Diffusion Kurtosis in a symptomatic rat model of Huntington's Disease: selective grey and white matter pathology

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Background Huntington's Disease (HD) is a dominantly inherited neurodegenerative disorder. One important focus of HD research is to identify biomarkers of HD neuropathology and progression. Since it is established that before the appearance of clinical symptoms, cell death has already occurred [1], neuroimaging techniques have gained wide acceptance in HD research. Transgenic models, which are closely related to human pathology, allow the examination before onset and further progression of neurodegeneration, using translational tools and complementary techniques. Recently, Diffusion Kurtosis Imaging (DKI) was proposed to quantify the non-Gaussian nature of the diffusion process in biological tissue [2-3]. Non-Gaussian diffusion results from diffusion barriers, such as cell membranes and water compartmentalization and is therefore an indicator of microstructural complexity. *In the present study, we used the microstructural sensitivity of DKI, to detect neurodegeneration in symptomatic tgHD rats and WT littermates. The data presented herein support significant micro-structural changes in white and grey matter structures of TgHD rats.*

Method *In vivo* MR diffusion experiments were carried out on 15 rats (n=7 WT and n=8TgHD) at the age of 16 months. DKI images (9.4T Bruker Biospec scanner - Ettlingen, Germany) were acquired using a spin echo EPI sequence with the following parameters: 30 non-collinear gradient directions, TR/TE=6500/24ms, δ=5ms/Δ=12ms, NEX=4, acquisition matrix = 96*64, in plane resolution of 0.3*0.3 mm^2 and slice thickness=0.6 mm. Eight *b*-values (0, 400, 800, 1200,1600, 2000, 2400 and 2800 s/mm^2) were used along each direction. During experiments respiration rate and temperature were continuously monitored, and kept constant. *Data analyses:* DKI data were realigned using the 'diffusion II toolbox' in SPM5 and processed using Matlab routines to generate the DTI (fractional anisotropy - FA, mean diffusivity - MD, Radial diffusivity – RD, axial diffusivity - AD) and DKI (mean kurtosis - MK, radial kurtosis - RK, axial kurtosis - AK, kurtosis anisotropy - KA) parametrical maps. Region of interest analysis (ROI) was performed by a manual segmentation of grey (*hippocampus; caudate putamen*) and white matter (*corpus callosum and external capsula*) structures. Statistical analyses were done using SPSS (SPSS; Statistical Package for Social Sciences, version 16.0).

Results and Discussion The diffusion parameters for which a significant difference was found are presented in *figure 1*. The pathological hallmark of HD is a widespread neuronal degeneration, mostly within the caudate putamen, followed by white matter abnormalities and cortical dysfunction [4]. We observed a trend towards an increase in FA *(p=0,08)* in white matter (external capsula). However, DKI revealed a significant increase in KA *(p=0.03)* and RK *(p=0.02)* in the same white matter structure. This is the first time that white matter alterations are reported in the TgHD ratmodel. In the caudate putamen, we observed a similar increase of following DT and DK parameters *(FA: p=0.04; KA: p=0.01; RK: p=0.03)*. This could be explained by the ongoing dynamic process of huntingtin aggregation, starting at 9 months of age and strongly present at the age of 12 months in the caudate putamen [5-6]. Similar to the late-onset form of the human disease, TgHD rats exhibit adult-onset, slowly progressive phenotypes with impairments in motor, cognitive and affective behavior and nuclear inclusions [5]. In addition, behavioral analyses, histology [7] and DKI [8] revealed already an early phenotype at the age of postnatal day 10. As these data are part of a multimodal study (including, behaviour and histology), ongoing analysis of these measures could reveal possible correlations. By studying the more widespread neuropathological features of HD in genetically engineered animal models, both established and novel neuroimaging tools are essential for the modeling of the effect of potential treatment on specific brain regions.

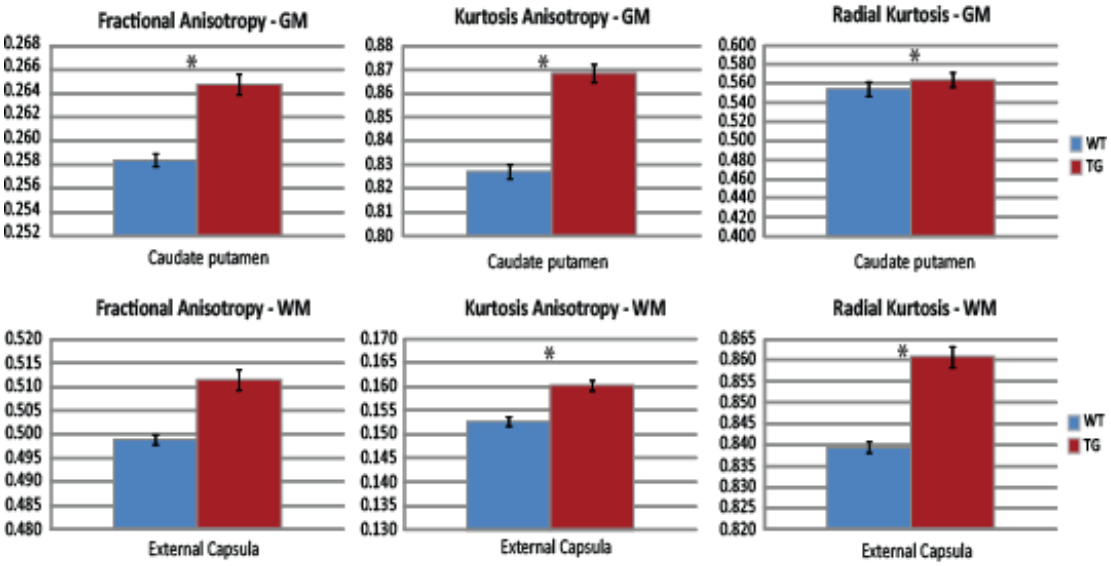

Figure 1: Mean and Standard error of diffusion parameters measured in grey (GM) and white matter (WM): (top) FA, KA and RK of the caudate putamen is significantly higher in the GM of the TgHD group; (bottem) FA, KA and RK of the external capsula are significantly higher in the WM of the TGHD group. P values are < 0.05.

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