Received: 3 January 2023 | Accepted: 23 March 2023

DOI: 10.1111/ene.15806

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

# Divergent cognitive trajectories in early stage Huntington's disease: A 3-year longitudinal study

Saul Martínez-Horta[1,2,3,4] | Jesús Perez-Perez[1,2,3,4] | Javier Oltra-Cucarella[5] | Frederic Sampedro[1,2,3] | Andrea Horta-Barba[1,2,3,4] | Arnau Puig-Davi[1,2,3,4] | Javier Pagonabarraga[1,2,3] | Jaime Kulisevsky[1,2,3,4]

[1]Movement Disorders Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[2]Biomedical Research Institute (IIB-Sant Pau), Barcelona, Spain

[3]Centro de Investigación en Red-Enfermedades Neurodegenerativas, Madrid, Spain

[4]European Huntington's Disease Network, Ulm, Spain

[5]Departamento de Psicología de la Salud, Universidad Miguel Hernández de Elche, Elche, Spain

**Correspondence**
Jaime Kulisevsky, Movement Disorders Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Mas Casanovas 90 – 08041 Barcelona, Spain.
Email: jkulisevsky@santpau.cat

Javier Oltra-Cucarella, Departamento de Psicología de la Salud, Universidad Miguel Hernández de Elche, Elche, Spain.
Email: joltra@umh.es

**Funding information**
Instituto de Salud Carlos III; Huntington's Disease Society of America

## Abstract

**Background and purpose:** Cognitive impairment is a central feature of Huntington's disease (HD), but it is unclear to what extent more aggressive cognitive phenotypes exist in HD among individuals with the same genetic load and equivalence in other clinical and sociodemographic variables.

**Methods:** We included Enroll-HD study participants in early and early–mid stages of HD at baseline and with three consecutive yearly follow-ups for whom several clinical and sociodemographic as well as cognitive measures were recorded. We excluded participants with low and large CAG repeat length (CAG < 39 & > 55), with juvenile or late onset HD, and with dementia at baseline. We explored the existence of different groups according to the profile of cognitive progression using a two-step *k*-means cluster analysis model based on the combination of different cognitive outcomes.

**Results:** We identified a slow cognitive progression group of 293 participants and an aggressive progression group (F-CogHD) of 235 for which there were no differences at the baseline visit in any of the measures explored, with the exception of a slightly higher motor score in the F-CogHD group. This group showed a more pronounced annual loss of functionality and a more marked motor and psychiatric deterioration.

**Conclusions:** The rate of progression of cognitive deterioration in HD is strongly variable even between patients sharing, among other variables, equivalent CAG repeat length, age, and disease duration. We can recognize at least two phenotypes that differ in terms of rate of progression. Our findings open new avenues to study additional mechanisms contributing to HD heterogeneity.

KEYWORDS
cognition, Enroll-HD, Huntington's disease, neuropsychology, phenotypes

## INTRODUCTION

In Huntington's disease (HD), progressive cognitive and behavioral changes are core features of the disease, and subtle cognitive changes can be detected as early as 15 years before the motor-based clinical diagnosis is made [1]. Throughout the disease progression, cognitive features evolve from subtle to mild and major cognitive impairment [2–4].

In HD, CAG repeats length is inversely associated with the age at onset and age at death, with the severity, and with the rate of clinical progression [5–8]. CAG repeat length, however, accounts for only 60% of the interindividual variability in the age at onset, and it is clinically evident that there is great heterogeneity in the way the disease progresses among patients with equivalent CAG repeat length [9]. The influence of mechanisms other than those mediated by CAG repeat length appears to contribute significantly to this variability [10].

  

Several genetic and environmental modifiers have been identified. Among these, the role of specific gene locus, single nucleotide polymorphisms, CAA interruptions, RNA toxicity, DNA repair polymorphisms, and environmental factors stand out [6, 11–14].

Cognitive presentation and progression in HD have also been associated with CAG repeat length [15, 16]. However, the timing and pattern of progression of cognitive deterioration in HD vary greatly between patients, even when disease stage, age, education level, and CAG repeat length are similar [2, 10, 17]. Again, this heterogeneity suggests that mechanisms other than CAG repeat length, disease stage, or the disease burden also contribute to cognitive heterogeneity in HD [18]. This idea is in line with what we observe in cognitive impairment in other forms of neurodegenerative dementias, where multiple phenotypes exist for the same disease or primary etiopathological mechanism (i.e., phenotypes of Alzheimer disease or frontotemporal degeneration).

The identification of cognitive endophenotypes differing between individuals with equivalent disease burden would allow investigation of potential underlying contributors and selection of the most appropriate outcome measures in the context of clinical trials [17].

The main aim of our study was to explore whether different cognitive phenotypes—in terms of rate of progression of global cognition—occurs in early and early–mid stages of HD, and whether these phenotypes are more or less dependent on critical clinical and sociodemographic variables such as CAG repeat length, age, disease duration, or medication.

## METHODS

### Participants and study design

All the clinical and sociodemographic data were obtained from the fifth released dataset of the Enroll-HD study: A Prospective Registry Study in a Global Huntington's Disease Cohort (CHDI Foundation) [19]. The Enroll-HD study is a longitudinal, observational, multinational study (NCT01574053) conceived as a global clinical research platform designed to facilitate clinical research in HD. All participants provided informed consent in accordance with the International Conference on Harmonization–Good Clinical Practice guidelines, and all participating centers were required to obtain approval from their local ethics committee. Further details are available at the website: enroll-hd.org.

