# Tracking the neurodegeneration pattern of the anterior thalamic radiation in Huntington Disease

Montserrat Domingo-Ayllon[1,2] Clara Garcia-Gorro[1,3], Saül Martinez-Horta[5,6], Jesus Perez-Perez[5,6], Jaime Kulisevsky[5,6,7], Nadia Rodriguez-Dechicha[8], Irene Vaquer[8], Susana Subira[8,9], Matilde Calopa[10], Esteban Muñoz[11,12,13], Pilar Santacruz[11], Jesus Ruiz-Idiago[14,15], Celia Mareca[14], Ruth de Diego-Balaguer[1,3,4,16], Estela Camara[1,3*]

1 Cognition and Brain Plasticity Unit [Bellvitge Biomedical Research Institute – IDIBELL], 08097 L'Hospitalet de Llobregat, Barcelona, Spain. 2 Radiology Department, University Hospital Joan XXIII, Tarragona, Spain. 3 Department of Cognition, Development and Education Psychology, Universitat de Barcelona, Barcelona, Spain. 4 Institute of Neurosciences, Universitat de Barcelona, Barcelona, Spain. 5 European Huntington's Disease Network. 6 Movement Disorders Unit, Dept of Neurology, Biomedical Research Institute Sant Pau (IIB-Sant Pau), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. 7 CIBERNED (Center for Networked Biomedical Research on Neurodegenerative Diseases), Carlos III Institute, Madrid, Spain. 8 Hestia Duran I Reynals. Hospital Duran i Reynals, Hospitalet de Llobregat (Barcelona), Spain. 9 Departament de Psicologia Clínica i de la Salut, Universitat Autònoma de Barcelona, Barcelona, Spain. 10 Movement Disorders Unit, Neurology Service, Hospital Universitari de Bellvitge, Barcelona, Spain. 11 Movement Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain. 12 IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer), Barcelona, Spain. 13 Facultat de Medicina, University of Barcelona, Barcelona, Spain. 14 Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona. 15 Hospital Mare de Deu de la Mercè, Barcelona, Spain. 16 ICREA (Catalan Institute for Research and Advanced Studies), Barcelona, Spain.

ecamara@ub.edu

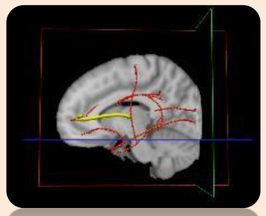
## INTRODUCTION

### What is Huntington's disease (HD)?

- An autosomal dominant neurodegenerative disease, affecting primarily the basal ganglia and conditioning a progressive decline in cognitive, psychiatric and motor domains
- Good model to study neurodegenerative diseases thanks to its monogenic nature (CAG) that allows to track preclinical and clinical phases of neurodegeneration [1,2]

### What is the anterior thalamic radiations (ATRs)?

- A projection tract connecting anterior and mediodorsal thalamic nuclei to prefrontal and anterior cingulate cortices [3]
- As part of cortico-basal ganglia-thalamo-cortical loop, ATRs are expected to be affected [4-8] and track the neurodegeneration evolution in HD

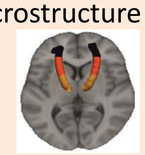


**GOALS**

1. To describe the **spatial and temporal progression** of ATR neurodegeneration in HD using a MRI multimodal and multivariate approach
2. To infer **pathophysiological mechanisms** involved in HD neurodegeneration from the extracted biomarkers

