Mutation-related apparent myelin, not axon density, drives white matter pathology in premanifest Huntington's disease: Evidence from in vivo ultra-strong gradient MRI

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BACKGROUND. **White matter (WM)** alterations have been observed **early in Huntington's disease (HD) progression** [1,2] but their **aetiology** remains unknown. We exploited **ultra-strong-gradient MRI** to tease apart **contributions** of **myelin** and **axon** density to WM changes in **premanifest HD**. **Behavioural measures** were employed to explore **disease-related brain-function relationships.**

METHODS: DATA ACQUISITION.

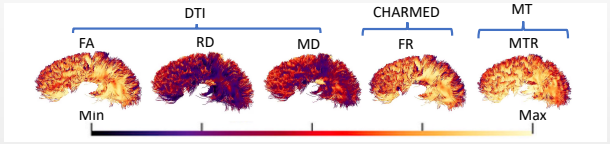
- **Subjects:** 25 premanifest HD patients and 25 age- & sex-matched healthy controls:

Group	Gender male/ female (%)	Mean age (range)	Mean CAG (range)	Mean DBS (range)
HD patients (n = 25)	15(60)/ 10(40)	42.04 (21-70)	41.4 (37-45)	235.94 (61.5-450)
Controls (n = 25)	14(56)/ 11(44)	43.19 (27-71)	-	-

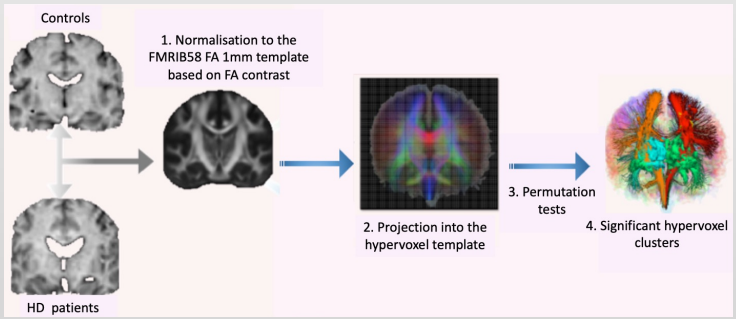
- **MRI: 3T Siemens Connectom system** with ultra-strong (300 mT/m) gradients [3].
- Diffusion-weighted images were fitted to the **DTI** and **CHARMED** diffusion models [4][5] to compute **FA, RD, AD and Fr. MTR** maps [6] were also computed.
- **Tractography of the corpus callosum (CC)** performed with TractSeg [7] and multi-shell constrained spherical deconvolution (MSMT-CSD) [8]. **Seven portions of the CC** were delineated.
- **Cognitive and motor assessments:** encoding, storage, updating, inhibition, switching, verbal & spatial working memory, motor speed, attention.

METHODS: DATA ANALYSIS.

1. **Tractometry [9]** of the CC:

