Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Prodromal Cognitive Changes as a Prognostic Indicator of Forthcoming Huntington's Disease Severity: A Retrospective Longitudinal Study

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Abstract: Background: Cognitive changes in Huntington's disease (HD) precede motor manifestations. ENROLL-HD platform includes four cognitive measures of information processing speed (IPS). Our group is eager to seek clinical markers in the life stage that is as close as possible to the age of onset (ie, the so called prodromal HD phase) because this is the best time for therapeutic interventions.
Objectives: Our study aimed to test whether cognitive scores in prodromal ENROLL-HD mutation carriers show the potential to predict the severity of motor and behavioral changes once HD became fully manifested.
Methods: From the global ENROLL-HD cohort of 21,343 participants, we first selected a premanifest Cohort#1 (ie, subjects with Total Motor Score (TMS) <10 and Diagnostic Confidence Level (DCL) <4, $N = 1.222$). From this cohort, we then focused on a prodromal Cohort#2 of subjects who were ascertained to phenoconvert into manifest HD at follow-up visits (ie, subjects from 6 · TMS·9 and DCL <4 to TMS≥10 and DCL = 4, $n = 206$).
Results: The main results of our study showed that low IPS before phenoconversion in Cohort#2 predicted the severity of motor and behavioral manifestations. By combining the four IPS cognitive measures (eg, the Categorical Verbal Fluency Test; Stroop Color Naming Test; Stroop Word Reading; Symbol Digit Modalities Test), we generated a Composite Cognition Score (CCS). The lower the CCS score the higher the TMS and the apathy scores in the same longitudinally followed-up patients after phenoconversion.
Conclusions: CCS might represent a clinical instrument to predict the prognosis of mutation carriers who are close to manifesting HD.

Huntington's disease (HD) typically manifests in adulthood with disability depending on clinical signs and symptoms progressively affecting movements (eg, chorea, dystonia, parkinsonism, impaired ocular movements, limb incoordination, loss of balance)[1] as well as behavior (eg, obsessions, perseveration, aggressiveness, depression and propensity to suicide)[2] and cognition (eg, abnormal executive functions, memory, language, social cognition).[3–5]

HD can be predicted by a molecular genetic test which identifies a trinucleotide expanded mutation >35 CAG repeats in Huntingtin gene (*HTT*) on chromosome 4.[6] Clinical diagnosis is generally based on the assessment of motor signs by using the Unified Huntington's Disease Rating Scale (UHDRS),[7,8] even though cognitive and behavioral changes may subtly anticipate the specific neurological manifestations.[7–9] For example, cognitive changes affecting executive functions occur early in life before the onset of motor manifestations.[10–12] Terms such as premanifest (ie, far from age at onset) or prodromic (ie, near to age at onset) life stages are used to describe the time before manifest

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Keywords: presymptomatic stage, cognitive changes, cognitive score, prognostic index, disease severity.
Received 6 June 2023; revised 30 November 2023; accepted 2 January 2024.
Published online 00 Month 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13975

symptoms appear, while phenoconversion identifies the time when a subject's clinical status changes from a prodromal into a visible manifest phase.[8] Recent research has highlighted biological, cognitive and functional brain changes occurring many years before disease presentation,[11,13] while other approaches have identified composite clinical measures to either track the progression of HD[14] or to provide prognostic indexes before visible clinical manifestations.[15,16]

Recently, a new, research oriented, Integrated Staging System (ISS) was proposed to minimize the bias resulting from clinicians' subjective assessments. This system incorporates data on initial volumetric brain striatal changes (ie, stage 1), or UHDRS-Total Motor Score (TMS) and Symbol Digit Modality Test (SDMT) (ie, stage 2), in the attempt to replace the obsolete terminology associated with premanifest and prodromal HD conditions.[17] ISS was specifically tailored to clinical trials and includes a practical approach to instantly check whether a given subject is a candidate for that particular experimental trial.[17]

However, the ISS and other models such as the Prognostic Index Normed for HD (PIN-HD) only included SDMT among the cognitive ENROLL-HD measures.[15–17]

In such a complex scenario, we aimed to investigate whether the early cognitive scores that are collected in ENROLL-HD before HD becomes manifest may predict the severity of future neurological and psychiatric symptoms. In this work, we sought to retrospectively recapitulate the life stage of mutation carrier subjects who were longitudinally monitored and were initially premanifest at a basal visit, later showing phenoconversion at the follow up visits, ie, they exhibited full neurological manifestations.