## PARTICIPANTS & METHODS

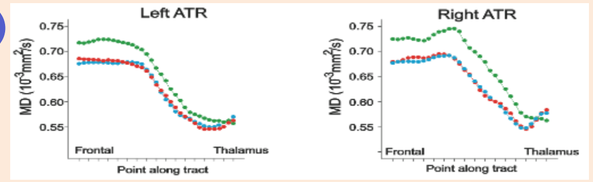
- **Participants:** 31 HD gene-expansion carriers (13 pre-, 18 manifest); 24 controls
- **Clinical evaluation:** UHDRS [9]
- **Imaging assessment**
  - **3D T1-weighted MPRAGE sequence** to define **anatomy** (FreeSurfer GM segmentation)
  - **Multi-echo GRE sequence** to obtain relaxometry maps [10] in order to estimate **iron content**
  - **Diffusion-weighted sequence** post-processed by means of TRACULA [11,12] in order to assess **white matter** (WM) **microstructure** through mean, radial and axial diffusivities (MD, RD, AD)
  - **MRSpectroscopy** (LCModel) [13] centered in middle portion of left ATR to quantify **metabolites** (NAA, Creatine, Choline, Glutamate, Glutamate/Glutamine, Inositol)
- **Statistical analysis**
  - **Three approaches** for assessment of iron and WM microstructure
    - Average
    - Along the tract [14, 15]
    - Division of ATR in three segments



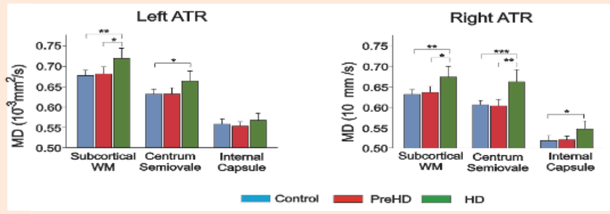

  - **MANOVA – post-hoc Tukey** for subgroup comparison of diffusion indexes, relaxometry values and metabolite concentrations
  - **Pearson test** for correlations between neuroimaging biomarkers and clinical measures
  - **p < 0.05** with FDR correction for multiple comparisons

## RESULTS

**1**

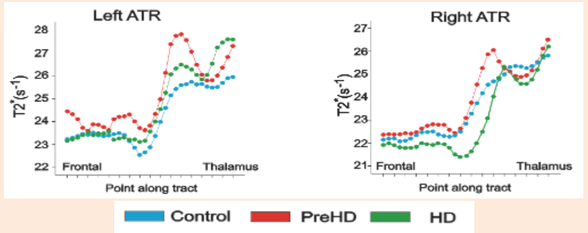



**Premanifest** individuals displayed increased AD in both ATR compared to controls
**Manifest** patients exhibited reduced microstructure integrity of both ATR with bilateral increases in MD, RD and AD related to controls and premanifest



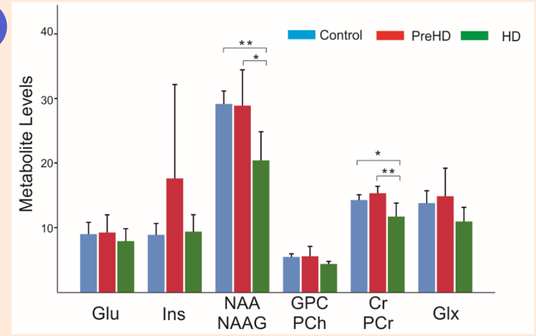

By segments, this reduced ATR integrity in manifest patients exhibited **a gradient** from subcortical WM (more affected) to deep WM (less affected) **for the left ATR** and was **more extensive and more severe for the right ATR**

**2**




**Premanifest** individuals compared to controls showed increased iron content in left ATR
**Manifest** patients showed lower iron levels than premanifest and controls in the right ATR and higher iron levels than controls in left ATR

**3**




**Manifest** patients showed reduced NAA and creatine compared to premanifest and controls

**4**

**Positive** correlation between **iron and glutamate in HD gene carriers** (non-significant after FDR)
**Negative** correlation between **creatine and MD/AD in HD gene carriers** (non-significant after FDR)
**Positive** correlation between **glutamate and predicted age of onset in premanifest** individuals
**Negative** correlation between **choline and CAP in manifest** patients

