A Phenotypic Atlas for Huntington Disease Based on Data From the Enroll-HD Cohort Study

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Abstract

Background and Objectives
The variable CAG repeat expansion in the huntingtin gene and its inverse relationship to motor dysfunction onset are fundamental features of Huntington disease (HD). However, the wider phenotype (including non-motor features) at particular CAG lengths, ages, and functional levels is less well-characterized. The large number of participants in the Enroll-HD observational study enables the development of a phenotype atlas that summarizes the range and distribution of HD phenotypes, including outliers and possible clusters, with respect to various CAG repeat lengths, age ranges, and declining functional levels.

Methods
Enroll-HD is an ongoing prospective longitudinal observational study that collects natural history data, releasing periodic data sets, in people with HD (PwHD) and controls. Core assessments at annual visits focus on behavioral, cognitive, motor, and functional status. Periodic data set 5, used for the development of the first iteration of the Enroll-HD Phenotype Atlas (EHDPA), included all eligible data collected through October 31, 2020. The atlas is based on subsets (cells) of descriptive data for all motor, cognitive, psychiatric, and functional measures that are routinely collected at most Enroll-HD sites, analyzed by single CAG lengths and 5-year age blocks.

Results
Data from 42,840 visits from 15,982 unique PwHD were available for analysis. At baseline, participants had a mean ± SD age of 48.9 ± 13.9 years and CAG repeat length of 43.4 ± 3.6 and 54.1% were female. The EHDPA includes 223 age-by-CAG subsets for CAG repeats between 36 and 69 with five-year age brackets starting from 20–24 years up to 85–89 years. The atlas can be browsed at enroll-hd.org/for-researchers/atlas-of-hd-phenotype/.

Discussion
The EHDPA summarizes the spectrum and distribution of HD phenotypes, including outliers and possible clusters, in all domains of disease involvement for the range of CAG repeat lengths, ages, and functional levels. Its availability in an easy-to-use online format will assist clinicians in tracking disease progression in PwHD by identifying phenotypic features most associated with loss of function and enabling conversations related to prognosis. The observable patterns in the EHDPA should also catalyze more formal multidomain characterization of motor, cognitive, and psychiatric progression and their relationships to functional decline and disease modifiers.

Trial Registration Information
Enroll-HD is registered with clinicaltrials.gov: NCT01574053.

Glossary

EHDPA = Enroll-HD Phenotype Atlas; **HD** = Huntington disease; **PCA** = principal component analysis; **PDS5** = periodic data set 5; **PwHD** = people with HD; **SDMT** = symbol digit modality test; **TMS** = total motor score; **UHDRS** = Unified Huntington's Disease Rating Scale.

Introduction

Huntington disease (HD) is an inherited autosomal dominant neurodegenerative disease caused by an unstable expansion of CAG repeats in exon 1 of the huntingtin gene (*HTT*) on chromosome 4 that encodes the huntingtin protein (HTT). The variable CAG repeat expansion in the huntingtin gene and its inverse relationship to motor dysfunction onset and survival are fundamental features of the disease.[1,2] However, much of the literature addressing the influence of CAG length in HD has focused on the concepts of age at motor diagnosis[3] or age of motor onset,[4] and the wider phenotype (including non-motor features) at particular CAG lengths, ages, and functional levels is less well-characterized.

Enroll-HD is a clinical research platform and the world's largest observational study for families affected by HD.[5] Others have previously used this platform to develop a clinical dashboard that allows comparison of total motor score (TMS), total functional capacity, and symbol digit modality test (SDMT) score of an individual against a defined Enroll-HD cohort, controlling for age and CAG repeat length.[6] We report here the development of a new Enroll-HD Phenotype Atlas (EHDPA) that expands upon this concept to allow similar comparisons for a wider range of motor, cognitive, and behavioral aspects of HD that have all been measured as part of the Enroll-HD study.[5] The online atlas has been developed to assist clinicians to better visualize (through tables, charts, and/or illustrations) and understand the relationships between age; CAG repeat length in the *HTT* gene; and key markers of phenotypic onset, function, and progression in HD.