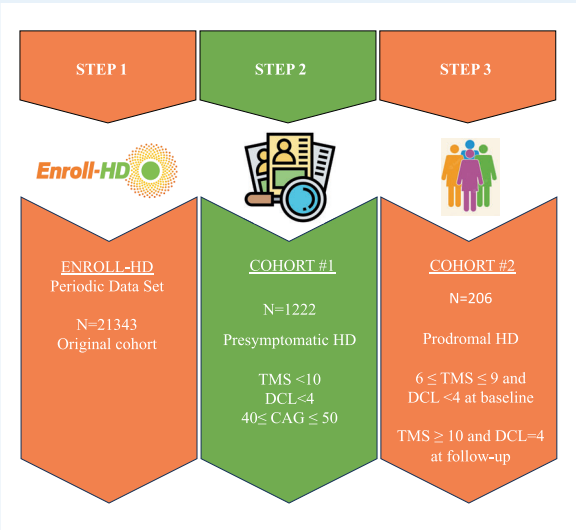

Figure 1. Subjects' stratification criteria. Description of the original cohort, Cohort#1 and Cohort#2. Cohort#2 included subjects who were ascertained for phenoconversion into full manifest Huntington's disease at follow-up visits.

Methods

ENROLL-HD, Experimental Design and Cohort' Stratification

ENROLL-HD is a large research platform currently including more than 20,000 participants from 156 clinical sites in 23 countries. The ENROLL-HD criteria categorize as premanifest those subjects who are gene-positive with no specific motor signs of HD, ie, with UHDRS–TMS <10 units and Diagnostic Confidence Level (DCL) <4.[7,18] These individuals show preserved independence with normal daily functionality, as reflected by a Total Functional Capacity (TFC) scale score of 13.

Our retrospective longitudinal study aimed to analyze those premanifest subjects who crossed the edge of TMS = 10 during a longitudinal follow-up. According to the ENROLL-HD criteria, these were the subjects who phenoconverted into manifest HD and were expected to show a DCL = 4.

To select the premanifest population, we analyzed data from the global ENROLL-HD cohort of 21.343 participants (Periodic DataSet#5 – PDS#5). In our patients' stratification, we excluded two groups: (1) subjects with expanded mutations less than 40 and above 50 CAG repeats, in order to obtain a population as homogeneous as possible, thus also taking out of study early or late onset cohorts with potentially different HD progression[17,19]; (2) subjects with previous/ongoing serious psychiatric manifestations, suicidal ideation, and alcohol or drug abuse. All these characteristics are well documented in the ENROLL-HD dataset.

Firstly, we selected subjects with TMS < 10 and DCL <4 (Cohort#1). This was the whole cohort of premanifest subjects because they showed a DCL score lower than 4. From this cohort, we selected individuals with TMS score between 6 and 9. These subjects showed a TMS score beyond the value of 5 units. Typically, subjects with TMS lower than 6 are considered free from neurological manifestations because they overlap the same fluctuation of TMS observed in the general population.[20] From this cohort of subjects with a TMS score between 6 and 9 (ie, <10), we focused only on subjects who were retrospectively ascertained to have phenoconverted along their follow-up visits (n = 206) (Cohort#2). This final cohort of subjects crossed the border from a TMS < 10 to a TMS≥10 and from a DCL <4 to a DCL = 4 (Fig. 1). We considered the mean interval between the last prodromal evaluation and the first examination where Cohort#2 subjects exhibited manifest HD.

Finally, we calculated the following predictive burden scores CAG-Age Product (CAP)[21,22] and the PIN-HD,[15] to confirm a prognostic difference between phenoconverters and non-phenoconverters. Differently from CAP score, PIN-HD was specifically developed as a predictor of motor progression, thus including clinical measures such as the TMS and the SDMT, a cognitive measure including a motor

TABLE 1 *Demographic, clinical, and genetic characteristics of the study sample*

Demographic clinical and genetic features	Cohort #1: 1222 premanifest HD subjects	Cohort #2: 206 prodromal HD subjects	*P*
Age mean ± SD (range)	37.9 ± 10.2 (20–73)	46 ± 10.8 (21–73)	$P < 0.0001$
Educational level, in years mean ± SD (range)	14.7 ± 3.5 (5–21)	14.3 ± 3.3 (5–21)	NS
Gender (F – %)	759–62.2%	130–63.1%	NS
CAG repeat mean ± SD (range)	42.5 ± 2.1 (40–50)	43.1 ± 2.3 (40–50)	NS
TMS mean ± SD (range)	1.5 ± 2.1 (0–5)	7.6 ± 1.1 (6–9)	$P < 0.0001$

Abbreviations: SD, standard deviation; F, female; NS, not significant; TMS, Total Motor Score.

component.[15,16] Demographic and clinical characteristics are summarized in Table 1.

Clinical Measures

UHDRS neurological and functional assessments and Problem Behavioral Assessment-short form (PBA-s)[23] are in supporting information. According to the ENROLL-HD protocol, the cognitive evaluation includes four UHDRS tests that assess executive functions and information processing speed (IPS): (1) Categorical Verbal Fluency Test (VFT), in which participants have to produce as many words as possible from a semantic category (ie, animals) in 60 s; (2) Stroop Color Naming test (SCN), in which participants are requested to name as many colors as possible in 45 sec of randomly presented tokens (ie, three colors—blue, red, green) and (3) Stroop Word Reading test (SWR), where participants read as many words as possible in 45 sec of randomly presented tokens (three color words—blue, red, green) printed in black ink; (4) The Symbol Digit Modality Test (SDMT), in the written response format, requires participants to use a coded key to match nine numerical digits with nine symbols in 90 sec. Participants were given 10 practice items before starting the test. In all cases, the lower the scores the more marked the cognitive decline.