We focused on participants who presented the common clinical characteristics used in the context of disease-modifying clinical trials [20]. Accordingly, we included only symptomatic participants in the early and early–mid stages (Shoulson and Fahn stages I or II) [21]. This criterion was determined by a diagnostic confidence level of 4 at baseline, indicating the presence of unequivocal motor abnormalities of HD with a confidence level of 99%, and a total functional capacity (TFC) score at baseline of >6 [22]. To avoid the influence of CAG expansions in the low-penetrance range (CAG = 36–39) and the influence of large expansions (CAG > 55), we only included participants in the range of CAG repeats between 40 and 55. To avoid the influence of juvenile and late onset forms of the disease, we included participants who were aged between 21 and 60 years [23, 24] at diagnosis or when the first symptom of HD appeared. Moreover, from among the available data, we selected participants for whom baseline and three consecutive annual follow-up visits containing all the required assessments described below were available.

We excluded participants who had a history of severe traumatic brain injury, neurological disorders other than HD, epilepsy, drug abuse, noncompensated systemic disease (i.e., diabetes), or a Mini-Mental State Examination (MMSE) score at baseline suggestive of significant cognitive impairment (MMSE < 26) [25].

To explore whether findings were characteristic of the HD population or whether they also occurred in the general population, we included a group of healthy controls (HC). This group was made up of gene-negative relatives and healthy controls with sociodemographic characteristics similar to those of the HD participants (details in Appendix S1). A parallel exploratory analysis was conducted with this sample. To avoid the possible influence of intermediate alleles in this population, we included only HC with a CAG length of <27.

A total of 528 HD participants and 566 HC fulfilled all the inclusion/exclusion criteria. The items comprising these criteria are described in detail in Appendix S1.

### Assessments

We collected baseline data regarding CAG repeat length, age, age at diagnosis, disease duration, years of education, first main symptom, and motor phenotype (choreatic, rigid–akinetic, or mixed). The CAG-Age Product (CAP) score, a measure of disease burden relative to lifelong exposure to mutant Huntingtin (mHTT), was calculated using the following formula: age × (CAG − 33.5) [26]. To determine differences in the frequency with which different CAG expansion sizes predominated in the sample, we defined four categories: (i) CAG repeat length between 40 and 42; (ii) CAG = 43–46; (iii) CAG = 47–50; and (iv) CAG >50 [6].

At every visit (at baseline and at 12-, 24-, and 36-month follow-ups), we collected data from the Unified Huntington's Disease Rating Scale–Total Motor Score (UHDRS-TMS) [22], the TFC, the functional independence score (FIS), pharmacological treatment, severity of neuropsychiatric symptoms according to the Problems Behavior Assessment for Huntington's Disease–Short Form (PBA-s) [27], the Symbol Digit Modalities Test (SDMT), the Stroop word-reading test (SWRT), and the MMSE. The assessments are described in detail in Appendix S1.

### Cluster analysis

We explored the possible existence of different cognitive groups based on the rate of progression of changes at 36-month follow-up

in global cognition and in two measures which, given their sensitivity to change in HD, are always used in the context of clinical trials, and are used to obtain composite measures such as the composite UHDRS [28]. Thus, the SDMT, the SWRT and the MMSE were used in a two-step *k*-means cluster analysis. The optimal number of clusters was calculated using the average silhouette method [29]. The second step was to classify the whole sample according to the final number of clusters. To apply this model, we calculated the difference score between baseline and 36 months for each cognitive outcome. We then normalized these difference scores to *z*-scores, and all the resulting *z*-scores were used in the cluster analysis.

### Statistical analysis

Clinical and sociodemographic variables were subjected to independent *t*-test comparisons for continuous variables and $\chi^2$ for categorical variables. Repeated measures analysis of variance (ANOVA) and *t*-tests were conducted to explore the effects between the cognitive groups over time, as linear models are valid for any distribution for samples of size 500, as is the case in the present work irrespective of normality of residuals [30].

Using $\chi^2$ tests, we compared the frequency of several variables in each group. These variables were (i) pharmacological treatments; (ii) the frequency with which different expansion sizes predominated in each; (iii) the first motor, cognitive, neuropsychiatric, or mixed symptoms related to HD; and (iv) the frequency with which motor phenotypes (choreatic, rigid–akinetic, or mixed) predominated at time of disease onset.

We analyzed the association of demographic, clinical, and cognitive variables at baseline with cognitive outcomes at 36 months using a stepwise forward logistic regression. The first step included age, sex, education, CAG repeat length, UHDRS-TMS, and TFC. In the second step, scores from the MMSE, SDMT, and SWRT were added to the model. In the third step, the scores from the PBA-s were added. Goodness of fit was assessed with the Hosmer–Lemeshow test, with a nonsignificant finding ruling out gross lack of fit [31]. All the statistical analyses were done using the SPSS statistical package v28.0.0.0, and a $p<0.05$ was considered significant.

## RESULTS

### Cluster analysis

The sample consisted of 528 early-to-early–mid HD patients with a mean age (SD) at baseline of 49.5 (10.1), a mean CAG repeat length of 43.7 (3.1), a mean age at onset of 43.9 (9.0) years, and a mean disease duration of 5.45 (4.2) years; 47.9% were women. Table 1 shows all the demographic and clinical characteristics of the cohort. The two-step cluster analysis revealed two main groups (silhouette index = 0.546; Appendix S1), differentiated by a relatively benign or slow (S-CogHD) versus a more aggressive or fast cognitive progression profile (F-CogHD).

The S-CogHD consisted of 293 participants (55% of the sample; 46.1% women), and the F-CogHD group consisted of 235 participants (45% of the sample; 50.2% women). As seen in Table 1, the two groups showed equivalent scores at baseline in almost all the variables. The only difference between groups at baseline was found in the UHDRS-TMS, which was 3.88 (3.88) points higher in the F-CogHD group ($t_{528}=3.39$, $p<0.005$). A figure depicting the frequencies of used medication, initial symptoms, and CAG groups is presented as Appendix S1.

