordingly for the 3 and 1.5 months timepoints. The volume was calculated based on the mean Jacobian determinant in the ROI.

Results

YAC128 mice show atrophy in the CPu bilaterally and in white matter tracts (corpus callosum, anterior comissure, external capsule, fimbria) starting from 1.5 months, and progressing to 6 months (Fig.1). Cortical atrophy was observed at 6 months. The total brain volume of YAC128 mice was significantly smaller than WT at 6 months (Fig.2A) while the CPu volume was lower at 1.5 months but became insignificant after normalization to total brain volume (Fig.2B&C).

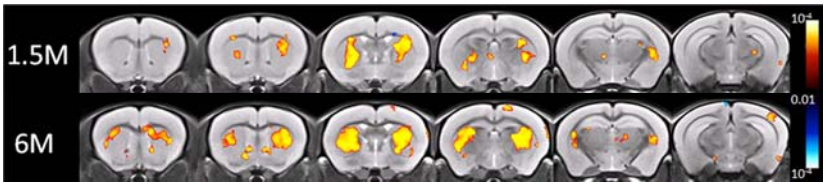

Figure 1. TBM results at 1.5 and 6 months ($p<0.01$, cluster size 500 voxels). Red-yellow: structure is bigger in WT, blue-light blue: structure is bigger in YAC128.

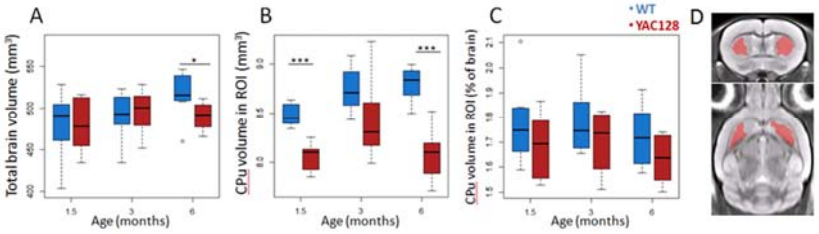

Figure 2. Group comparison of A) total brain volume, and CPu volume in the ROI shown in (D) B) without and C) with normalization by total brain volume. *p<0.05, **p<0.01, ***p<0.001 (2-tailed t-test).

Discussion

Progressive atrophy in multiple regions of the YAC128 mouse brain was detected in the presymptomatic stage, consistent with previous ex vivo, cross-sectional MRI studies and stereological studies[6,9]. In particular, the posterior portion of CPu started to show atrophy as early as 1.5 months. Imaging of the symptomatic stage is in progress. Once completed, a full history of the structural pattern of neurodegeneration can be mapped.

Conclusion

Understanding the longitudinal structural changes in brains of YAC128 mice will help to identify vulnerable regions that can be used to track disease progression and assess the therapeutic effects of candidate interventions. This will lay the path for evaluation of preclinical treatment trials of HD and related neurodegenerative diseases.

References

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