Statistical Analysis

In presymptomatic Cohort#1 ($n = 1222$), we assessed the relationships between cognitive scores by Spearman's correlation analysis at baseline (SDMT, VFT, SCN, SWR) and either motor (TMS score, oculomotor, coordination, chorea, dystonia, tongue, gait, parkinsonism, dysarthria) or behavioral scores (Depression sub-score—DepSc; Irritability sub-score—IrrSc; Apathy sub-score—ApSc; Perseverative/Obsessive sub-score—PeObSc; Psychosis sub-score—PsySc), after a two-year follow-up. No or negligible relationships, ie, r values comprised between −0.2 and 0.2, were discarded. Correlations were assumed to be significant if Spearman's adjusted *P*-values ≥0.05; False Discovery Rate was controlled using the Benjamini–Hochberg method. We have opted to use Spearman's instead of Pearson's test since we could not assume the normality of the variables or the existence of linear relationships between them. Normality assessment was performed using the Shapiro-Wilks test. The same analysis was performed on Cohort#2 (206 prodromal HD subjects that phenoconverted in the follow-up visits), where variables measured during the prodromal phase (TMS between 6 and 9, DCL <4) were averaged through time points and then correlated with all the variables recorded during the manifest phase (TMS≥10, DCL = 4) at the exact time point where each patient exhibited the maximum TMS score. A histogram showing the time spans from the first prodromal visit to the one when the maximum TMS score was assessed for Cohort#2 patients is available in Figure S4. The choice to average the prodromal variables is due to the duration of the prodromal phases, which varied through patients. We have instead opted to take the maximum TMS of the manifest phase, as we wanted to capture the symptomatic peak of each phenoconverted patient. Then the assessment of the potential connection between prodromal cognitive performance and either motor or behavioral variables measured during the manifest phase and recorded, as specified above, when the TMS value was the highest for each patient, was performed through multiple linear regression analysis. Since we were interested in evaluating the cognition scores as prognostic indicator, we iteratively used the manifest motor and behavioral variables as response variables for the linear model, while prodromal cognitive, motor, and behavior variables, CAG, and sex were used as independent variables:

$$y_{manifest} \sim Y_{prodromal} + C_{prodromal} + CAG + sex$$

where Y is the set of motor and behavior variables, C is the set of cognitive variables, and $y \in Y$ is iteratively each of the variables in Y. In order to determine whether the cognitive variables and CAG were informative for the response variable, this model was fitted repeatedly, with the cognitive variables and CAG being individually removed from the independent variables set at each iteration.

Moreover, in a separate analysis, we approximated the disease progression speed using the linear regression slope of the TMS as a function of time, considering the time points spanning the prodromal and the early manifest phase, which is the phase in which patients with mild symptoms are at ISS stage 2.[12] We correlated this measure with an ensemble of four prodromal cognitive

scores, ie, SDMT, VFT, SCN, and SWR. In order to embody these scores into a single comprehensive variable, scores were first averaged over the prodromal stage, then standardized, and finally subjected to Principal Component Analysis (PCA). A *Composite Cognition Score* (CCS) resulted from the equation:

$$CCS = \frac{v_1}{\sigma_1}(x_1 - \mu_1) + \frac{v_2}{\sigma_2}(x_2 - \mu_2) + \frac{v_3}{\sigma_3}(x_3 - \mu_3) + \frac{v_4}{\sigma_4}(x_4 - \mu_4)$$

where x_1, x_2, x_3, x_4 are SDMT, VFT, SCN, and SWR, respectively; v is the first PCA's eigenvector; σ is the standard deviations vector of the four average prodromal cognitive scores; μ is the means vector. Therefore, we categorized patients into three groups based on their initial cognitive status: group 1 included patients with CCS < −2.375 (ie, *CCS*-1.5 SD); group 2 included patients with −2.375 (*CCS*-1.5 SD) ≤ CCS ≤ + 2.375 (ie, *CCS*+1.5 SD); group 3 included patients with CCS > +2.375 (*CCS*+1.5 SD). We then correlated each group with the TMS slopes of its patients using the Kendall's tau test; differences between the three groups were evaluated using the Mann–Whitney U test. We considered 0.05 as the p-value significance threshold.