Each cognitive test was subjected to a repeated measures ANOVA using the factors "group" (S-CogHD and F-CogHD) and "time" (baseline, 12 months, 24 months, and 36 months). For the MMSE score, a significant group by time interaction was found ($F_{3,\ 525}=48.97$, $p<0.001$). Post hoc *t*-test comparisons showed that this effect was driven by significant differences between groups in the mean MMSE score at 12 months, in the rate of annual change from baseline to 12 months ($t_{528}=-6.02$, $p<0.001$), and in the rate of annual change at 36 months ($t_{528}=-5.96$, $p<0.001$). Accordingly, these data revealed a mean rate of change in the MMSE at 36 months with respect to the baseline visit of −0.1 (1.7) points in the S-CogHD group, and 2.3 (2.3) points in the F-CogHD group ($t_{528}=-11.8$, $p<0.001$; see Table 1). Paired *t*-tests showed the MMSE remained stable at follow-up visits in the S-CogHD group. Conversely, in the F-CogHD group, a significant pattern of annual decline was found at 12 months ($t_{235}=7.7$, $p<0.001$), and at 36 months ($t_{235}=6.1$, $p<0.001$), and between 36 months and baseline ($t_{235}=14.9$, $p<0.001$; see Figure 1).

For the SDMT, repeated measures ANOVA using the same factors showed an equivalent group-by-time interaction ($F_{3,\ 525}=99.55$, $p<0.001$) as found in the MMSE. This effect was driven by significant differences in the mean SDMT score at 12 months, and in the rate of annual change at 12 months ($t_{528}=-8.27$, $p<0.001$), at 24 months ($t_{528}=-3.39$, $p<0.005$), and at 36 months ($t_{528}=-5.67$, $p<0.001$). A mean rate of change at 36 months with respect to the baseline of −1.32 (5.3) was found in the S-CogHD group, and −9.54 (6.0) in the F-CogHD group ($t_{528}=-16.3$, $p<0.001$). A pattern of significant decline between visits in the SDMT performance was found in both groups. In the S-CogHD group, a significant decline was found between 12 and 24 months ($t_{293}=2.23$, $p<0.05$), between 24 and 36 months ($t_{293}=3.46$, $p<0.005$), and between baseline and 36 months ($t_{293}=4.24$, $p<0.001$). This pattern of decline was more pronounced in the F-CogHD group and was found between baseline and 12-month follow-up ($t_{235}=9.89$, $p<0.001$), between 12- and 24-month follow-up ($t_{235}=6.35$, $p<0.001$), between 24- and 36-month follow-up ($t_{235}=10.39$, $p<0.001$), and between baseline and 36-month follow-up ($t_{235}=24.2$, $p<0.001$).

On the SWRT, repeated measures ANOVA showed an equivalent group by time interaction as found with the MMSE and the SDMT ($F_{3,\ 525}=75.38$, $p<0.001$). This effect was driven by significant differences between groups in the mean SWRT score at 12 months, and in the rate of annual change at 12 months ($t_{528}=-6.22$, $p<0.001$), at 24 months ($t_{528}=-3.58$, $p<0.001$), and at 36 months

**TABLE 1** Baseline clinical and sociodemographic characteristics of the sample and clinical and sociodemographic characteristics of the two groups at baseline and consecutive follow-ups.

| | All HD sample, $n = 528$ | | S-CogHD, $n = 293$ | | | | F-CogHD, $n = 235$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Characteristic | Baseline, mean (SD) | Range | Baseline (SD) | 12 months | 24 months | 36 months | Baseline (SD) | 12 months | 24 months | 36 months | $p$[a] |
| Age, years | 49.52 (10.0) | 21–70 | 50.1 (10.1) | | | | 48.75 (9.9) | | | | 0.115 |
| Gender, % female | 47.9 | | 46.1 | | | | 50.2 | | | | |
| Education, years | 13.60 (1.2) | 8–16 | 13.63 (1.2) | | | | 13.57 (1.2) | | | | 0.594 |
| CAG[b] | 43.78 (3.1) | 40–55 | 43.6 (3.1) | | | | 44.03 (3.1) | | | | 0.097 |
| CAG groups, % | | | | | | | | | | | |
| 40–42 | 47.3 | | 49.1 | | | | 45.1 | | | | 0.355 |
| 43–46 | 36.6 | | 34.8 | | | | 38.7 | | | | 0.354 |
| 47–50 | 11.7 | | 11.6 | | | | 11.9 | | | | 0.912 |
| >50 | 4.4 | | 4.4 | | | | 4.3 | | | | 0.919 |
| CAP[c] | 486.67 (88.7) | 262–1118 | 485.11 (102.12) | | | | 488.62 (68.54) | | | | 0.638 |
| Age at onset, years | 43.95 (9.1) | 21–60 | 44.50 (9.3) | | | | 43.17 (8.5) | | | | 0.084 |
| Initial main symptom, % | | | | | | | | | | | |
| Motor | 53.5 | | 53.3 | | | | 54.8 | | | | 0.786 |
| Cognitive | 10.1 | | 9.6 | | | | 10.7 | | | | |
| Psychiatric | 18.1 | | 17.5 | | | | 18.8 | | | | |
| Mixed | 0.6 | | 19.2 | | | | 15.8 | | | | |
| Other | 17.7 | | 0.3 | | | | 0.9 | | | | |
| Disease duration | 5.45 (4.5) | 0–20 | 5.43 (4.5) | | | | 5.42 (4.0) | | | | 0.990 |
| Medication, % | | | | | | | | | | | |
| Anesthetics | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | – |
| Anticonvulsants | 11.9 | | 9.9 | 11.9 | 13.7 | 14.7 | 14.5 | 15.3 | 19.1 | 21.3[d] | 0.107 |
| Antiparkinsonian | 4 | | 3.4 | 3.1 | 3.8 | 4.1 | 4.7 | 4.3 | 5.1 | 5.1 | 0.459 |
| Neuroleptic | 37.9 | | 33.8 | 36.5 | 41.0 | 46.1 | 43 | 45.5[d] | 50.2[d] | 54.9[d] | <0.05 |
| Psychoanaleptic | 46.2 | | 46.4 | 49.1 | 50.5 | 55.3 | 46 | 51.5 | 55.3 | 56.2 | 0.916 |
| Antichoreic | 8 | | 6.5 | 8.5 | 10.2 | 11.6 | 9.8 | 16.2[d] | 18.3[d] | 18.3[d] | 0.163 |
| UHDRS-TMS | 25.05 (13.1) | 5–85 | 23.32 (12.8) | 25.68 (13.7)[e] | 28.33 (15.7)[e] | 29.67 (16.4)[e,f] | 27.20 (13.2) | 30.19 (13.3)[d,e] | 34.26 (15.1)[d,e] | 38.94 (15.8)[d,e,f] | <0.005 |
| Predominant motor phenotype, % | | | | | | | | | | | |
| Hypokinetic–rigid | 12.9 | | 12.8 | | | | 13 | | | | 0.945 |