Methods

Enroll-HD Periodic Data Set 5

Enroll-HD (NCT01574053) is a prospective longitudinal observational study that collects natural history data in PwHD and community controls (18 years and older).[5,7] The study began in 2012 and is ongoing in 23 countries at 155 sites across 4 continents. Core assessments at annual visits focus on behavioral, cognitive, motor, and functional status conducted using a battery of validated and widely accepted assessments, e.g., the Unified Huntington's Disease Rating Scale (UHDRS).[8] Periodic data set 5 (PDS5), used for the development of this atlas, contained data from 21,116 Enroll-HD participants (16,120 PwP and 4,996 community controls) from 71,682 visits with an average longitudinal follow-up of 2.3 years.

Development of the Enroll-HD Phenotype Atlas

The EHDPA was purposefully designed for presentation as an interactive website [enroll-hd.org/for-researchers/atlas-of-hd-phenotype/] where plots and tables can be easily browsed. PDF reports containing the same information and table summaries of the underlying data are also available for download through the site. eFigure 1 (links.lww.com/NXG/A655) provides a case example of the clinical application of the atlas.

Analyses for the EHDPA were limited to PwHD; community controls were not included. The Table lists Enroll-HD assessments that are included in the atlas. The EHDPA is based on subsets of data containing single CAG lengths and five-year age blocks. A minimum of 6 observations were required to generate statistics and associated plots for each age range and CAG combination. Because of deidentification risk, results for sparse combinations with 5 or fewer observations were suppressed. Furthermore, such sparse cells may not reliably represent measurement distributions. We report on the 223 unique age-CAG combination cells with at least 6 observations available.

Statistical Analysis

To maximize the number of observations available for generation of descriptive statistics, data from all available visits for every eligible participant were reported. Missing data were ignored in these descriptive analyses, except for cognitive data for creating the cognitive principal component (PC) scores

Table Measurements Used to Build the HD Phenotypic Atlas

Domain	Scale/scores used
Motor	UHDRS total motor score Each motor subscore
Cognitive	Symbol digit modality test Verbal fluency (letter and category) Stroop Color and Word Test (the Word Condition) Trails A and B Tests Mini-Mental Status Examination
Behavioral	Problem Behavior Assessment (PBA) scores HADS depression/anxiety and Snaith irritability scales Additional depression and irritability scales Three items from suicidal thought instrument
Functional	Total Functional Capacity (plus all subscales) Independence Scale Functional Assessment (FAS)

Abbreviation: UHDRS = Unified Huntington's Disease Rating Scale.

(described below). The frequency of partially missing data is included with the age and CAG descriptive reports within the atlas.

Standardized scores were also included in the age and CAG descriptive reports to facilitate comparisons of these measures. These standardized scores (Z scores) are expressed in standard deviaitons from the mean Enroll HD gene-expanded outcome values.

When the entirety of the HD gene–expanded data is analyzed, all cognitive scores used in the atlas (with the partial exception of the Mini-Mental Status Examination [MMSE]) are highly and similarly correlated. This suggests that the aspect(s) of cognition relevant to HD are common to all of them and can be expressed most precisely using a single composite of these scores (the PC score). As part of the atlas development process, we performed a principal component analysis (PCA) that demonstrated that 84% of the total variance in the underlying cognitive scores can be accounted by this common aspect of cognition (eTable 1, links.lww.com/NXG/A655). As a convenient summary of measured cognition, we report this PC score in several of the plots and report tables. As with standardized versions of the individual outcomes, the PC score is scaled such that the mean is 0 and the SD is 1 when jointly considering all observations used in the analysis.

PCA requires complete data, and some participants were missing one or more cognitive scores. This was most frequently due to nonadministration of some measures at some sites because the protocol considered those assessments optional (extended). In the context of repeated measures per participant, we performed multiple imputation of these missing data using multilevel predictive means matching—a technique that combines related information from both the same visit, and also the participant's other visits, to impute plausible values for the missing data.[9] The PCA was performed after pooling 10 imputations of the missing data.

There was no generation of hypothesis-testing *p*-values or confidence intervals. Furthermore, aside from the cognitive PC score, there was no modeling or smoothing of the data. All plots and reports were generated using R 4.0.2. We used the R packages *mice* 3.11.0 and *miceads* 3.10–28 to perform multiple imputation for the PC analysis.