TABLE 2 *Cohort #1 Spearmen's r (and related level of significance) between cognitive domains at baseline and TMS and PBA subscores two years later*

		SDMT	VFT	SCN	SWR
Oculomotor	r	−0.16	−0.07	−0.07	−0.08
	P	<0.0001	0.02	0.05	0.02
Coordination	r	**−0.29**	−0.12	−0.17	−0.17
	P	**<0.0001**	0.0002	<0.0001	<0.0001
Chorea	r	−0.16	−0.07	−0.1	−0.07
	P	<0.0001	0.04	0.002	0.05
Dystonia	r	−0.04	−0.05	−0.05	−0.02
	P	0.28	0.13	0.19	0.57
Tongue protrusion	r	−0.06	−0.01	−0.02	−0.04
	P	0.09	0.77	0.53	0.21
Gait	r	−0.15	−0.06	−0.08	−0.1
	P	<0.0001	0.09	0.02	0.001
Parkinsonism	r	−0.02	−0.01	−0.05	−0.08
	P	0.63	0.72	0.17	0.01
Dysarthria	r	−0.07	−0.04	−0.06	−0.05
	P	0.05	0.27	0.06	0.15
TMS	r	**−0.26**	−0.12	−0.16	−0.18
	P	**<0.0001**	0.0002	<0.0001	<0.0001
DepSc	r	−0.07	−0.03	−0.02	−0.02
	P	0.04	0.45	0.52	0.62
IrrSc	r	−0.09	−0.03	−0.04	−0.02
	P	0.006	0.36	0.2	0.61
ApSc	r	−0.07	−0.13	−0.04	−0.07
	P	0.04	<0.0001	0.24	0.04
PeObSc	r	−0.09	−0.04	−0.04	0
	P	0.007	0.32	0.24	0.98
PsySc	r	−0.07	0	−0.02	−0.03
	P	0.02	0.99	0.62	0.46

Abbreviations: SDMT, Symbol Digit Modality Test; VTF, Categorical Verbal Fluency Test; SCN, Stroop Color Naming Test; SWR, Stroop Word Reading Test. TMS, Total Motor Score; DepSc, depressed mood PBA-s subscale; IrrSc, irritability PBA-s subscale; ApSc, apathy PBA-s subscale; PeObSc, obsessions/perseverative thinking PBA-s subscale; PsySc, delusions/paranoid thinking PBA-s subscale. Statistical significance and r ≥ 0.2 or r ≤ −0.2 are highlight in bold.

Finally, we tested the difference in TMS progression among the groups by implementing a linear mixed model, in which time and CCS were treated as fixed effect variables, while the patient was treated as a random effect variable, associated with a patient-specific intercept coefficient. This regression model can be formalized as follows: TMS ~ time x group + (1|patient). The "group" variable was considered discrete, in contrast to how it was done for the Kendall's tau test. The mixed linear model was optimized by maximizing the Restricted Maximum Likelihood (REML).[24] The Satterthwaite method[25] was applied to approximate the degrees of freedom, and an unstructured covariance matrix type was used for the random factors. In order to demonstrate whether cognitive scores are informative of TMS progression regardless of other clinical variables that are available at baseline, we further repeated the analysis using the following formula: TMS ~ time * CCS + time*CAG + time*start_age + (1|patient). We have observed that the only statistically relevant weight is associated with the time: CCS interaction term (Fig. S3).

Results

Cohort#1 included the whole original cohort of 1222 pre-manifest HD subjects with TMS < 10 and DCL <4 (759 females and 463 males), with a mean age of 37.9 ± 10.2 years (range 20–73 years), mean education level of 14.7 ± 3.5 years (range 5–21 years), mean expanded CAG repeat number of 42.5 ± 2.1 (range 40–50 CAG repeats) and a mean TMS of 1.5 ± 2.1 (range 0–9 TMS score).

Cohort#2 included 206 prodromal HD subjects selected from Cohort#1, who showed TMS score between 6 and 9 at baseline, then phenoconverted at the follow-up visits (130 females and 76 males), with a mean age of 46 ± 10.8 years (range 21–73 years), mean education level of 14.3 ± 3.3 years (range 5–21 years), mean expanded CAG repeat number of 43.1 ± 2.3 (range 40–50 CAG repeats) and mean TMS of 7.6 ± 1.1 (range 6–9 TMS score). The mean interval between the last prodromal clinical assay and the first clinical assay where they exhibited TMS≥10 and manifest HD, was 1.97 ± 1.16 years.

Cohort#2 of phenoconverted individuals showed: (1) a disease burden CAP higher than subjects who did not progress towards manifest HD, at the last ENROLL-HD follow-up visit (324.3 ± 58.5, $n = 206$ vs. 288.5 ± 65.2; $n = 583$, $P < 0.0001$); and (2) a PIN-HD higher than subjects who did not progress towards manifest HD (0.2 ± 0.7, $n = 206$ vs. 0.6 ± 0.7; $P < 0.0001$, $n = 583$). Other differences between the two groups have been reported in Table S4. The study design and cohort stratification are described in Figure 1.