## CONCLUSIONS

- ATR disintegration began in premanifest and progressed in extent and severity in manifest
- WM damage was **more extensive in right** ATR that could translate a **higher vulnerability** [16, 17] and showed a **spatial gradient in left** ATR in favour of the **dying-back hypothesis** [18, 19]
- Iron increase in left ATR of **premanifest** individuals might uncover **dysregulated myelination** [20, 21] or **abnormal ferritin accumulation** [22] resulting in **oxidative stress** and **ferroptosis** [23, 24]
- NAA and creatine decreased exclusively in **manifest** patients suggesting **neuronal loss** [24] and **mitochondrial dysfunction** [25]
- The **multimodal multivariate approach with along-the-tract analysis** allow for a more comprehensive evaluation of neurodegeneration

**[1]** Reiner A, Dragatsis I, Dietrich P. *International Review of Neurobiology*. 2011;98:325-372. **[2]** Muller M, Leavitt BR. *J Neurochem*. 2014;130(3):328-350. **[3]** Cho ZH, Law M, Chi JG, et al. *World Neurosurg*. 2015;83(1):54-61. **[4]** Vonsattel JP, Myers RH, Stevens TJ, et al. *J Neuropathol Exp Neurol*. 1985;44(6):559-577. **[5]** Della Nave R, Ginestroni A, Tessa C, et al. *Am J Neuroradiol*. 2010;31(9):1675-1681. **[6]** Faria A V., Ratnanather JT, Tward DJ, et al. *NeuroImage Clin*. 2016;11:450-460. **[7]** Johnson EB, Ziegler G, Penny W, et al. Published online 2021. **[8]** Furlong LS, Jakabek D, Power BD, et al. *Psychiatry Res - Neuroimaging*. 2020;298(August 2019). **[9]** Group HS. *Mov Disord*. 1996;l(2):136-142. **[10]** Baudrexel S, Volz S, Preibisch C, et al. *Magn Reson Med*. Published online 2009. **[11]** Yendiki A, Panneck P, Srinivasan P, et al. *Front Neuroinform*. 2011;5(October):1-12. **[12]** Yendiki A, Koldewyn K, Kakunoori S, et al. *Neuroimage*. 2014;88:79-90. **[13]** Provencher SW. *NMR Biomed*. 2001;14(4):260-264. **[14]** Rosas HD, Wilkens P, Salat DH, et al. *NeuroImage Clin*. 2018;20(September 2017):236-242. **[15]** Yendiki A, Reuter M, Wilkens P, et al. *Neuroimage*. 2016;127:277-286. **[16]** Mamah D, Conturo TE, Harms MP, et al. *Psychiatry Res - Neuroimaging*. 2010;183(2):144-150. **[17]** Mamiya PC, Richards TL, Kuhl PK. *Front Psychol*. 2018;9(FEB):1-10. **[18]** Bartzokis G, Lu PH, Tishler TA, et al. *Neurochem Res*. 2007;32(10):1655-1664. **[19]** Blumenstock S, Dudanova I. *Front Neurosci*. 2020;14(February). **[20]** Blockx I, De Groof G, Verhoye M, et al. *Neuroimage*. 2012;59(2):957-967. **[21]** Gomez-Tortosa E, MacDonald ME, Friend JC, et al. *Ann Neurol*. 2001;49(1):29-34. **[22]** Simmons D, Casale M, Alcon B, et al. *Sixth Rep World Nutr Situat Geneva*. 2007;479(March):132. **[23]** Wu J rui, Tuo Q zhang, Lei P. *J Mol Neurosci*. 2018;66(2):197-206. **[24]** Thomsen MS, Andersen MV, Christoffersen PR, et al. *Neurobiol Dis*. 2015;81:108-118. **[25]** Gubellini P, Picconi B, Di Filippo M, et al. *Biochim Biophys Acta - Mol Basis Dis*. 2010;1802(1):151-161.