Standard Protocol Approvals, Registrations, and Patient Consents
The Enroll-HD study is performed in accordance with the Declaration of Helsinki. All participating sites received institutional review board approval, and all participants provided written informed consent to take part in the study (including consent for research genotyping). Additional optional components that require participant consent include biosampling for banking purposes, family history assessment, linking of clinical information collected in other studies, and willingness to be contacted regarding participation in future studies.[5,7]

Data Availability
Periodic data set 5 is accessible through the Enroll-HD website (enroll-hd.org/) to those with data security and privacy measures meeting standards described on the website. Access to nontransformed, nonaggregated, or suppressed data may be obtained through request, subject to approval by the Scientific Review Committee that weighs the scientific merit of the proposed project against the increased risk of participant identification.

Results

Description of the Data Set Used
Data from 42,840 visits from 15,982 unique participants were available for analysis. At baseline, participants had a mean ± SD age of 48.9 ± 13.9 years and CAG repeat length of 43.4 ± 3.6 and 54.1% were female. Using this data set, we generated 223 age-by-CAG subsets for each CAG repeat number between 36 and 69 with 5-year age brackets starting from 20–24 years to 85–89 years. The numbers of observations available for each age-by-CAG cell are listed in eTable 2 (links.lww.com/NXG/A655).

Overview of the Enroll-HD Phenotype Atlas
The full online atlas contains the following categories of plots and reports:

1. Box plot series summarizing age-related trends for a specific CAG length and assessment.
2. Box plot series summarizing CAG-length–related trends for a specific age range and assessment.
3. Heat maps illustrating patterns of mean and median scores across all possible age and CAG length combinations for a specific assessment.
4. Domain correlations illustrating the inter-relationship among assessment measures within a specific domain for a specific CAG length and age range combination. For motor, cognitive, and behavioral domains, the pairwise scatterplots of all assessments are illustrated along with corresponding correlation coefficients. There are also cross-domain plots containing key measurements from each of these domains plus the UHDRS Independence Scale.
5. Descriptive statistics reports for each assessment containing all age and CAG length box plots for a specific assessment. These reports also include tables of the statistical values (medians, quartiles, outlier boundaries) that are graphically displayed in the box plots, as well as auxiliary tables indicating age and CAG distributions available for each box plot.
6. Descriptive statistical reports for each age and CAG length combination, available as downloadable PDF

files. These contain a comprehensive overview of all assessment measures for a specific CAG length and age range combination. These reports contain descriptive statistics tables, bar plots of mean and median assessment scores, plus domain correlation plots.

To facilitate comparison among assessments, detailed reports in PDF form can also be viewed and downloaded within the atlas. There are reports available for each assessment measure and across all measures for each specific CAG-age combination. Each figure is supported by tables of the underlying summary statistics; there are tables of summary statistics for each measure and for standardized (z-score) versions of the measures. The standardized scores allow easy comparison of severity across measures within the selected CAG-age category. The means and medians for these measures are also illustrated with accompanying bar plots.

Visualization of Trends Within the Atlas

For most measures, visualization of age-related trends for a specific CAG length revealed a consistent increase beginning in the age range 40–44 years, with skewed scores for the 55–59 years and younger age ranges. Figure 1 illustrates a representative box plot series for UHDRS motor scores across age for CAG = 42. Although unusual, motor scores elevated substantially above the age and CAG norm do occur throughout the age range.

Figure 2 illustrates box plot series summarizing CAG-length–related trends for participants aged 45–49 years. Cognitive function as assessed by the principal component composite (Figure 2A) and SDMT (Figure 2B) clearly declined with higher CAG lengths. The similarity of the 2 series is a result of the very high correlations among the cognitive scores (including the symbol digit test) that contribute to the

