Exploratory 7T MRS in Huntington's disease gene carriers.

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I**ntroduction**. Huntington's Disease (HD) is a hereditary genetic disease which presents with motor, cognitive and behavioural symptoms. Mean age at onset is 40 years of age with a mean disease duration of 20 years. The cause is a mutation in the IT15 gene which is found on the short arm of chromosome 4. This leads to an expanded CAG repeat resulting in the synthesis of an abnormal Huntingtine-protein (Htt). To date, the major manifestation of Htt has been demonstrated in brain tissue whereby Htt's toxic effects have been shown to lead to atrophy and neuronal death. Gaining further understanding of the pathophysiology of brain changes in HD is crucial in light of developing neuroprotective interventions or treatments. To date, imaging techniques have shown structural and functional abnormalities in various brain structures in HD gene carriers [1]. Low field MRS has shown generalised changes in the relatively large brain structures in gene carriers [2,3,4]. Ultra high field (7T) MRS has the potential to perform measurements in individual anatomical brain structures, with increased spatial and spectral resolution and improved signal to noise. By performing MRS at this field strength, we expect to find differences in brain metabolites which can serve as markers for disease progression.

Methods. Six pre-manifest and two manifest gene carriers were recruited from the outpatient clinic, only those with Shoulson & Fahn stage 2 or lower (TFC≥7) and CAG-repeat ≥40 were included. Due to the low number of manifest participants no differentiation was made. Eleven partners, spouses or non gene carrying siblings were included as healthy controls. Scanning was performed on a 7 Tesla Achieva whole body scanner (Philips Healthcare, Best, The Netherlands) with a NOVA Medical quadrature transmit and 16 channel receive coil. For accurate planning, a high resolution, 3DT1 was acquired that rendered axial, sagittal and coronal reconstructions covering the basal ganglia and brainstem. In the caudate nucleus (CN), frontal lobe, putamen, hypothalamus and thalamus STEAM single voxel MRS was acquired with following scan parameters: TR/TE/TM = 2000/19/25 ms, BW 4kHz, 2048 data points and 128 averages. Water suppression used a frequency-selective RF pulse and gradient spoiling and six saturation bands, one on each side of the voxel, were also applied to suppress signal from surrounding tissue. All scans included a reference scan without water suppression. MRS data were analyzed with the LCModel [5], using the unsuppressed water as an internal reference. A water content of 65% was assumed. A basis set simulated for all metabolites under investigation plus lipids and macro molecules was used. Concentrations of and the ratio to Cre were evaluated for Ala, Cho, Cre, GABA, Gln, Glu, Lac, Ins, NAA, NAAG, Scyllo and Tau. Metabolites that showed a Cramér-Rao lower bound (CRLB) > 30% were excluded for further analysis. Statistical analysis consisted of independent t-tests for gene carriers vs. non gene carriers for each metabolite using SPSS 16.0.2 (SPSS Inc, Chicago, USA).

Results. Figure 1 shows typical planning of the MRS voxels. Independent t-tests showed a significantly lower NAA concentration in the caudate nucleus in gene carriers as compared to non gene carriers (4.96 ± 1.05 vs 6.35 ± 1.19 mM, p = 0.017, pat/ctrl = 8/11). Also, the NAA/Cre ratio in the CN was reduced in gene carriers (0.75 ± 0.15 vs 0.93 ± 0.18, p = 0.042, pat/ctrl = 8/11). The choline concentration in the thalamus was found to be higher in gene carriers (1.82 ± 0.21 vs 1.57 ± 0.25 mM, p = 0.035, pat/ctrl = 8/11) and in the hypothalamus, gene carriers showed significantly higher mI/Cre ratio (1.96 ± 0.43 vs 1.47 ± 0.29, p = 0.012, pat/ctrl = 7/10) and a tendency for higher Glu/Cre ratio (1.37 ± 0.47 vs 1.01 ± 0.21, p = 0.055, pat/ctrl = 6/10). No significant differences between gene carriers and non gene carriers were found for metabolite concentrations or metabolite/Cre ratios in the putamen and frontal lobe.
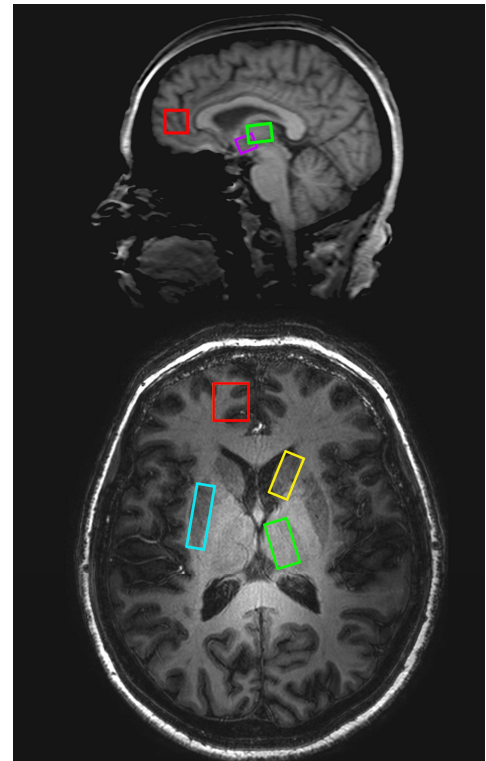

Figure 1. Typical examples of single voxel planning for frontal lobe (red), caudate nucleus(yellow), putamen(blue), hypothalamus (purple) and thalamus (green)

Conclusions. Gene carriers with Huntington's disease show significantly lower NAA concentration and NAA/Cre ratio in the caudate nucleus as compared to non gene carriers. This corresponds with the findings of previous MRI studies showing structural changes beginning in the CN, years before disease onset (1). Furthermore, this study demonstrates that choline levels in the thalamus and mI/Cre ratio in the hypothalamus are elevated in HD gene carriers. As the gene carriers in this study were predominantly pre-manifest, these findings point to early brain metabolite change, making 7T MRS a promising tool for tracking neuropathological progression even before clinical symptoms appear. Moreover, MRS can be applied to identify targets for neuroprotective treatments and also as a monitoring tool for treatment effects. Further research with a larger sample size will be performed to enable comparison of pre manifest and manifest gene carriers.

References: 1. Bohanna I, Brain Res. Rev. 58, 209-225, 2008; 2. Sánchez-Pernaute R, Neurology 53, 806-812, 1999; 3. Gómez-Ansón B, Neurology, 68, 906-910, 2007; 4. Van Oostrom J, Brain Res. 1168, 67-71, 2007; 5. Provencher S, Magn Reson Med 30, 672, 1993.