ALTERED IRON AND MYELIN IN PREMANIFEST HUNTINGTON'S DISEASE MORE THAN 20 YEARS BEFORE CLINICAL ONSET: CROSS-SECTIONAL DATA FROM HD-YAS

Nicola Z. Hobbs[1], Eileanoir B. Johnson[1], Christopher S. Parker[2], Rachael I. Scahill[1], Sarah Gregory[1], Marina Papoutsi[1,3], Paul Zeun[1], Katherine Osborne-Crowley[4], Jessica Lowe[1], Akshay Naira[1,5], Carlos Estevez-Fraga[1], Kate Fayer[1], Geraint Rees[6], Hui Zhang[2], Sarah J. Tabrizi[1,7] & the HD-YAS Investigators

[1]Huntington's Disease Centre, Department of Neurodegenerative disease, UCL Queen Square Institute of Neurology, UK. [2]Centre for Medical Image Computing, Department of Computer Science, UCL, UK. [3]IXICO Plc, UK. [4]Division of Equity, Diversity and Inclusion, University of New South Wales, Australia. [5]Max Planck University College London Centre for Computational Psychiatry and Ageing Research, UCL Queen Square Institute of Neurology, UK. [6]University College London Institute of Cognitive Neuroscience, University College London, UK. [7]Dementia Research Institute at University College London, UK

Background

Recently, the HD Young Adult Study (HD-YAS) demonstrated subtle neurodegenerative changes in a premanifest cohort ~24 years before predicted clinical onset, despite no evidence of cognitive or psychiatric impairment.

Aims

We aimed to further characterise these very early premanifest changes using exploratory whole-brain analyses.

We used novel MR imaging techniques to examine macro- and micro-structure across the brain, and to estimate myelin and iron content.

Methods

62 preHD (~24 years from predicted clinical onset) and 61 controls from HD-YAS were included, Table 1.

Single time point, single site 3T MRIs were acquired, including:

1. **Structural T1W scans** to assess grey- and white-matter volume.
2. **Multi-shell diffusion weighted imaging (DWI)** to generate measures of white-matter microstructure.
3. **Multiparametric maps (MPMs)** to estimate myelin and iron content from magnetization transfer (MT), proton density (PD), longitudinal relaxation (R1) and effective transverse relaxation (R2*).

We assessed:

- Group differences in imaging measures between preHD and controls.
- Associations between imaging measures and disease burden score (DBS) and CSF neurofilament light (NfL).

Analyses controlled for confounding variables (e.g. age, sex, TIV) and multiple comparisons using familywise error (FWE) 0.05.

	PreHD (N=62)	Controls (N=61)	P value
Age (years)	29.08 (5.59) 19-40	29.15 (5.50) 20-39	p=0.95
Sex Male Female	33 29	37 24	p=0.48
UHDRS TMS	0.48 (1.04) 0-5	0.11 (0.32) 0-1	p=0.01
Total Functional capacity	13 (0) 13-13	13 (0) 13-13	-
CAG repeat length	42.18 (1.64) 39-47	NA	-
Estimated years to onset	23.60 (5.88) 10.02-36.13	NA	-

Table 1 Demographic information for the HD-YAS cohort included in this study. Data presented as mean (SD) range.

Results

MPM group differences: R1 and R2* were significantly increased in preHD compared with controls, suggesting increased iron in the putamen, globus pallidum and external capsule (Fig. 1).

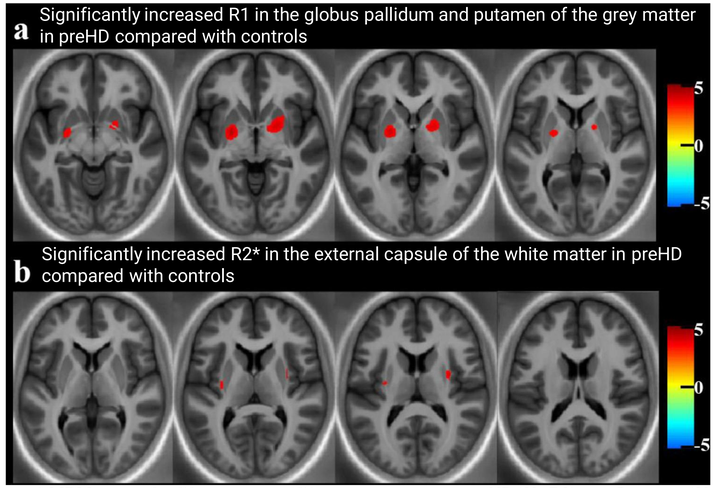

Figure 1 MPM data: significant group differences between preHD (N=54) and Controls (N=57). Results displayed as T-scores for clusters significant at a voxel-wise threshold of p<0.001, corrected at a cluster-wise threshold of p<0.05 FWE and are corrected for age, sex and TIV.

There was no evidence that MT or PD differed between groups.

MPM associations: In preHD, lower cortical R2*, suggestive of reduced myelin or iron, was significantly associated with higher CSF NfL in the frontal lobe and parieto-occipital cortices (Fig. 2).

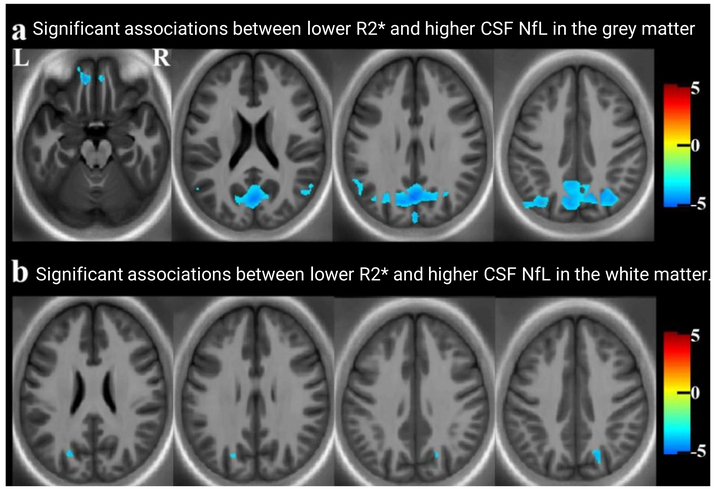

Figure 2 Significant associations between MPM maps and CSF NfL in preHD (N=50). Results displayed as T scores for clusters significant at a voxel-wise threshold of p<0.001, corrected at a cluster-wise threshold of p<0.05 FWE and corrected for age, sex and TIV.

Volumetric & diffusion imaging: No results were significant at corrected levels.

Conclusions

1. Disease-related processes are occurring in both subcortical and cortical regions more than 20 years before predicted clinical onset of HD.
2. Increased iron in subcortical structures and the surrounding white matter is an early feature of premanifest HD.
3. The early rise of CSF NfL in preHD is related to early degenerative processes in the cortex, leading to reductions in regional iron and myelin levels.

Contact: Nicola Hobbs (n.hobbs@ucl.ac.uk)

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