Presymptomatic detection of brain abnormalities in a transgenic ratmodel for Huntington' disease using in vivo Diffusion Tensor Imaging.

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Background **Huntington's disease (HD)** is an autosomal neurodegenerative disorder characterized by diffuse brain atrophy, although the most substantial neuronal loss occurs in the caudate and putamen. It has been shown in carriers of HD that regional cerebral atrophy and white matter changes already occur during the preclinical phase [1]. **Diffusion tensor imaging (DTI)** has been widely used for detailed analyses of **brain connectivity, tissue morphology and pathology** and has been shown to specifically trace neurodegenerative changes such as axonal degeneration, demyelization and cell swelling in demyelization disorders and Alzheimer disease. Previous DTI studies performed by our lab have successfully demonstrated neurodegenerative changes in a lesion model of HD [2]. Transgenic models provide the advantage of mimicking the human pathology more closely and in addition they display a more progressive course of the disease. The animals exhibit adult-onset neurological phenotypes with reduced anxiety, cognitive impairments, and slowly progressive motor dysfunction as well as typical histopathological alterations in the form of neuronal nuclear inclusions in the brain, which appear at around the age of 6 – 9 months [3].

Aim *We aimed at revealing the **first signs** of neurodegeneration by investigating changes of microstructure and neuroconnectivity in very young (2 months old) **transgenic animals,** using Diffusion Tensor Imaging. The results of this study will be highly valuable for pre-clinical screening as well as for the understanding of the specific underlying pathogenesis of these diseases.*

Method *MRI:* In total, 24 presymptomatic animals (n=12 TG and n=12 WT) were used in the present study [3]. At the age of 2 months, high resolution (voxel size: 0.136µm x 0.136µm) DTI (FSE DTI: TR/TE = 2200/34ms, 14 averages, b= 800 s^2/mm, diffusion sensitizing gradients along 7 directions) of the entire rat brain (coronal slices, slice thickness: 0.43mm) was performed on a 9.4Tesla Bruker Biospec (Ettlingen, Germany), under 1.5-2% isoflurane anesthesia. The measurements took 4 hours, during which respiration and temperature were continuously monitored, whereby temperature was kept constant at 37,1±0,01 and breathing rate 56,0±0,5 bpm. *Data analyses:* Diffusion Tensor Images were processed using in house developed Matlab routines to generate the **eigenvalue (λ_1, λ_2, λ_3) and fractional anisotropy (FA) maps**. Quantitative indices were calculated including **axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD) and fractional anisotropy (FA)**. Region of interest analysis (ROI) was performed by segmenting different grey and white matter structures (striatum – CP, internal and external capsule - CI/CE, corpus callosum - CC, deep cerebral white matter - DCWM and fimbria hippocampus - FI) and furthermore the ventricles on the different DTI maps using AMIRA software (Amira 3.1; Mercury Computer systems, San Diego USA). Statistical analyses (non-parametric) were done using SPSS (SPSS; Statistical Package for Social Sciences, version 14.0).

Results and discussion Of all white matter structures investigated, only **DCWM** displayed a significant difference ($p<0.05$) between the TG and WT groups showing a decrease in FA (Figure 1). These changes in FA suggest that the preclinical expression of HD is a result of abnormalities in distinct white matter tracts which could be related to a decrease in number or density of axons, diminished meyelination or a decreased orientational coherence of the fiber tracts [1].

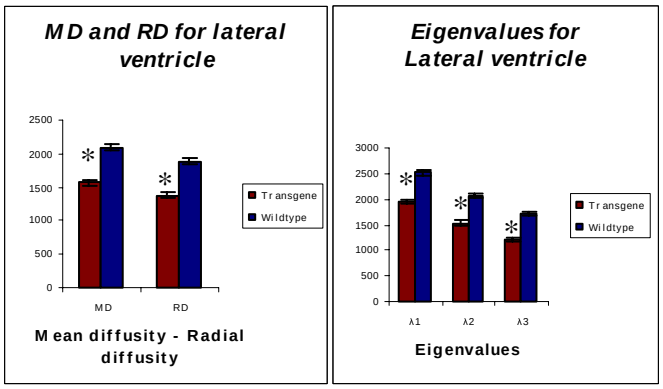

Figure 2: (left) MD and RD values and (right) eigenvalues (λ_1, λ_2, λ_3) measured in the lateral ventricle of respectively TG and WT animals, showed significant differences between both groups.

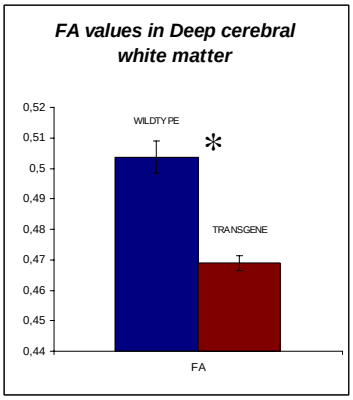

Figure 1 (right): FA values measured in the DCWM respectively of TG and WT animals.

Furthermore, significant changes (MD and RD decrease, $p<0.05$) could be detected in the lateral ventricle (Figure 2) but not in the other ventricles. These data might suggest a change in composition of CSF which was reported earlier in HD patients [4]. On the other hand, we would then expect to notice these changes in all the ventricles, which we did not. The DTI changes might also be related to alterations in CSF flow and/or turbulence. As the lateral ventricle is the only ventricle where the subventricular zone (SVZ) is situated, the distorted DTI values in an ROI covering this ventricle might reveal modification at the level of the SVZ as well. This has been reported in HD patients and in several other neurodegenerative diseases [5].

The present study reveals early presymptomatic changes in a particular white matter structure and at the level of the lateral ventricle in a TG rat model for HD using in vivo DTI tools. As these data are part of a longitudinal multimodal study (including PET, behavior and histology), ongoing analysis of these repeated measures will reveal whether progressively other white matter structures and other ventricles will become affected.

References

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