principal component score. By contrast, Figure 2C illustrates the CAG pattern of chorea severity for this age range. The mean total chorea score measured in individuals aged 40–44 years predictably increases with increasing CAG length up to 50 repeats, beyond which the mean total chorea score appears to be stable or possibly even trend downward. Bearing in mind that more severe chorea is represented by higher scores, this plot is nearly a mirror image of the cognition plots. We must caution against overinterpretation of apparent trend reversals for the lowest and highest CAG lengths. The widths of the boxes in Figure 2 are proportional to the sample sizes in the age-CAG cells. There is often sparse representation of CAG lengths below 40 or above 49. Furthermore, participants within these cells may be a biased representation of the underlying population. HD is only partially penetrant in CAG lengths less than 40, and the Enroll-HD data over-represent those with penetrance. Reversed or stable trends at high CAG lengths may also represent selection bias relative to the population based on ability and willingness to participate in Enroll-HD visits.
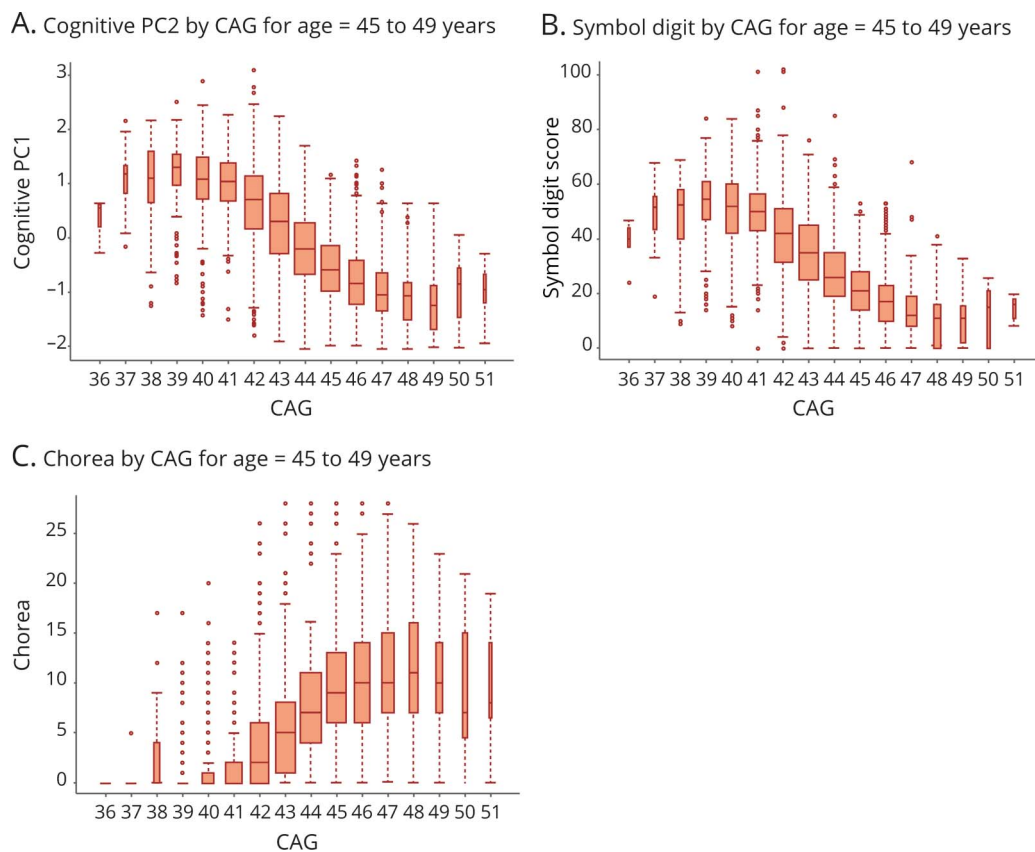
Heat maps illustrating patterns of mean scores across all possible age and CAG length combinations are shown for mean UHDRS Independence Scale (Figure 3A) and UHDRS Chorea Score (Figure 3B). Compared to the Independence Scale, the choreas vs CAG relationship is less variable for ages 30 and above. This suggests that chorea may not be the predominant motor manifestation in adult-onset HD with higher CAG repeats. After mean chorea scores of approximately 8 are reached, further increases in mean scores are less clearly dependent on CAG length or age (this suggests that chorea may not be as predominant within the motor manifestation as the disease progresses in severity). Analogous heat map plots are also available for medians.