**TABLE 1** (Continued)

| Characteristic | All HD sample, $n = 528$ | | S-CogHD, $n = 293$ | | | | F-CogHD, $n = 235$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline, mean (SD) | Range | Baseline (SD) | 12 months | 24 months | 36 months | Baseline (SD) | 12 months | 24 months | 36 months | $p$[a] |
| Choreic | 15.5 | | 16.6 | | | | 14.7 | | | | 0.545 |
| Mixed | 71.6 | | 70.6 | | | | 72.4 | | | | 0.664 |
| TFC, % | 10.75 (1.9) | 7–13 | 10.85 (1.9) | 10.39 (2.1)[e] | 9.16 (2.4)[e] | 9.74 (2.3)[e,f] | 10.62 (1.9) | 9.78 (2.1)[d,e] | 9.16 (2.5)[d,e] | 8.42 (2.5)[d,e,f] | 0.169 |
| Stage I | 58.3 | | 60.1 | | | | 56.2 | | | | 0.367 |
| Stage II | 41.7 | | 39.9 | | | | 43.8 | | | | 0.367 |
| FIS | 22.45 (2.5) | 13–25 | 22.64 (2.6) | 22.10 (2.9)[e] | 21.37 (3.5)[e] | 20.93 (3.7)[e,f] | 22.23 (2.6) | 21.0 (3.3)[d,e] | 19.98 (4.0)[d,e] | 18.71 (4.6)[d,f,e] | 0.067 |
| SDMT | 32.25 (10.8) | 5–68 | 32.74 (11.1) | 33.18 (11.5) | 32.49 (11.8)[e] | 31.42 (12.2)[e,f] | 31.65 (10.4) | 28.16 (10.1)[d,e] | 25.88 (10.1)[d,e] | 22.10 (9.8)[d,e,f] | 0.250 |
| SWRT | 69.68 (17.8) | 24–121 | 69.81 (18.2) | 69.02 (19.2) | 67.13 (19.4)[e] | 65.23 (19.2)[e,f] | 69.51 (17.4) | 62.75 (17.7)[d,e] | 57.43 (18.3)[d,e] | 50.45 (16.9) [d,e,f] | 0.846 |
| MMSE | 27.99 (1.2) | 26–30 | 27.94 (1.4) | 27.91 (1.8) | 27.66 (1.9)[e] | 27.84 (1.7) | 28.06 (1.3) | 26.97 (2.4)[d,e] | 26.73 (2.5)[d] | 25.77 (2.7)[d,e,f] | 0.357 |
| Yearly change | | | | | | | | | | | |
| UHDRS-TMS | | | | 2.36 (7.9)[e] | 2.64 (8.4)[e] | 1.33 (8.0)[e,f] | | 2.98 (8.1)[e] | 4.07 (8.8)[e] | 4.68 (8.9)[d,e,f] | |
| TFC | | | | −0.46 (1.2)[e] | −0.32 (1.3)[e] | −0.31 (1.3)[e,f] | | −0.83 (1.4)[d,e] | −0.62 (1.5)[d,e] | −0.73 (1.4)[d,e,f] | |
| FIS | | | | −0.53 (1.6)[e] | −0.73 (2.1)[e] | −0.44 (2.3)[e,f] | | −1.22 (2.5)[d,e] | −1.02 (2.6)[e] | −1.26 (2.5)[d,e,f] | |
| SDMT | | | | 0.44 (5.4) | −0.68 (5.2)[e] | −1.07 (5.3)[e,f] | | −3.48 (5.4)[d,e] | −2.27 (5.4)[d,e] | −3.78 (5.5)[d,e,f] | |
| SWRT | | | | −0.79 (11.3) | −1.88 (10.5)[e] | −1.89 (9.5)[e,f] | | −6.75 (10.3)[d,e,f] | −5.32 (11.4)[d,e,f] | −6.97 (11.4)[d,e,f] | |
| MMSE | | | | −0.03 (1.7) | −0.24 (1.9)[e] | 0.17 (1.8) | | −1.08 (2.1)[d,e] | −0.24 (2.3) | −0.96 (2.4)[d,e,f] | |

Abbreviations: CAP, CAG-Age Product; FIS, functional independence score; HD, Huntington's disease; MMSE, Mini-Mental State Examination; SDMT, Symbol Digit Modalities Test; SWRT, Stroop word-reading test; TFC, total functional capacity; UHDRS-TMS, Unified Huntington's Disease Rating Scale–Total Motor Score.

[a]Probability value for the *t*-test between S-CogHD baseline data and F-CogHD baseline data.

