Characterization of age-dependent brain atrophy in presymptomatic YAC128 Huntington disease mice
Ling Guo1, Xuan Vinh To1, Xin Hong1, Reshmi Rajendran1, Si Kang Lew1, Yee Ling Tan1, Yihui Huang2, Michael R. Hayden2,3, Mahmoud A. Pouladi2,3, and Kai-Hsiang Chuang1
1Singapore BioImaging Consortium, Agency for Science, Technology and Research, Singapore, Singapore, 2Translational Laboratory in Genetic Medicine, Agency for Science, Technology and Research, Singapore, Singapore, 3Department of Medicine, National University of Singapore, Singapore, Singapore

Introduction
Huntington disease (HD) is a neurodegenerative disorder characterized by decline of motor and cognitive abilities1. Magnetic resonance imaging (MRI) in human HD patients has revealed striatal, white matter and cortical atrophy2-4. 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 gene5 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 old6. 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, 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-PCNN7 with manual editing. Images were linearly registered to a mouse brain template8 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 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).

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 studies6,9. 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