Figure 1 Representative Box Plot Series for UHDRS Motor Scores Across Age for CAG = 42
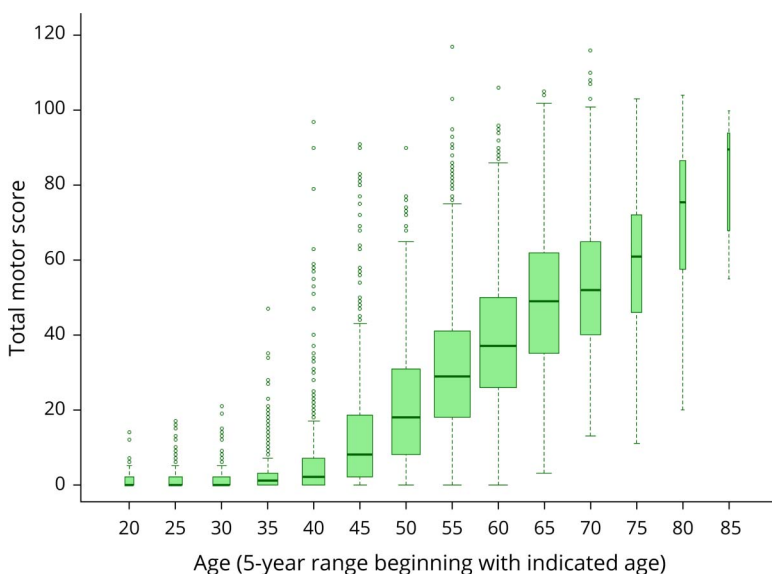
The proportion of the data in each age group is represented by the width of the corresponding box.

Figure 2 Representative Box Plot Series Summarizing CAG-Length–Related Trends for Participants Aged 45–49 Years

A. Cognitive PC2 by CAG for age = 45 to 49 years

B. Symbol digit by CAG for age = 45 to 49 years

C. Chorea by CAG for age = 45 to 49 years

(A) Principal component composite, (B) symbol digit modality test, (C) chorea severity. The proportion of the data in each age group is represented by the width of the corresponding box.

Domain correlations illustrating the inter-relationship among assessment measures for participants aged 35–39 years with a CAG length of 45 are shown for psychiatric/behavioral domain (Figure 4) and across motor (TMS), cognitive (principal component score), and daily function (UHDRS Independence Scale) domains (Figure 5). Figure 5 clearly illustrates notable and similar correlations among the UHDRS TMS, cognitive principal component score, and UHDRS Independence Scale. For the psychiatric/behavioral domain, no single measure is a good summary of overall severity. However, irritability and apathy scores from the Problem Behavior Assessment for Huntington Disease (PBA)[10] show the highest association with other measures of overall HD severity, including functional measures. Nonetheless, these behavioral measures have weaker correlations with the other measures and with each other. Similar patterns are seen for most CAG-age combinations available in the atlas.

Discussion

The EHDPA summarizes the spectrum and distribution of HD phenotypes, including outliers and possible clusters, in all domains of disease involvement for the range of CAG lengths, ages, and functional levels. Examination of the nature and frequency of outliers in these profiles may help identify phenotypic variation reflecting the effect of secondary genetic, comorbid, and environmental influences on disease progression. The atlas is available on the Enroll-HD website as a user-friendly tool for clinicians, researchers, and health care professionals. The data aid in understanding the age-dependent features of HD as CAG lengths vary. The EHDPA readily illustrates whether the typical range varies widely or not for a given CAG length and age range, allowing judgment of the degree to which an individual's phenotype is atypical. The huge sample size allows detailed observational summaries by 5-year age range for each CAG length as well as enabling the development of descriptive plots relating specific measurements to age and CAG.

There are some limitations in interpretation of the EHDPA that users should understand. To maximize the number of observations available, data from all available visits for every eligible participant were reported. There is, therefore, a degree of nonindependence between repeated annual observations from the same participants. Such nonindependence of observations would need to be accounted for in potential future hypothesis-driven testing and modeling of these data. Although

Figure 3 Representative Heat Maps Illustrating Patterns of Mean Scores Across All Possible Age and CAG Length Combinations