[b]CAG repeat length.

[c]CAP score = age × (CAG − 33.5).

[d]Probability value $<0.05$ for the *t*-test between S-CogHD and F-CogHD.

[e]Paired *t*-test $p < 0.05$ with respect to previous visit.

[f]Paired *t*-test $p < 0.005$ between baseline and 36-month follow-up.

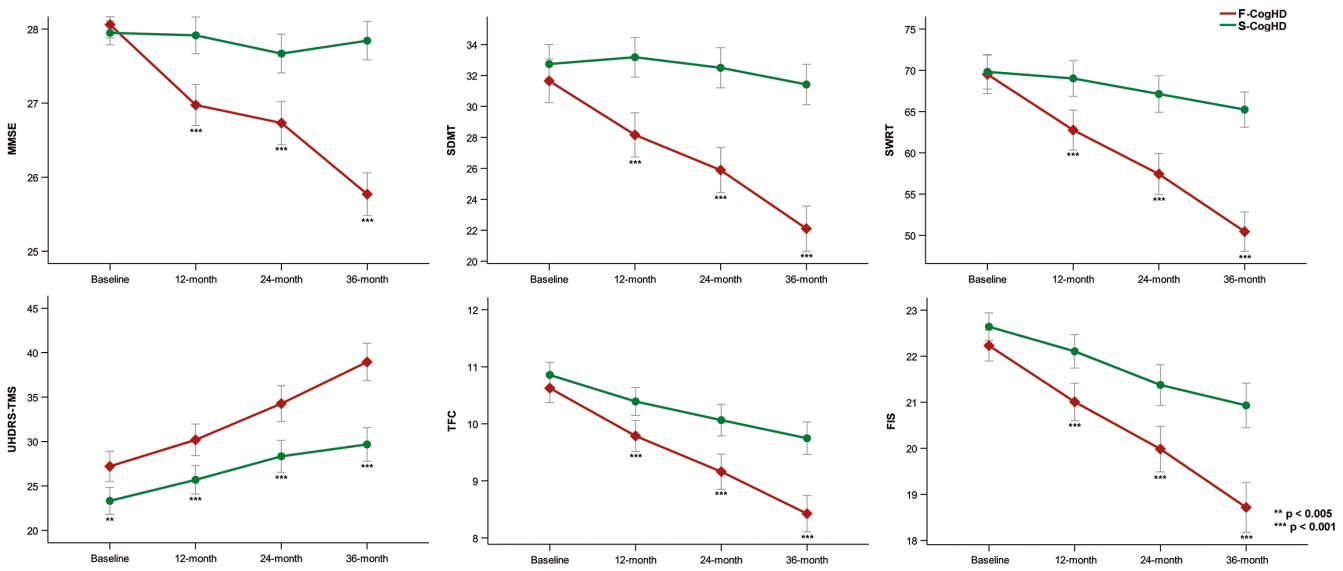


**FIGURE 1** Trajectories of main cognitive, motor, and functional assessments along 3-year follow-up in the two different cognitive groups. The figure shows the differences in the progression profile throughout follow-up in the S-CogHD and F-CogHD groups. The top row shows the cognitive outcomes and the bottom row the motor and functional outcomes. Bars represent the mean ± SEM. FIS, functional independence score; MMSE, Mini-Mental State Examination; SDMT, Symbol Digit Modalities Test; SWRT, Stroop word-reading test; TFC, total functional capacity; UHDRS-TMS, Unified Huntington's Disease Rating Scale–Total Motor Score. [Colour figure can be viewed at wileyonlinelibrary.com]

($t_{528} = -5.57$, $p < 0.001$). A mean rate of change at 36 months with respect to baseline of −4.57 (11.3) points was found in the S-CogHD group, and of −19.05 (11.9) in the F-CogHD group ($t_{528} = -14.1$, $p < 0.001$). A pattern of significant decline between visits was seen in the SWRT performance in both groups. In the S-CogHD group, this decline was found between 24 months and 12 months ($t_{293} = 3.06$, $p < 0.005$), between 36 months and 24 months ($t_{293} = 3.38$, $p < 0.005$), and between 36 months and baseline ($t_{293} = 6.91$, $p < 0.001$). This pattern of decline was more pronounced in the F-CogHD group and was found between baseline and 12 months ($t_{235} = 9.98$, $p < 0.001$), 24 months ($t_{235} = 7.11$, $p < 0.001$), and 36 months ($t_{235} = 9.37$, $p < 0.001$), and between baseline and 36 months ($t_{235} = 24.35$, $p < 0.001$).

Participants in the F-CogHD group also showed a greater annual decrease in the UHDRS-TMS, the FIS, and the TFC. Regarding medication, no differences were found at baseline. Anticonvulsants were more frequently used at 36-month follow-up ($\chi^2 = 3.91$, $p = 0.048$) and neuroleptics and antichoreic medications were more frequently used in this group after the 12-month visit.

Regarding neuropsychiatric symptoms (Appendix S1), scores for apathy were higher in the F-CogHD group at 24-month and 36-month visits, and disoriented behavior was also higher in this group at the 36-month visit. Over the follow-up visits, the S-CogHD group showed a significant amelioration in depressive mood at 12 months and in anxiety at 24 months. They also showed worsening of perseverative behavior at 12 months, but this was not followed by worsening in the subsequent visits. The F-CogHD group showed significant worsening in perseverative behavior at 24 months, in apathy at 24 and 36 months, and in aggressive behavior, obsessive–compulsive behavior, and disoriented behavior at 36 months. Paired *t*-test comparisons between visits in the S-CogHD group showed significant increases in apathy ($t_{293} = -2.39$, $p < 0.05$) and perseverative behavior ($t_{293} = -3.2$, $p < 0.005$) between baseline and 36-month visit. In the F-CogHD group, the same comparison showed significant increases in apathy ($t_{235} = -3.9$, $p < 0.001$), perseverative behavior ($t_{235} = -4.1$, $p < 0.001$), obsessive–compulsive behavior ($t_{235} = -3.1$, $p < 0.005$), and disoriented behavior ($t_{235} = -5.1$, $p < 0.001$).