Correlation and Causality between Cognitive Scores, Motor Impairment, and Behavioral Domain

In Cohort#1, the only significant negative correlation was observed between the baseline SDMT score and both coordination (r = −0.29, $P < 0.0001$) and TMS total score (r = −0.26, $P < 0.0001$), after a two-year follow-up period (Table 2 and Fig. 2).

In Cohort#2, a significant negative correlation was observed between SDMT (r = −0.41, $P < 0.0001$), VFT (r = −0.26, $P = 0.002$), SCN (r = −0.22, $P = 0.01$) and SWR (r = −0.25, $P = 0.003$) averaged scores in prodromal HD before phenoconversion and the worst coordination sub-score in manifest HD follow-ups after phenoconversion. We additionally found a significant negative correlation between SDMT (r = −0.24, $P = 0.007$) averaged scores in prodromal HD and the worst gait sub-score in the manifest HD follow-ups after phenoconversion.

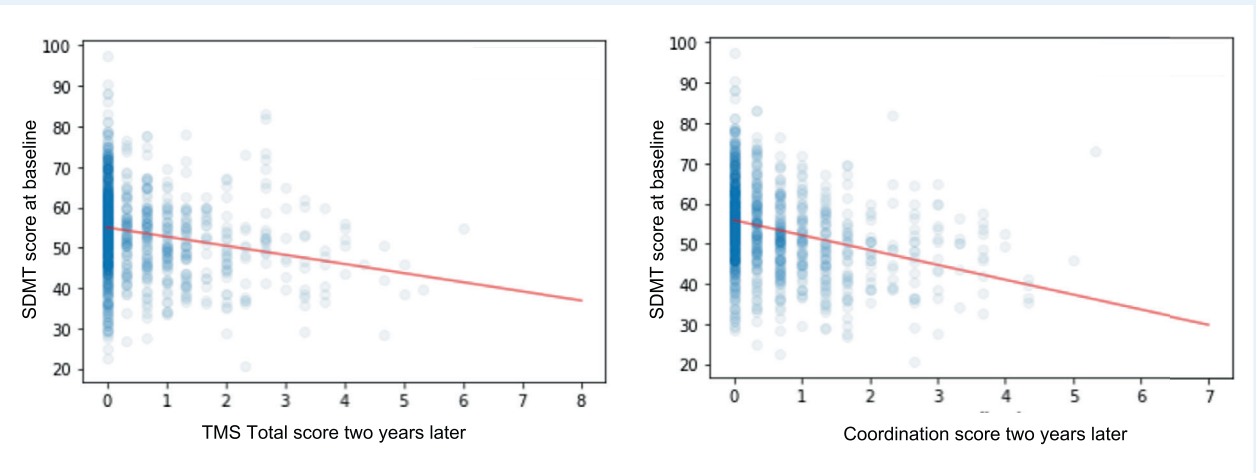

Figure 2. Correlation between baseline SDMT score and TMS (left) and coordination (right) after two years. SDMT, Symbol Digit Modalities Test; TMS: Total Motor Score.

Furthermore, we highlighted a significant negative correlation between SWR in prodromal HD and the parkinsonism sub-score in manifest HD ($r = -0.2$, $P = 0.03$). Finally, we showed significant negative correlations between SDMT ($r = -0.35$, $P < 0.0001$), VFT ($r = -0.26$, $P = 0.002$), SCN ($r = -0.26$, $P = 0.002$) and SWR ($r = -0.22$, $P = 0.01$) scores in prodromal HD and TMS score in manifest HD follow-ups after phenoconversion (Table 3 and Fig. S1). We additionally computed the same correlation at the baseline prodromal stage (Table S3).

A multiple linear regression analysis was performed in order to find direct causal relationships between cognitive functions in the prodromal HD phase and motor and behavior signs in the manifest HD phase within Cohort#2 (regression weights in Fig. S3). We confirmed the worsening of the coordination sub-score in patients with a low SDMT score at prodromal phase ($P = 0.019$) and, additionally, a low prodromal SDMT was also associated with Apathy (ApSc) increase when HD became manifest ($P = 0.021$). Moreover, we found that a prodromal SWR score was associated with more pronounced parkinsonism in manifest

TABLE 3 *Cohort #2 Spearmen's r (and related level of significance) between cognitive domains in prodromic stage of the disease and TMS and PBA subscores in the manifest stage of the disease*

