First Demonstration that Brain Training alters Macro- and Micro-structure in a Mouse Model of Huntington's Disease

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Introduction Huntington's Disease (HD) is a fatal neurodegenerative disease, characterised by atrophy in the striatum, and the development of cognitive and motor deficits. Cognitive stimulation has been found to improve behavioural performance in a mouse model of HD[1]. The neurobiological basis underpinning this functional gain has yet to be studied.

In vivo macrostructural (T2-weighted) MRI has previously been applied in mouse models of HD to study change in brain tissue volume. However, in vivo diffusion MRI - to assess tissue microstructure, and diffusion tractography - to reconstruct white matter pathways, have not yet been applied preclinically with algorithms capable of resolving crossing fibers. Our objective was to investigate whether long-term cognitive training produced alterations in brain macrostructure and/or microstructure, detectable with in vivo T2-weighted MRI and diffusion MRI respectively. Notably, this is the first study to apply tractography using in vivo diffusion MRI data in a mouse model of HD.

Materials and Methods YAC128 transgenic HD mice and age-matched wild-type (WT) mice were trained daily for 30-minutes on a serial implicit learning task[2] throughout their lifetime. At 21 months old, 22 trained mice (11 YAC 128, 11 WT) and 22 untrained mice (11 YAC128, 11 WT) underwent in vivo MRI on a 9.4 T magnet using a 2D Rapid Acquisition with Refocused Echoes (RARE) T2-weighted sequence: FOV = 15.4 x 15.4 mm, slice thickness = 400 µm, 30 slices, in-plane resolution = 120 x 120 µm, TR/TE=4000/35 ms. In a subset of animals (n = 32), a 4-shot DTI-EPI sequence was also acquired: 27 slices of thickness = 320 µm, FOV = 22.4 mm x 22.4 mm, acquisition matrix = 96 x 96, TR/TE=14604/TE 20 ms, with diffusion weighting (δ=4ms, Δ=10ms, b = 1000 s/mm^2) in 30 directions and 5 non-diffusion weighted images. Following this, a battery of behavioural tests was performed on all animals (rotarod test, locomotor activity, watermaze).

Regions of interest (ROI's) were drawn manually for the striatum and cortex in 5 slices that demonstrated clear anatomical landmarks. Diffusion weighted images were corrected for motion/distortion and partial volume contamination[3]. Tractography based on constrained spherical deconvolution[4] (CSD, lmax = 6) was performed and mean tensor-based parameters and tract volume were obtained for the cortico-striatal and callosal pathways.

Results

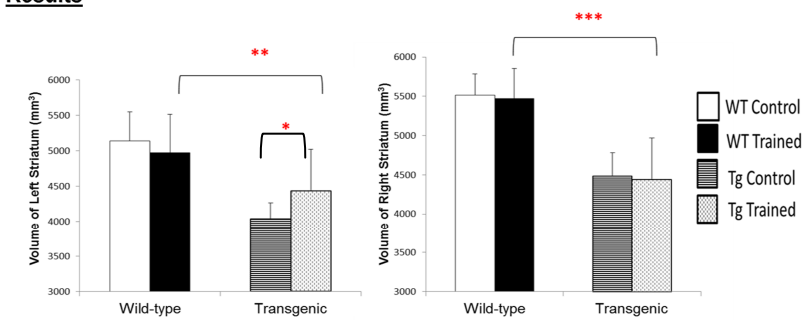

Fig. 1. Training-induced macrostructural change. Volume of striatal ROI in WT and transgenic mice, ANOVA, * p<0.05, ** p<0.01, *** p<0.001. Error bars represent 1 standard deviation (SD). Striatal hemispheres were analysed separately due to a genotype*training interaction. Striatal volume (left and right) and cortical volume (not shown) was significantly lower in transgenic animals, p<0.01. Whole brain volume was not affected by genotype. A disease-modifying effect of training is seen in transgenic mice; the degree of genotype-induced atrophy is reduced in trained animals. Because mice were scanned at the end of their natural lifespan, some mice died naturally before this time. This skewed the gender distribution in the untrained WT group (white bars); this group was excluded from the statistical analysis in all figures.

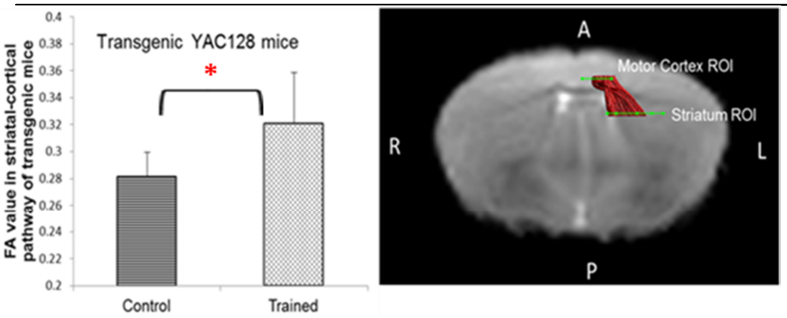

Fig. 2. Training-induced microstructural change. Fractional anisotropy (FA) was significantly higher in trained transgenic mice compared to untrained transgenic mice, in the pathways between the striatum and motor cortex in the left hemisphere, p<0.05, reconstructed using CSD-based tractography. There was no significant difference in the other diffusivity indices or tract volume. There was no effect of training in the genu of the corpus callosum (not shown). Error bars = 1 SD.

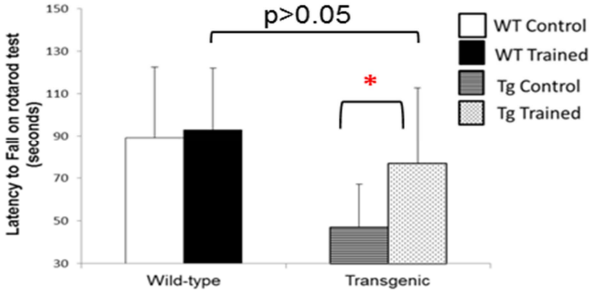

Fig. 3. Training-induced motor recovery. Latency to fall (secs) was significantly improved (* p<0.05) in trained transgenic animals compared to untrained transgenic mice on the rotarod test, the classic motor performance test in HD mouse studies. There was no effect of training on locomotor activity over a 24-hour period or on watermaze performance (not shown). Error bars = 1 SD.

Discussion Intensive cognitive training not only produces functional gain but also produces macro-structural and microstructural changes in a transgenic mouse model of Huntington's Disease. Three converging outcome measures demonstrate a beneficial disease-modifying effect of training: a reduction in disease-related atrophy in the striatum, an increase in fractional anisotropy in striatal-cortical tracts, and functional gains in motor performance. Not only is this the first study to successfully apply in vivo diffusion tractography in a mouse model of HD, and the first to demonstrate that tract-specific measurements provide sensitivity to detect microstructural changes following a behavioural intervention in a mouse model of disease, this study has important implications for translational research and the evaluation of therapeutics.

References [1]Wood N et al. *Neurobiol Dis*. 2011; 42(3):427-37. [2]Trueman R et al. *Eur J Neurosc*. 2007; 25(2):551-8. [3]Pasternak O et al. MRM. 2009; 62(3):717-30. [4]Tournier JD et al. *Neuroimage*. 2007; 1; 35:1459-72. **Acknowledgments.** Funded by the Wellcome Trust and EHDN