## Risk of fast decline

The logistic regression showed that the risk of belonging to the F-CogHD group was associated with age (odds ratio [OR] = 1.03, 95% confidence interval [CI] = 1.003–1.065, $p = 0.033$), UHDRS-TMS (OR = 0.96, 95% CI = 0.94–0.98, $p < 0.001$), PBA Perseveration (OR = 0.89, 95% CI = 0.79–0.99, $p = 0.036$), and PBA Obsessive–Compulsive Disorder (OCD) scores (OR = 1.13, 95% CI = 1.01–1.27, $p = 0.033$).

As baseline scores on the cognitive tests were not associated with the risk of showing fast decline at the 36-month follow-up, we analyzed whether cognitive change at 12 months would be significant to predict decline 36 months after baseline assessment. For this purpose, we developed a linear regression-based reliable change index (RCI) approach in which scores at 1-year follow-up were regressed on age, sex, education, and baseline scores separately for the MMSE, SDMT, and SWRT [32]. A linear approach was selected because it shows both true positive and true negative ratios similar to the logistic approach and also a mean accuracy close to 95% for samples of size 500 [33].

In each RCI, participants were labeled as showing reliable change if the standardized discrepancy between expected and observed

scores (i.e., *z*-scores) at 1-year follow-up was equal to or lower than −1.64 (see Appendix S1). Participants were labeled as showing reliable cognitive decline (RCD) if they showed reliable change on one or more of the three cognitive variables, and the RCD variable was entered in a logistic regression together with age, baseline UHDRS-TMS, SDMT, SWRT, MMSE, PBA Perseveration, and PBA OCD scores to analyze the risk of fast decline at the 36-month follow-up. This analysis showed that the risk of cognitive decline 36 months after baseline was best predicted by the RCD variable (OR = 3.36, 95% CI = 1.99–5.64, $p < 0.001$), followed by PBA OCD scores (OR = 0.87, 95% CI = 0.78–0.98, $p = 0.019$), UHDRS-TMS (OR = 1.03, 95% CI = 1.02–1.05, $p < 0.001$), and age (OR = 0.97, 95% CI = 0.96–0.99, $p = 0.009$). Again, none of the baseline cognitive scores was significant to predict decline at 36-month follow-up. Using Bonferroni correction, only RCD and UHDRS-TMS would remain statistically significant.

The exploratory analysis in HC was performed in a sample of 566 participants. Their mean age was 49.13 (13.69) years, and thus comparable to that of the HD sample ($t_{566} = -0.04$, $p = 0.965$). The k-means analysis found two main groups consisting of 135 (HC-Cluster-1) and 431 (HC-Cluster-2) participants, respectively. HC-Cluster-1 was slightly older than HC-Cluster-2 ($t_{566} = 1.19$, $p = 0.048$), and at baseline, they had lower scores on the SDMT than participants in HC-Cluster-2 ($t_{566} = -2.18$, $p < 0.05$). They also had higher scores on the MMSE than participants in HC-Cluster-2 ($t_{566} = 7.45$, $p < 0.001$). To sum up, in HC, dissimilar patterns of progression were explained by subjects being older and performing worst at baseline. The specific details and figures regarding the analysis in this group are presented as Appendix S1.

## DISCUSSION

Our findings show that within a sample of HD patients representing the usual target population in clinical trials, two distinct cognitive phenotypes can be identified based on the progression of cognitive decline at 36 months. These cognitive phenotypes were not determined as a function of CAG repeat length, age, disease duration, or other core clinical variables at baseline. The S-CogHD group showed a pattern of slow yearly cognitive and functional decline, whereas the F-CogHD group exhibited a significantly more aggressive pattern of progression. These findings were not replicated in the HC group.

Identifying these two cognitive phenotypes has important implications. First, it will allow us to explore in future studies the biological mechanisms that mediate the expression of these phenotypes. Second, it will be of importance in the design and analysis of clinical trials, because to date, main endpoints in interventional trials do not take into account the possible existence of a substantial heterogeneity in cognitive trajectories among patients.

That no differences were found in regard to the frequency of the various CAG repeat ranges, basal CAG repeat length, age, or disease duration emphasizes that disease burden and disease duration are not the only mechanisms involved in the expression of more aggressive forms of the disease. Among the various mechanisms that could contribute to this variability, it is worth considering the accumulated evidence on factors that contribute to phenotypic variability in HD [5–7, 9–14]. But these results may also serve to bring into focus other possibilities that also deserve to be explored. This includes, for example, studying the role of other secondary proteinopathies (i.e., tau pathology) whose specific role in HD is largely unknown [34–37].

Regarding the UHDRS-TMS, despite the difference of 3.8 points observed, it does not provide confirmation that patients in the F-CogHD group presented worse motor symptoms than patients in the S-CogHD, because 3.8 points may not be clinically evident. However, it does not go unnoticed that this worse motor score could also reflect a more aggressive global clinical phenotype in the F-CogHD group [28]. Taking into account that in both groups the patients are in the same range in terms of disease stage, this difference does not seem to indicate that we are dealing with two clearly different groups in terms of the clinical evolution of the disease. We found that reliable change at 1-year follow-up is a better predictor of fast cognitive decline at 36 months than baseline age and UHDRS-TMS. These results show that cognitive variables could be used to predict cognitive change more accurately than motor scores. These results are in line with the results reported in mild cognitive impairment, in which cognitive scores are better predictors of progression to Alzheimer disease than demographic variables or biomarkers [38]. However, further studies must explore whether, independently of disease burden, different phenotypes in terms of global progression (motor, cognitive, and functional) may also exist and of course should explore in detail to what extent this minimum difference of 3.8 points could contribute to a worse performance in cognitive tasks—something that, in our opinion, is frankly improbable.

