Progressive neuroanatomical changes in the YAC128 mouse model of Huntington's Disease

J. P. Lerch[1], J. B. Carroll[2], M. van Eede[1], M. R. Hayden[2], and R. M. Henkelman[1]

[1]Mouse Imaging Centre, Hospital for Sick Children, Toronto, Ontario, Canada, [2]Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, British Columbia, Canada

Introduction

As in human Huntington's Disease (HD), the phenotype of the YAC128 mouse model of HD is progressive, with early cognitive deficits followed by striatal and cortical atrophy[1,2]. A recent exploratory MRI analysis of 8 month old YAC128 mice, representing a very early stage of the disease process, found increases in cortical thickness in the somatosensory cortex alongside the expected but subtle decreases in striatal volume[3,4]. Here we add a new cohort of 12 month old YAC128 mice to take advantage of the whole brain coverage of MRI in order to ascertain the progressive nature of HD.

Methods

FVB/N (Charles River, Wilmington, MA) wild-type mice and YAC128 transgenic HD model mice maintained on a FVB/N background were anaesthetized at 8 and 12 months of age with 9 mice per group (for a total of 36 mice). MR scans were acquired using fixed brains in their skulls with T2 FSE scans at 32µm isotropic voxels on a 7T Varian console. A model-independent average of all scans was created and segmented into 62 separate structures by non-linear alignment towards a pre-existing atlas [5]. Cortical thickness was computed at every point of the cortex by solving Laplace's equation between the inside and outside of the cortex[3]. Prior to these analyses extra-cortical CSF was removed to ensure accurate segmentation of the cortical boundary [6].

Results

Striatal atrophy, the hallmark of HD, worsened over those four months, decreasing from a 3.4% ($p<0.02$) reduction relative to wild-types at 8 months of age to a 6.3% ($p<0.002$) reduction at 12 months. Regions of the somatosensory cortex previously found to be thicker in 8 month old YAC128 compared to age matched wild-types were thinner at 12 months of age ($p < 0.009$).

Discussion

YAC128 mice show progressive atrophy over time, with the striatum being most affected. Brain regions that were larger in YAC128 mice than wild-type controls at 8 months of age, such as the sensorimotor cortex, decline significantly with time. This reinforces our previous hypothesis that the early stage thickening of the somatosensory cortex is a compensatory response to the ongoing degeneration of the striatum which disappears with continued disease progression.

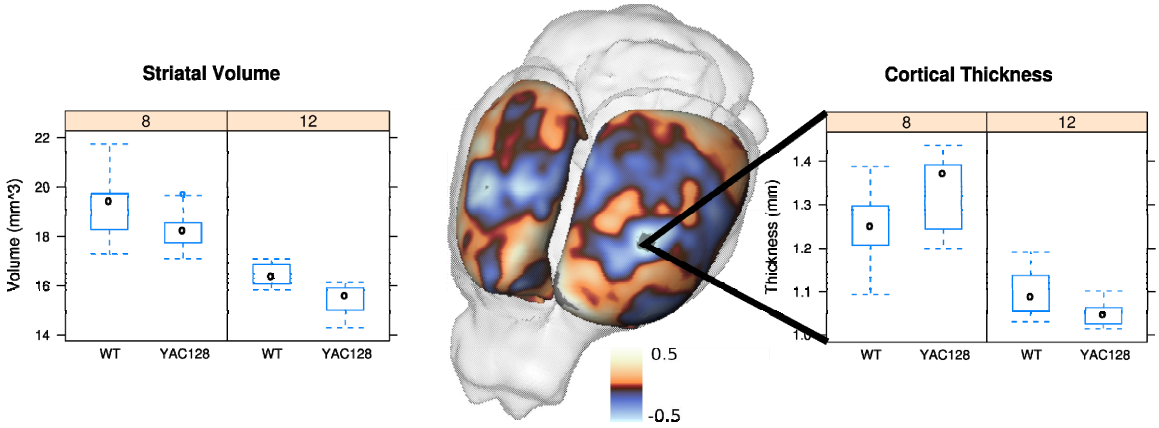

Fig 1: Striatal volume at 8 and 12 months of age is shown on the left, with the interaction between genotype and age in mm mapped onto the cortex in the middle and illustrated at a single vertex in the box and whiskers plot on the right. The interaction was significant at a 5% False Discovery Rate at this point.

References:

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