		SDMT	VFT	SCN	SWR
Oculomotor	r	−0.15	−0.09	−0.13	−0.09
	P	0.15	0.52	0.25	0.52
Coordination	r	**−0.41**	**−0.26**	**−0.22**	**−0.25**
	P	**<0.0001**	**0.002**	**0.01**	**0.003**
Chorea	r	−0.03	−0.10	−0.07	0
	P	0.88	0.46	0.63	0.99
Dystonia	r	−0.03	−0.07	0.04	0.05
	P	0.86	0.62	0.82	0.74
Tongue protrusion	r	−0.12	−0.09	−0.02	−0.03
	P	0.33	0.52	0.92	0.84
Gait	r	**−0.24**	−0.19	−0.12	−0.17
	P	**0.007**	0.05	0.33	0.09
Parkinsonism	r	−0.09	0.01	−0.11	**−0.2**
	P	0.49	0.94	0.38	**0.03**
Dysarthria	r	−0.19	−0.06	−0.17	**−0.2**
	P	0.04	0.71	0.08	**0.03**
TMS	r	**−0.35**	**−0.26**	**−0.26**	**−0.22**
	P	**<0.0001**	**0.002**	**0.002**	**0.01**
DepSc	r	−0.02	0.08	0.1	0.13
	P	0.92	0.61	0.45	0.24
IrrSc	r	0.12	0.1	0.14	0.1
	P	0.33	0.44	0.2	0.44
ApSc	r	−0.17	−0.04	−0.1	−0.09
	P	0.1	0.78	0.46	0.52
PeObSc	r	−0.14	−0.06	0.01	−0.02
	P	0.22	0.71	0.97	0.9
PsySc	r	−0.10	0.02	0.05	0.04
	P	0.46	0.92	0.74	0.78

Abbreviations: SDMT, Symbol Digit Modality Test; VTF, Categorical Verbal Fluency Test; SCN, Stroop Color Naming Test; SWR, Stroop Word Reading Test. TMS, Total Motor Score; DepSc, depressed mood PBA-s subscale; IrrSc, irritability PBA-s subscale; ApSc, apathy PBA-s subscale; PeObSc, obsessions/perseverative thinking PBA-s subscale; PsySc, delusions/paranoid thinking PBA-s subscale. Statistical significance and $r \geq 0.2$ or $r \leq -0.2$ are highlight in bold.

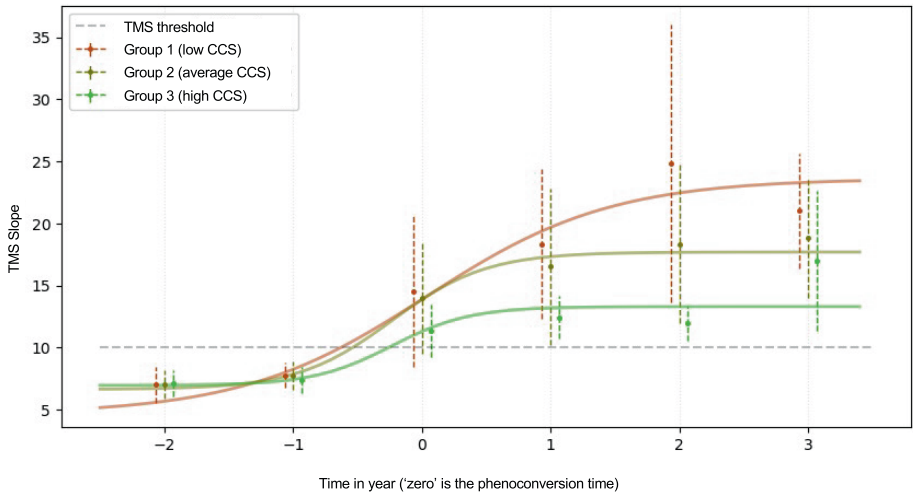

Figure 3. Total Motor Score (TMS) progression over time. TMS progression over time in patients' Cohort #2, split into three groups according to the CCS and centered on the year of phenoconversion (t = 0, TMS ≥10, DCL = 4); the TMS increase of the three groups was fitted by sigmoid-likely functions through mean squared error minimization; the growth functions have been forced to intersect 10 TMS (gray dashed line) in the time interval (−1,0]; dashed bars represent standard deviations.

HD (P= 0.032). A low prodromal VFT was found to be associated with a higher TMS score in manifest HD (P = 0.02). The presence of expanded CAG repeats increased the dysarthria sub-score in manifest HD (P = 0.022). CAG repeat length also affected the SDMT sub-score negatively in the manifest phase (P = 0.032), instead it was protective for depression (DepSc) (P = 0.037, Table S1).

Prodromal Cognitive Performance and TMS Progression

Letting the vector of the means of the four average prodromal cognitive scores be $\mu = [42.90, 19.30, 66.43, 86.14]$, their standard deviations be $\sigma = [10.62, 5.07, 13.07, 16.23]$, and the first PCA eigenvector be $v = [0.51, 0.4, 0.54, 0.54]$ (Table S2), the CCS formula mentioned above can be rewritten as follows:

$$CCS = \frac{0.51}{10.62}(SDMT - 42.9) + \frac{0.4}{5.07}(VFT - 19.3) + \frac{0.54}{13.07}(SCR - 66.43) + \frac{0.54}{16.23}(SWR - 86.14)$$