The main limitation of our study is that it does not allow exploration of the possible biological mechanisms contributing to the findings. Exploring the proportion of cases with CAA interruptions, or the frequency of certain genetic variants and haplotypes, may have shed light on the biological processes subserving our findings. Another limitation is that the cognitive profiling was performed using standardized but limited cognitive testing approaches. In this sense, we recognize that the MMSE may not be a very sensitive and useful measure in the context of HD, but it is an accepted measure of global cognition and, given that the MMSE is not used here for diagnostic purposes, we consider that it provides interesting information to be taken into account [18]. Thus, future studies with more exhaustive neuropsychological examinations should explore the cognitive profile of these subgroups and the extent to which certain anomalies in processes not covered in the current study are already detectable at baseline. Finally, an important limitation is the lack of an independent replication sample to check our findings.

To sum up, we provide new evidence regarding the heterogeneity of cognitive progression in the early and early–middle stages of HD. This heterogeneity, which is evident in a clinical setting to anyone familiar with the study of cognition in people with HD, has previously been studied in a very limited way. Here, we demonstrate that regardless of a number of clinical and sociodemographic variables, HD can be associated with very different cognitive trajectories in terms of progression over 3 years. Therefore, we must go deeper in identifying the mechanisms that could contribute to this cognitive heterogeneity, and we must emphasize the need to assume the existence of multiple possible phenotypes, forms of presentation, and progression of the disease, as has already been evidenced in other neurodegenerative processes.

## ACKNOWLEDGMENTS

The authors would like to thank all the patients and families for their participation in the Enroll-HD study. Data used in this work were generously provided by the participants in the Enroll-HD study and made available by CHDI Foundation. Enroll-HD is a global clinical research platform designed to facilitate clinical research in HD. Core datasets are collected annually from all research participants as part of this multicenter longitudinal observational study. Data are monitored for quality and accuracy using a risk-based monitoring approach. All sites are required to obtain and maintain local ethical approval. The individuals who contributed to the collection of the Enroll-HD are listed at https://enroll-hd.org/enrollhd_documents/2020-10-R1/Enroll-HD-Acknowledgement-list-2020-10-R1.pdf.

## FUNDING INFORMATION

The study was partially supported by funding from Instituto de Salud Carlos III and from the Huntington's Disease Society of America.

## CONFLICT OF INTEREST STATEMENT

S.M.-H. has received honoraria for lecturing from Teva, Zambon, UCB, and Roche, and reports grants from the Huntington's Disease Society of America (Human Biology Project) and from Fondo de Investigaciones Sanitarias from Instituto de Salud Carlos III. J.K. has received honoraria for advisory boards or lecturing from Teva, Zambon, UCB, Bial, General Electric, Sanofi, and Roche, and reports grants from Fundació la Marato de TV3, Fondo de Investigaciones Sanitarias from Instituto de Salud Carlos III, and Fondo Europeo de Desarrollo Regional. J.P. has served on advisory or speakers' boards and received honoraria from UCB, Zambon, AbbVie, Italfarmaco, Allergan, Ipsen, and Bial, and reports grants from Fundació la Marato de TV3 and Fondo de Investigaciones Sanitarias from Instituto de Salud Carlos III. The authors declare that there is no conflict of interest regarding the publication of this article.

## DATA AVAILABILITY STATEMENT

The protocol and the statistical analysis plan are available on request. The Enroll-HD study platform (https://www.enroll-hd.org/for-researchers/) makes available to interested researchers access to the available databases upon request and thus to the data used in this study.

## ETHICAL APPROVAL

All participants provided informed consent in accordance with the International Conference on Harmonization–Good Clinical Practice guidelines, and all participating centers were required to obtain approval from their local ethics committee. Further details are available at the website enroll-hd.org.

## ORCID

*Saul Martínez-Horta* https://orcid.org/0000-0003-0125-7249
*Frederic Sampedro* https://orcid.org/0000-0002-3933-1355
*Andrea Horta-Barba* https://orcid.org/0000-0003-0050-5466
*Arnau Puig-Davi* https://orcid.org/0000-0001-8883-4947

