Unsupervised clustering reveals longitudinal psychiatric signatures in Huntington's Disease

Audrey E. De Paepe[1,2]; Alexia Giannoula[3]; Ferran Sanz[3]; Laura Furlong[3]; Clara Garcia-Gorro[1,2]; Saül Martinez-Horta[4,5,6]; Jesus Perez-Perez[4,5,6]; Jaime Kulisevsky[4,5,6]; Nadia Rodriguez-Dechicha[7]; Irene Vaquer[7]; Susana Subira[7,8]; Matilde Calopa[9]; Esteban Muñoz[4,10,11,12]; Pilar Santacruz[10]; Jesus Ruiz-Idiago[13,14]; Celia Mareca[14]; Ruth de Diego-Balaguer[1,2,4,15]; Estela Camara[1,2,4]*

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

ecamara@ub.edu

INTRODUCTION

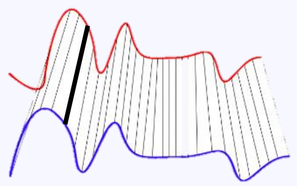
What is Huntington's disease?

- Progressive neurodegeneration
- Monogenic, but heterogeneous symptom evolution
- Psychiatric features do not linearly track disease course[1]

GOAL How do **shared psychiatric patterns** inform progression of Huntington's disease profiles?

How can we track psychiatric progression?

- **Disease Trajectories**[2] – Unsupervised clustering of patient progression with shared temporal patterns
- **Dynamic Time Warping (DTW) algorithm**[3] – Non-linear, aligns sequences with varying speed

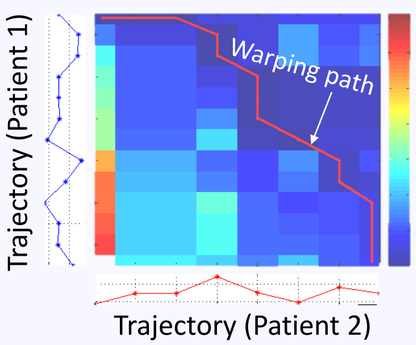


PARTICIPANTS & METHODS

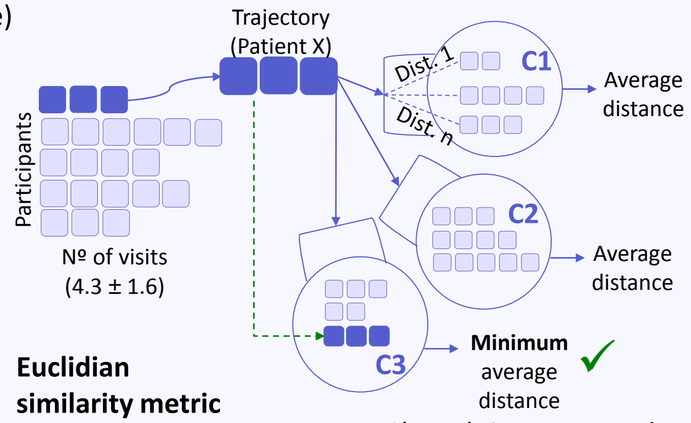
- **Participants:** 47 HD gene-expansion carriers (23 pre-, 24 manifest at baseline)
- **Psychiatric evaluation:** Short-Problem Behavior Assessment[4]

Depression Irritability Apathy ExecFunction

DTW



Disease Trajectories clustering[2]



Euclidian similarity metric

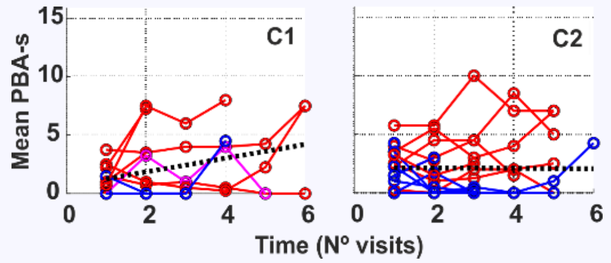
Shared time patterns!

Parameters:

- **Threshold**[2] - Is Trajectory X sufficiently similar to the cluster in question?
- **Lambda**[5] - Which feature contributes most to the given cluster?

RESULTS

1 Premanifest and manifest individuals cluster together



N = 11 total clusters

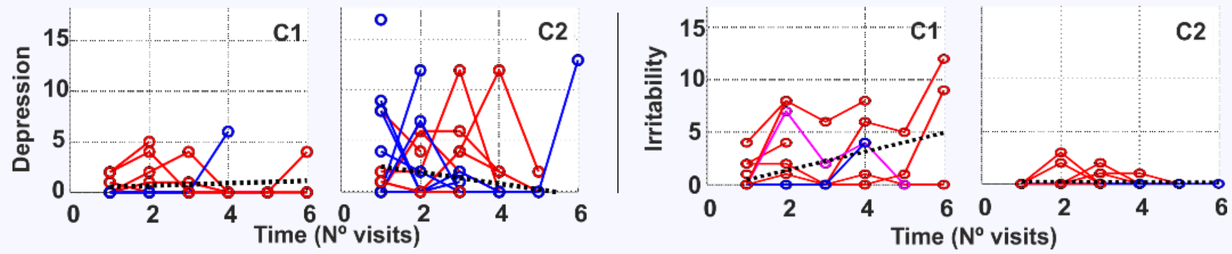
- Premanifest
- Phenoconverter
- Manifest

Fisher's exact test (*P* = .390)

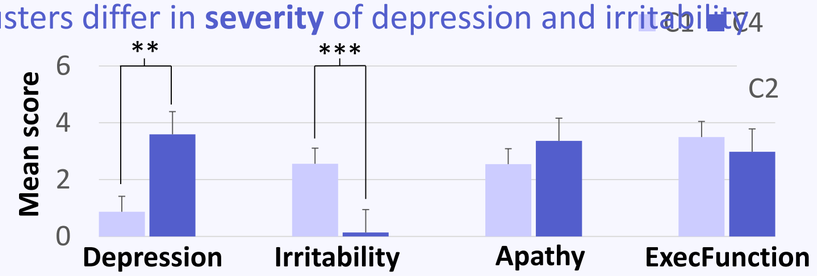
2 Psychiatric trajectories defined by non-depressive and non-irritable signatures

Lambda-assigned weights (%)

	Depression	Irritability	Apathy	ExecFunction	
C1	100	0	0	0	*N* = 10
C2	0	100	0	0	*N* = 15



3 Clusters differ in severity of depression and irritability



Wilcox test
Depression (*P* = .007)
Irritability (*P* < .001)

CONCLUSIONS

- HD patients present high variability in the psyquiatric trajectories
- Psychiatric signatures distinguished by changes in depression / irritability
- Apathy and executive dysfunction ↑ in both clusters

Future steps: Can brain correlates predict psychiatric signatures?

[1] Thompson JC, Harris J, Sollom AC, *et al. J Neuropsychiatry Clin Neurosci* 2012;:8. **[2]** Giannoula A, Centeno E, Mayer M-A, *et al. Bioinformatics* 2020;:btaa964. **[3]** Muller M. *Information Retrieval for Music and Motion*. Berlin, Heidelberg: : Springer 2007. **[4]** McNally G, Rickards H, Horton M, *et al. Journal of Huntington's disease* 2015;**4**:347–69. **[5]** Friedman JH, Meulman JJ. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 2004;**66**:815–49. **[6]** Biglan KM, Zhang Y, Long JD, *et al. Front Aging Neurosci* 2013;**5**.