A. Independence scale means
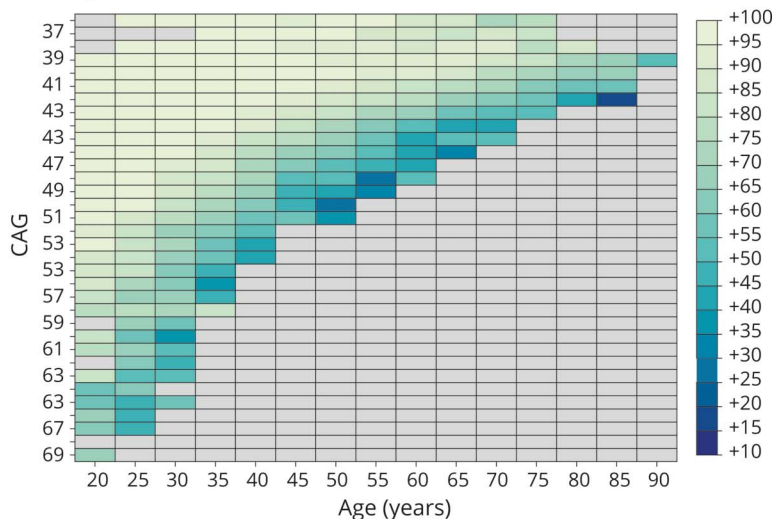
B. Chorea means
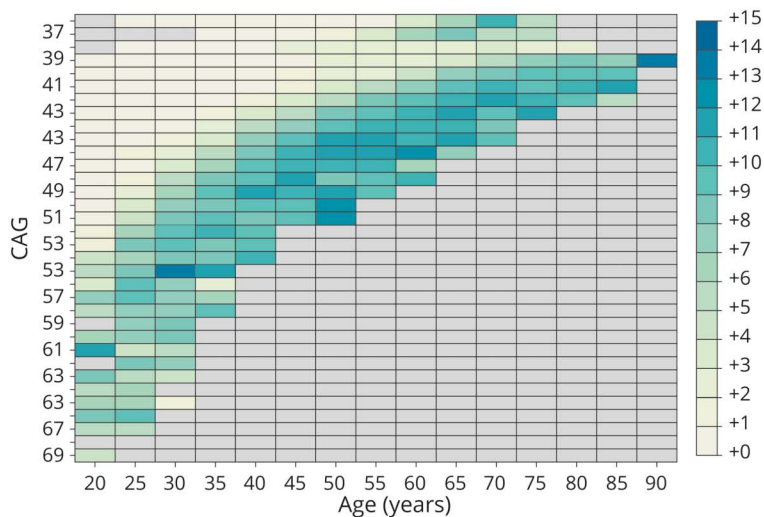
(A) UHDRS Independence Scale, (B) UHDRS Chorea scores. The scales at the right of the plots convert heat map colors to raw scores of the corresponding measures.

it is based on the largest observational HD database ever collected, this database is not a random sample of the entire population at risk. For example, the EHDPA illustrates phenotypes and the degree of variation in the assessments for the incompletely penetrant CAG repeat lengths of 36–39; for this range, there is the important caveat that the available sample is, at best, representative of the population in this age range that comes to clinical attention, but because of the partial penetrance, the EHDPA probably does not represent typical patterns for the whole population of individuals who have these repeat lengths.

Clinical features affecting participation in the Enroll-HD study may also bias the data, particularly at the severe end of the illness spectrum; for instance, the apparent stability of some features in advanced HD may instead be attributable to nonparticipation or drop-out among those with more severe

illness. These potential biases may also distort these age-dependent cross-sectional patterns if we interpret them as typical longitudinal progression for an individual. Unfortunately, substantial ideal data—repeated systematic measurements of the same people across several decades—simply do not exist, and the potential biases for non-participation may not be improved by increasing sample sizes unless the sources of study recruitment evolve substantially. As the Enroll-HD study continues, it will be important to use future periodic data sets to compare longitudinal within-person data with the disease course suggested by the atlas.

Future work could expand on the observable patterns in the atlas to produce a more formal multidomain characterization of motor, cognitive, and psychiatric progression and the relationship to functional decline and disease modifiers.[11,12] Inclusion of age-specific control data would help the clinician