## REFERENCES

1. Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. *Nat Rev Neurol*. 2014;10:204-216.
2. Martinez-Horta S, Sampedro F, Horta-Barba A, et al. Structural brain correlates of dementia in Huntington's disease. *Neuroimage Clin*. 2020;28:102415.
3. Peavy GM, Jacobson MW, Goldstein JL, et al. Cognitive and functional decline in Huntington's disease: dementia criteria revisited. *Mov Disord*. 2010;25:1163-1169.
4. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurol*. 2009;8:791-801.
5. Keum JW, Shin A, Gillis T, et al. The HTT CAG-expansion mutation determines age at death but not disease duration in Huntington disease. *Am J Hum Genet*. 2016;98:287-298.
6. Genetic Modifiers of Huntington's Disease Consortium, Electronic address ghmhe, genetic modifiers of Huntington's disease C. CAG Repeat Not Polyglutamine Length Determines Timing of Huntington's Disease Onset. *Cell*. 2019;178(887–900):e814.
7. Rosenblatt A, Kumar BV, Mo A, Welsh CS, Margolis RL, Ross CA. Age, CAG repeat length, and clinical progression in Huntington's disease. *Mov Disord*. 2012;27:272-276.
8. Gusella JF, MacDonald ME. Molecular genetics: unmasking polyglutamine triggers in neurodegenerative disease. *Nat Rev Neurosci*. 2000;1:109-115.
9. Djousse L, Knowlton B, Hayden M, et al. Interaction of normal and expanded CAG repeat sizes influences age at onset of Huntington disease. *Am J Med Genet A*. 2003;119A:279-282.
10. Genetic modifiers of Huntington's disease C. identification of genetic factors that modify clinical onset of Huntington's disease. *Cell*. 2015;162:516-526.
11. Gusella JF, MacDonald ME. Huntington's disease: the case for genetic modifiers. *Genome Med*. 2009;1:80.
12. Gusella JF, MacDonald ME, Lee JM. Genetic modifiers of Huntington's disease. *Mov Disord*. 2014;29:1359-1365.
13. Ciosi M, Maxwell A, Cumming SA, et al. A genetic association study of glutamine-encoding DNA sequence structures, somatic CAG expansion, and DNA repair gene variants, with Huntington disease clinical outcomes. *EBioMedicine*. 2019;48:568-580.
14. Rue L, Banez-Coronel M, Creus-Muncunill J, et al. Targeting CAG repeat RNAs reduces Huntington's disease phenotype independently of huntingtin levels. *J Clin Invest*. 2016;126:4319-4330.
15. Ranganathan M, Kostyk SK, Allain DC, Race JA, Daley AM. Age of onset and behavioral manifestations in Huntington's disease: an enroll-HD cohort analysis. *Clin Genet*. 2021;99:133-142.
16. McAllister B, Gusella JF, Landwehrmeyer GB, et al. Timing and impact of psychiatric, cognitive, and motor abnormalities in Huntington disease. *Neurology*. 2021;96:e2395-e2406.

17. Braisch U, Muche R, Rothenbacher D, et al. Identification of symbol digit modality test score extremes in Huntington's disease. *Am J Med Genet B Neuropsychiatr Genet*. 2019;180:232-245.
18. Martinez-Horta S, Horta-Barba A, Perez-Perez J, et al. Utility of the Parkinson's disease-cognitive rating scale for the screening of global cognitive status in Huntington's disease. *J Neurol*. 2020;267:1527-1535.
19. Landwehrmeyer GB, Fitzer-Attas CJ, Giuliano JD, et al. Data analytics from enroll-HD, a global clinical research platform for Huntington's disease. *Mov Disord Clin Pract*. 2017;4:212-224.
20. Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol*. 2013;12:637-649.
21. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. *Neurology*. 1979;29:1-3.
22. Group HS. Unified Huntington's disease rating scale: reliability and consistency. Huntington Study Group. *Mov Disord*. 1996;11:136-142.
23. Oosterloo M, Bijlsma EK, van Kuijk SM, Minkels F, de Die-Smulders CE. Clinical and genetic characteristics of late-onset Huntington's disease. *Parkinsonism Relat Disord*. 2019;61:101-105.
24. Fusilli C, Migliore S, Mazza T, et al. Biological and clinical manifestations of juvenile Huntington's disease: a retrospective analysis. *Lancet Neurol*. 2018;17:986-993.
25. Folstein MF, Folstein SE, McHugh PR. "mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
26. Penney JB Jr, Vonsattel JP, MacDonald ME, Gusella JF, Myers RH. CAG repeat number governs the development rate of pathology in Huntington's disease. *Ann Neurol*. 1997;41:689-692.
27. Callaghan J, Stopford C, Arran N, et al. Reliability and factor structure of the short problem behaviors assessment for Huntington's disease (PBA-s) in the TRACK-HD and REGISTRY studies. *J Neuropsychiatry Clin Neurosci*. 2015;27:59-64.
28. Schobel SA, Palermo G, Auinger P, et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. *Neurology*. 2017;89:2495-2502.
29. Kaufman L, Rousseeuw PJ. *Finding groups in data: an Introduction to cluster analysis*. Wiley; 1990.
30. Lumley T, Diehr P, Emerson S, Chen L. The importance of the normality assumption in large public health data sets. *Annu Rev Public Health*. 2002;23:151-169.
31. Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE. *Regression methods in biostatistics: linear, logistic, survival, and repeated measures models*. Springer; 2005.
32. Crawford JR, Garthwaite PH. Using regression equations built from summary data in the neuropsychological assessment of the individual case. *Neuropsychology*. 2007;21:611-620.
33. De Andrade MR, Diaz-Orueta U, Oltra-Cucarella J. Logistic versus linear regression-based reliable change index: a simulation study with implications for clinical studies with different sample sizes. *Psychol Assess*. 2022;34:731-741.
34. Fernandez-Nogales M, Cabrera JR, Santos-Galindo M, et al. Huntington's disease is a four-repeat tauopathy with tau nuclear rods. *Nat Med*. 2014;20:881-885.
35. Rodrigues FB, Byrne L, McColgan P, et al. Cerebrospinal fluid total tau concentration predicts clinical phenotype in Huntington's disease. *J Neurochem*. 2016;139:22-25.
36. Vuono R, Winder-Rhodes S, de Silva R, et al. The role of tau in the pathological process and clinical expression of Huntington's disease. *Brain*. 2015;138:1907-1918.
37. Baskota SU, Lopez OL, Greenamyre JT, Kofler J. Spectrum of tau pathologies in Huntington's disease. *Lab Invest*. 2019;99:1068-1077.
38. Oltra-Cucarella J, Sanchez-SanSegundo M, Ferrer-Cascales R. Alzheimer disease neuroimaging I. predicting Alzheimer's disease with practice effects, APOE genotype and brain metabolism. *Neurobiol Aging*. 2022;112:111-121.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Martínez-Horta S, Perez-Perez J, Oltra-Cucarella J, et al. Divergent cognitive trajectories in early stage Huntington's disease: A 3-year longitudinal study. *Eur J Neurol*. 2023;30:1871-1879. doi:10.1111/ene.15806