A runnable implementation of a CCS calculator is available for simulation upon request. By this formula, we divided patients in Cohort#2 into 3 groups (see Statistical analysis for details). CCS, categorized into the three groups, negatively correlated with TMS once HD manifested (Kendall's tau test, tau = −0.15, P-value = 0.011). Group 1 (low cognitive performance) showed a higher TMS slope (5.77 ± 5.18) with respect to Group 3 (high cognitive performance) (2.81 ± 2.41) (Mann–Whitney U test, U = 1969, P = 0.012). Also, Group 2 (average cognitive performance) exhibited a TMS slope (4.53 ± 3.4) higher than Group 3 (2.81 ± 2.41) (U = 170, P = 0.013). Conversely, patients with higher CCS (Group 3) showed a slower TMS total score progression once HD became manifest, in comparison with the other two groups (Fig. S2).

We also confirmed the differences in TMS increase among the three groups by proving that the effect of time on the TMS was higher in Group 1 than in both Group 2 (linear mixed model coefficient difference = 1.93; $P < 0.001$) and Group 3 (coefficient difference = 2.96; $P < 0.001$); similarly, we proved that the same effect in Group 2 was higher than in Group 3 (coefficient difference = 1.03, $P < 0.001$, see Fig. 3). Cognitive score trajectories in Cohort #2, divided into the 3 CCS-based subgroups, are reported in Figure S5.

Discussion

Our retrospective longitudinal study explored the life stages of HD mutation carriers who phenoconverted from a premanifest into a manifest HD phase. Currently, it is widely believed that this phase of the disease may strategically represent the best time for an experimental therapeutic, disease-modifier, intervention. The large ENROLL-HD dataset allowed us to approach a consistent population of ascertained "phenoconverters", ie, those subjects who were presymptomatic at a basal visit, with no specific clinical manifestations in the raters' opinion (ie, DCL <4), but crossed through the edge of normality based on the current clinical knowledge and according to the ENROLL-HD

protocol.[18,22,26] ENROLL-HD engages certified HD clinicians who are dedicated to the treatment and investigation of individuals with HD on a global scale. The platform employs standardized testing and the integration of cognitive measures, which have been used consistently and for a long time (eg, REGISTRY platform), therefore representing a practice-based clinical approach. Our study highlighted multiple correlations, both in premanifest subjects as a whole (ie, Cohort#1, $n = 1222$), including individuals relatively far from age at onset and prodromal subjects who were near the onset and later confirmed to phenoconvert at follow-up visits (ie, Cohort#2, $n = 206$). In Cohort#1, a correlation was already visible between low IPS at baseline visit and more pronounced coordination impairment two years later. Coherently, Cohort#2 showed a significant correlation between low performance in executive function/IPS before phenoconversion and more pronounced motor disabilities in the manifest HD phase (coordination, gait, parkinsonism and UHDRS-TMS). These findings paved the way for the interesting hypothesis that greater is the cognitive dysfunction (ie, IPS/executive functions) before motor onset, more severe is the expected motor decline in manifest HD.

To test such a hypothesis, we combined all four ENROLL-HD cognitive measures, which assess executive functions/IPS, and thereby we investigated whether such a combination could be predictive of motor impairment severity, once prodromal mutation carriers phenoconverted into a manifest HD phase. Among cognitive functions, the executive domain is specifically affected in HD with deficits in attention, set-shifting, social cognition and emotion recognition being highlighted long before motor clinical diagnosis.[10,11,27,28] By combining the four ENROLL-HD cognitive measures (SDMT, SWR, SCN and VFT), we generated the CCS. Interestingly, lower prodromal CCS was predictive of UHDRS-TMS increase once patients phenoconverted. This is in line with the potentially protective role of preserved cognition on the severity of HD progression.[29] More specifically, the prodromal CCS showed a stronger correlation with impaired coordination, which was scored by specific UHDRS sub-items in the manifest HD phase.

Our study has limitations. Firstly, we used an arbitrary UHDRS-TMS based methodology to select a cohort of subjects who were defined as prodromal. However, our retrospective study revealed that these subjects had their condition revaluated by ENROLL-HD certified clinicians, resulting in a change from DCL <4 to DCL = 4. Despite this limitation, TMS does still represent one of the best clinical markers of neurological HD progression, and it might be extended to both juvenile/pediatric-onset and late-onset individuals. Secondly, our prodromal cohort missed imaging data, which are not included in the ENROLL-HD data set. Of course, longitudinal imaging in a prone-to-phenoconvert population will highlight new brain patterns associated with clinical changes. For instance, it is worth mentioning that a specific pattern of fronto-striatal alterations was already described in prodromal HD,[30,31] in which a compensatory neural activity was reported during highly demanding executive tasks.[32] Our data offers new inputs to potentially corroborate these observations by integrating imaging analyses with measures such as the CCS in an attempt to highlight the early involvement of the fronto-striatal and other brain networks anticipating manifest HD.

