Brain behavior relationship in wild-type mice and a mouse model of Huntington's disease

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Introduction – In this study we examined brain-behavior correlations in mice using high resolution MRI and 4 different behavioural tests. Secondly, we investigated how these relationships might be altered in Huntington's disease (HD). For the latter we used YAC 128 mice, a mouse model of HD (1) which recapitulates many of the clinical features and characteristic neuronal changes of HD (2).

Methods – *Behavioral Testing*- All mice were tested repeatedly using a test battery consisting of the Rotarod, Forced-Swim test, Pre-pulse-Inhibition and Open Field test. *Specimen Preparation*- Twenty-three (9 wild-type FVB/N and 14 YAC128) brains were examined. At 12 months of age the mice were anesthetized and perfused. Following perfusion the heads were removed along with the skin, lower jaw, ears and the cartilaginous nose tip. The remaining skull structures containing the brain were placed in 4% PFA for 12 hours. After an incubation period of 5 days the skulls were transferred to PBS and 0.01% sodium azide and 2mM ProHance solution for at least 7 days. Imaging took place 12 to 21 days post-mortem. *MRI acquisition*- A multi channel 7.0 Tesla MRI scanner (Varian Inc., Palo Alto CA) with a 6cm inner bore diameter insert gradient was used to acquire anatomical images of the brains within the skulls. Three custom made coils were used to image three brains in parallel. The parameters used were optimized for grey/white matter contrast: a T2-weighted, 3D fast spin-echo sequence, with TR/TE=352/32 ms, four averages, field-of-view=14x14x25mm, matrix size=432x432x780 giving an image with 32 μm isotropic voxels. Total imaging time was 11.3h. *Data Analysis*- The MRI scans were non-linearly aligned to a three dimensional atlas of the mouse brain with 62 structures identified (3). The resulting deformation fields for each individual brain were used to calculate individual volumes. Only the 10 brain largest brain structures that constitute more then 3% of total brain volume were included in the following analysis. *Correlation Analysis*- Pearson product-moment correlation coefficients (r) were calculated between the behavioral test measures and the 10 brain structure volumes

Results– Strong ($r \geq 0.5$, or $r \leq -0.5$) linear brain behavior relationships between task performances and brain structure volumes were found for all behavioral measures in the wild-type mice: Rotarod time correlates positively with frontal lobe, striatum hypothalamus and amygdale and negatively with the entorhinal and cerebellar cortex (Fig. 1); forced swim immobile percentage correlates positively the hippocampus and negatively with the parieto-temporal cortex; Prepulse-inhibition shows the inverse pattern of the forced swim immobile percentage; open field test distance traveled correlates negatively with the hypothalamus and hippocampus, open field time resting shows the inverse. In the mouse model of HD none of the 13 correlations in the wild-type mice is present (Fig.1) and only 4 strong correlations, all different than in wild-type mice are found.

Discussion and Conclusion – The results demonstrate strong brain behavior correlations in the wild-type mice. A number of functional networks related to test performance can be identified: the cortico-subcortical motor system (frontal lobes and striatum) that is counterbalancing the cerebellar motor system; the stress and anxiety system (hypothalamus and amygdala); the cognitive gating system (parieto-temporal cortex); and the memory system (hippocampus). These correlations are an expression of learning related structural brain changes that are coupled with performance enhancements similar to those found in classical training experiments (4). The strong correlations found in the wild-type animals indicate that studying brain volumes and their relationships with behavioral performances is a very valuable way to study the brain networks tasked with controlling different aspects of behavior. The changed correlations in the disease model mice could provide some valuable insight into disease processes. The HD mice still clearly show training effects in their performances (Fig.1). However, disease related processes seem to interfere with the normally observed structural volume changes.

References- 1)Slow et al. *Hum. Mol. Genet.* 12 : 1555–1567 (2003), 2)Lerch et al. *Neuromiage* 39: 32-39 (2008), 3) Dorr et al. *Neuromiage* 42: 60-69 (2008), 4)Lerch et al. *ISMRM* (2008)

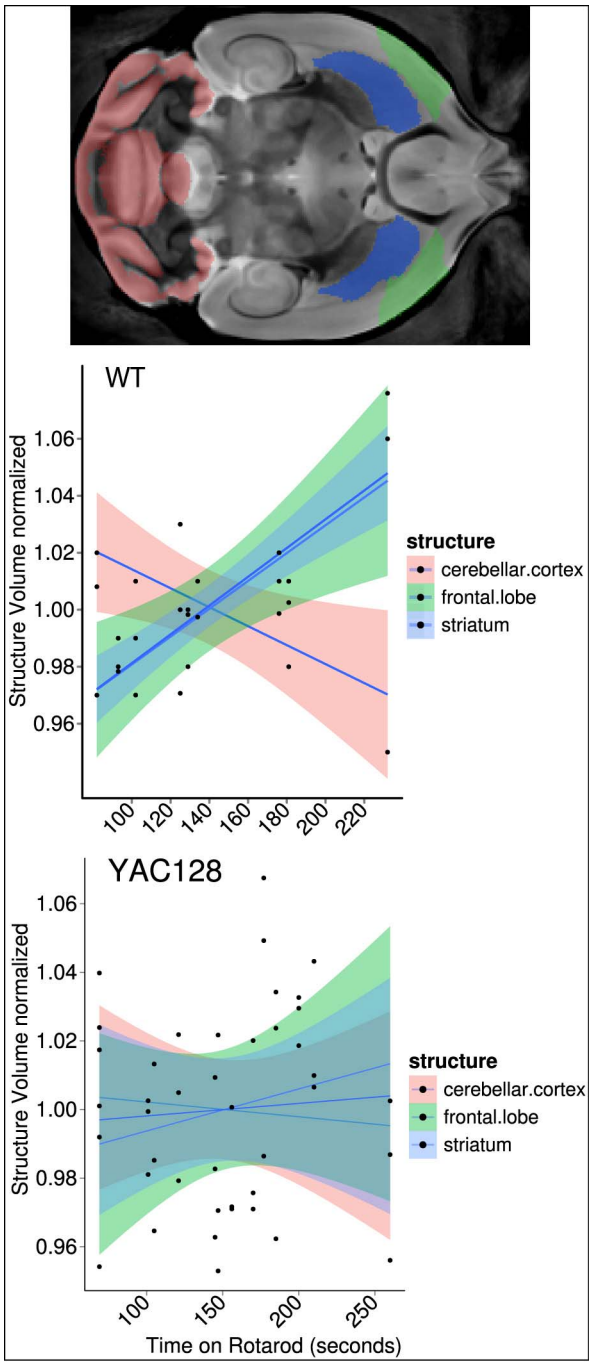

Fig 1: Strong brain behavior correlations are found in wild-type mice. Rotarod performance has a strong positive relationship with frontal lobe and striatal volume, and a strong negative relationship with cerebellar grey matter volume. No such relationship can be found in the mouse model of HD