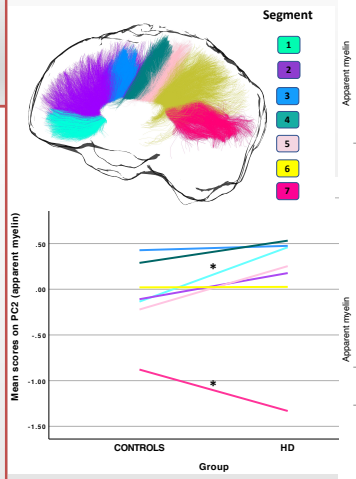


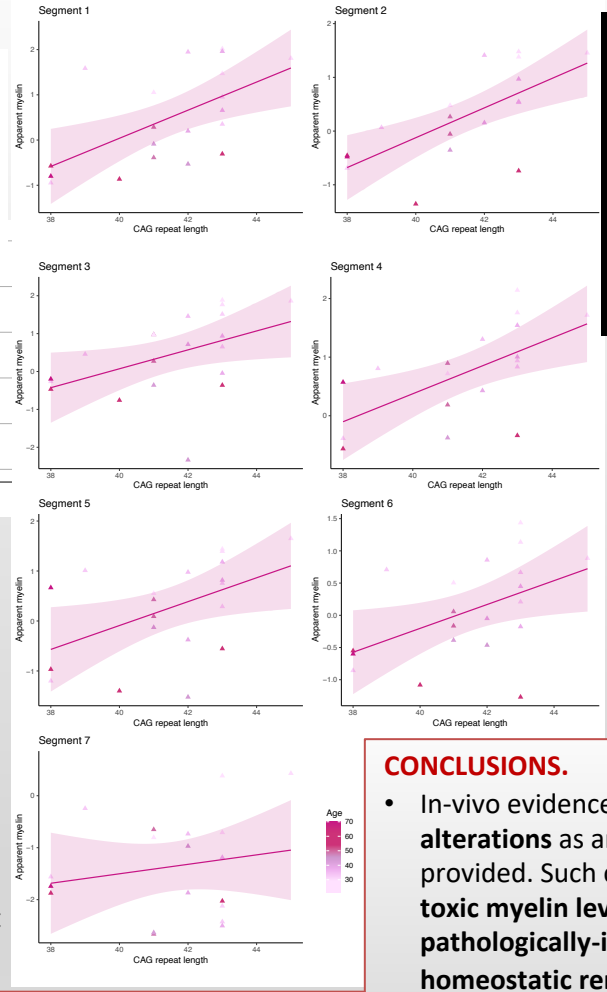
2. **PCA** extraction of an **"axon density"** and an **"apparent myelin"** component from the tractometry data to examine **group differences in region-specific WM changes across the CC**.
3. **Tract-based cluster analysis (TBCA) [10]** to explore **brain-wise WM abnormalities** in premanifest HD.

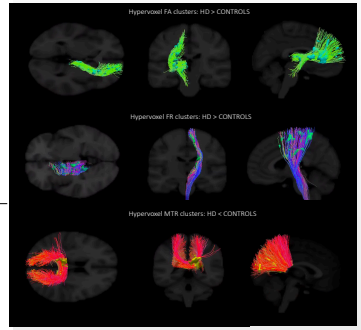


3. **PCA** extraction of a **composite cognitive score** reflecting general **executive functioning.**
4. **Spearman correlations** between **WM PCA components**, **cognitive PCA component**, **CAG** repeat length and disease burden score (**DBS**).

RESULTS.







1. **Apparent callosal myelin** was higher in patients in anterior callosal portions but lower in posterior portions compared to controls.
2. Apparent callosal myelin was positively **associated with CAG repeat length** but not with DBS.

3. TBCA revealed **decreased apparent myelin** in the posterior CC, **increased apparent axon density** in the left cortico-striatal tract and **selective degeneration/increased microstructural organization** in the right fronto-striatal projections.

CONCLUSIONS.

- In-vivo evidence for **callosal myelin alterations** as an early feature of HD is provided. Such changes might be due to: i. **toxic myelin levels because of pathologically-increased CAG size**; or ii. **homeostatic remyelination** in response to mutation-associated myelin breakdown.
- Outside the CC, other alterations can be detected, likely reflecting **axonal changes.**
- **Understanding WM changes in HD may aid discovery of new therapeutic approaches.**

REFS: [1] Paulsen JS et al. (2008), J Neurol Neurosurg Psychiatry. [2] Bartzokis et al. (2007), Neurochemical Research. [3] Jones DK et al. (2018), NeuroImage. [4] Pierpaoli C, Basser PJ (1996), Magn Reson Med. [5] Assaf Y, Basser PJ (2005), Neuroimage. Henkelman, R M, Stanisz, G J, & Graham, S J (2001), NMR in Biomedicine. Wasserthal J, Neher P, Maier-Hein KH (2018), NeuroImage. Jeurissen B, Tournier J-D, Dhollander T, Connelly A, Sijbers J (2014), NeuroImage. Jones DK, Travis AR, Eden G, Pierpaoli C, Basser PJ (2005), Magn Res Med. Luque Laguna PA et al. (2019), OHBM.