Of note, our prodromal phenoconverter cohort presented a CAP and PIN-HD scores higher than the cohort which did not phenoconvert: a piece of evidence which confirms that our Cohort#2 was really eligible as a phenoconverter HD population.

Our study supports the evidence that cognitive changes might anticipate and predict motor progression in neurodegenerative diseases. Specifically, executive functions are documented to be impaired early in HD patients' life[33] and are altered in several other neurological diseases. For example, SDMT does represent a critical measure in Multiple Sclerosis (MS)[34] and may predict gait impairment in this disease.[35] Other studies highlighted the role of SDMT as a potential marker of further independence decline[36] and its association with impairment of mobility in HD patients[37] and with impaired coordination in HD related diseases such as Spinocerebellar Ataxias type 1–3.[38] Also in Parkinson's disease (PD), SDMT has been shown to be an important risk factor in predicting the onset of freezing of gait within 5 years.[39] In our study, low prodromal SDMT score was also significantly associated with an increase of apathy, paving the way for new studies which may explore cognition-based assays to predict behavioral changes.

Even though we cannot raise conclusions on specific neurobiological mechanisms explaining the relationship between low prodromal CCS and worse physical and mental progression once HD fully manifests, our data offers clues to the interpretation of dysfunction in some brain regions. For example, the role of cerebellum was highlighted in HD and its metabolic dysfunction was related to cognitive and motor manifestations in both HD and MS.[40,41] Specifically, a correlation between IPS and coordination has been described in MS, thus leading to the hypothesis that such a relationship between cerebellar function and cognition may occur in neurodegenerative diseases.[42]

In conclusion, we found that CCS, based on tests which are currently used worldwide to measure executive functions within the most popular HD platform such as ENROLL-HD, shows the potential to predict the severity of physical decline and motor score worsening in HD. Our data have several implications in clinical and research practice. The CCS might represent a valuable tool to predict the prognosis of at-risk people who are close to manifest HD, thus addressing new cognitive rehabilitation approaches in the future. At the same time, CCS has a potential for being considered in clinical trials to test the efficacy of experimental drugs.

Acknowledgments

We are grateful to all families and patients from the LIRH Foundation Network of Huntington's disease patients' associations (eg, LIRH-Puglia, LIRH-Tuscany, LIRH-Sardinia, Noi Huntington) for their continuous support to LIRH research

initiatives. LIRH Foundation received funding from the Cure Huntington's Disease Initiative Foundation for collecting patient data and samples in the ENROLL-HD platform.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

S.i.M.: 1B, 1C, 3A, 3B
S.D.B: 2A, 2B, 3B
M.S.: 1C, 2C, 3A
S.M.: 1B, 1C, 3B
L.C.B.: 1C, 2C, 3B
C.C.: 1C, 2C, 3B
G.C.: 1C, 2C, 3B
T.M.: 2A, 2B, 2C, 3B
F.S.: 1A, 1B, 1C, 3A, 3B

Disclosures

Ethical Compliance Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the LIRH Foundation Institutional Review Board (Prot. No. 10.281022, approved on October 28, 2022). All ENROLL-HD sites were required to obtain and maintain local ethics committee approvals. Participants must have signed informed consent forms for their data to be included in the datasets. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: No funding sources have been received for this work. All authors declare that there are no conflicts of interest for this work.

Financial Disclosures for the Previous 12 Months: All authors report no financial disclosures for this work.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Multiple linear regression between cognitive functions in the prodromic phase and motor-behavior domain in the manifest stage of the HD variables. SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading; VFT, Categorical Verbal Fluency Test; TMS, Total Motor Score; DepSc, Depression sub-score.

Table S2. Factor loadings from principal component analysis (PCA). SDMT, Symbol Digit Modalities Test; VFT, Categorical Verbal Fluency Test; SCN, Stroop Color Naming Test; SWR, Stroop Word Reading.

Figure S1. Cohort #2 Spearmen's r between cognitive domains in prodromal stage of the disease and Total Motor Score subscores in the manifest stage of the disease. SDMT, Symbol Digit Modalities Test; VFT, Categorical Verbal Fluency Test; SCN, Stroop Color Naming Test; SWR, Stroop Word Reading; TMS, Total Motor Scorer; DepSc, depressed mood PBA-s subscale; IrrSc, irritability PBA-s subscale; ApSc, apathy PBA-s subscale; PeObSc, obsessions/perseverative thinking PBA-s subscale; PsySc, delusions/paranoid thinking PBA-s subscale. Statistical significance and $r \geq 0.2$ or $r \leq -0.2$ are highlighted in orange.

Figure S2. Difference in the Total Motor Score (TMS) slope in CCS subgroups. Group 1: low CCS score (median CCS < -1.5 SD); Group 2: average CCS score (-1.5 SD $\leq$ median CCS $\leq +1.5$ SD); Group 3: high CCS score (median CCS $> +1.5$ SD). CCS, Composite Cognition Score. $\star P < 0.01$.