T1rho Imaging as a Biomarker for Huntington's Disease Progression

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PURPOSE: Imaging biomarkers sensitive to Huntington disease (HD) progression prior to motor diagnosis may accelerate identification and evaluation of potential therapies. Magnetic resonance (MR) imaging provides a number of modalities that have been studied as potential biomarkers for HD progression including structural imaging, diffusion imaging, magnetization transfer imaging, spectroscopy, and functional imaging, which have been previously reviewed [1-3]. There is been growing interest in using quantitative MR parametric imaging as a biomarker for neurodegenerative disorders. Quantitative imaging has a number of advantages over existing MR imaging techniques including the ability to study changes in the relaxation time without the need to normalize. We investigated the potential value of T1ρ relaxation to detect pathological changes in premanifest HD (preHD) relative to other quantitative relaxation parameters (T2 and T2*).

METHODS: All participants in this study were enrolled in the PREDICT-HD study after receiving informed written consent in accordance with the local IRB. All subjects had previously undergone elective presymptomatic genetic testing. Those who were gene-expanded (CAG length greater than or equal to 36) but had not yet received a motor diagnosis were referred to as preHD participants (N=50). Those who were non-gene expanded (CAG at or below 30) were enrolled as control participants (N=26). Subjects were selected for this study were age and sex matched. For participants with the HD CAG gene expansion, the CAG-Age Product (CAP) score was computed as CAP=Age x (CAG-33.66) [4]. High-resolution anatomical imaging consisted of T1- and T2-weighted images. In addition, quantitative parametric imaging was conducted to compute T2, T2*, and T1ρ relaxation times. For T2 mapping, a 2D spin-echo sequence was acquired in the axial plane with 5 echoes acquired (TE=13.1, 26.2, 39.3, 52.4, 65.5ms; TR=3000ms, FOV=240x192mm; Matrix=256x204; slice thickness/gap = 2.0/0.0mm, IPAT=2). T2* mapping was performed using a 2D gradient-echo sequence collected in the axial plane with 4 echoes (TE=4.63, 20.0, 30.0, 40.0ms; TR=2300ms; flip angle=50°; FOV=240x192mm; Matrix=512x410; slice thickness/gap = 2.0/0.0mm, IPAT=2). Quantitative T1ρ mapping was performed using a coronal segmented 3D gradient echo sequence with spin-lock pulses added (TE=2.5ms, TR=5.6ms, field-of-view = 220×220×200 mm3, sampling matrix = 128×128×40, flip angle = 10º; IPAT=2, spin-lock frequency = 330 Hz, spin-lock times = 10, 55 ms). Relaxation times were estimated for each relaxation parameter (T1ρ, T2, and T2*) using a mono-exponential fit. Voxel based approaches were used to analyze the relaxation parameters. The preHD subjects were classified into a high CAP group (≥368) and a low/mid CAP group (<368), which were compared to each other as well as the control group. A secondary analysis used CAP score as covariate in the analysis of the preHD subjects to determine which relaxation parameters changed with disease progression.

RESULTS: The voxel-wise analysis of the T1ρ parametric images showed significant increases in the T1ρ relaxation times in the posterior regions of the putamen and in the nucleus accumbens bilaterally in the high CAP group as compared to controls. Prolonged T1ρ relaxation times were also seen in some cortical areas including the insula and superior and transverse temporal gyri. A direct comparison between the high CAP and low/mid CAP groups found a statistically significant elevation of the T1ρ relaxation times within the striatum. These regions also exhibited a statistically significant relationship with CAP score. Quantitative T2 imaging showed virtually no differences between groups. The T2* relaxation changes were almost exclusively confined to the globus pallidus and were evident when comparing both the low/mid and high CAP groups to controls. No differences were seen when comparing the high CAP group to the low/mid CAP group.

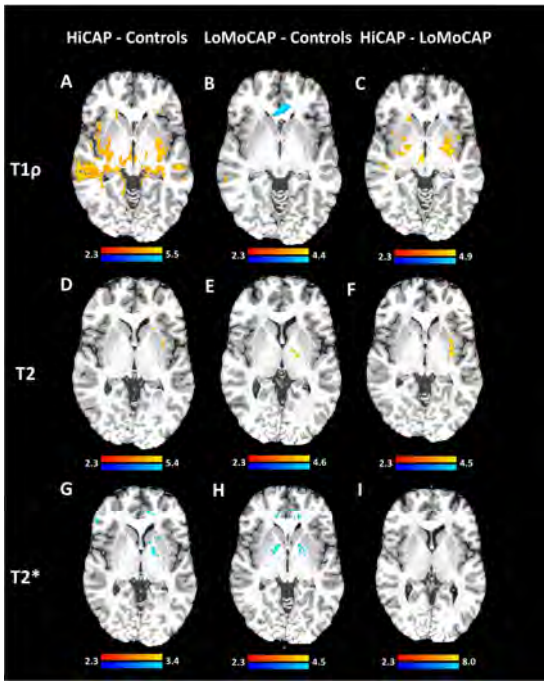

Fig 1. Changes in quantitative relaxation parameters (T1ρ, T2, and T2*) in premanifest HD.

DISCUSSION: This study employed multiple quantitative MR parametric imaging approaches to study changes in tissue properties of subjects in the premanifest stage of HD. Using these quantitative imaging sequences, changes in T1ρ relaxation times were found, predominately in the striatum, and showed a significant relationship with disease progression in premanifest HD as measured by CAP score. T2* relaxation times showed significant changes in the premanifest HD subjects, but no significant relationship with disease progression was found. T2 mapping showed relatively little change between the premanifest HD and control subjects. Since the T1ρ changes were independent of T2 changes this suggests that the relaxation changes were associated with changes in chemical exchange. The observed elevation of T1ρ relaxation times is consistent with evidence for metabolic abnormalities in HD. Glucose and pH have emerged as two of the leading factors to influence T1ρ relaxation times by changing proton exchange [5-7]. An increase in the T1ρ relaxation times is consistent with a decreased glucose concentration. Premanifest HD subjects have been shown to have a decreased glucose uptake in the striatum[8-10]. The increased T1ρ relaxation times in the striatum would also be consistent with an acidosis within this region possibly resulting from impaired energy metabolism in HD and or lactate accumulation. Interestingly, acidosis has been suggested to contribute to HD-related pathology and blocking acid-sensing ion channel might alleviate Huntington disease pathology [11].

References: **[1]** Bohanna I, el al. Brain Research Reviews 2008. **[2]** Weir DW, et al. Lancet Neurology 2011. **[3]** van den Bogaard S, el al. Front Biosci 2012. **[4]** Zhang Y, el al. AJMG Part B 2011. **[5]** Magnotta VA, et al. PNAS USA 2012. **[6]** Jin T, et al. NeuroImage 2013. **[7]** Kettunen MI, et al. MRM 2002. **[8]** Antonini A, et al. Brain 1996. **[9]** Ciarmiello A, et al. JNM 2006. **[10]** van Oostrom JC, Neurology 2005. **[11]** Wong HK, et al. HMG 2008.