Figure 4 Psychiatric/Behavioral Domain Correlations Illustrating the Inter-Relationship Among Assessment Measures for Participants Aged 35–39 Years With a CAG Length of 45
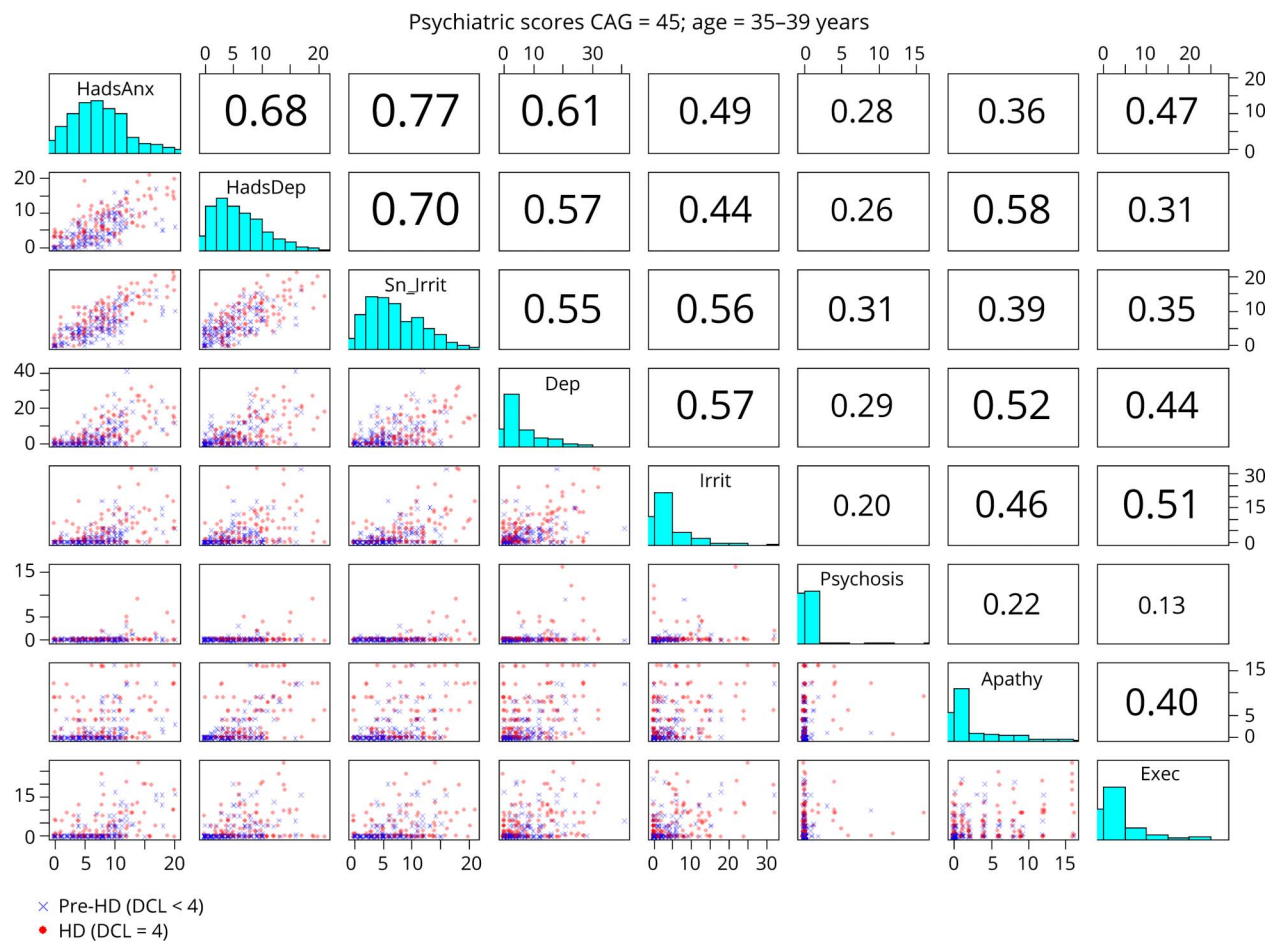
Scatterplots of individual participant data for all pairwise combinations of measures are displayed beneath the diagonal. For scales with a limited number of values such as the PBA Apathy, a small amount of random noise is added so that the density of various score combinations is illustrated. The points within the scatterplots are coded to distinguish whether the participant has been given a clinical motor diagnosis of manifest HD by virtue of the highest possible score of 4 on the UHDRS clinician diagnostic confidence limit rating scale (DCL). This is meant to provide some sense of the degree to which the severity of combinations of measures separates so-called motor manifest vs premanifest HD. Absolute values of the Pearson correlation coefficients for each measurement pair are displayed above the diagonal with font sizes roughly proportional to their magnitude. The diagonal cells contain histograms of the individual distributions of the measures. hadsAnx = HADS Anxiety Scale, hadsDep = HADS Depression Scale, Sn_Irrit = Snaith Irritability Scale, dep = PBA Depression, irrit = PBA Irritability, psychosis = PBA Psychosis, apathy = PBA Apathy, exec = PBA Executive Function, DCL = UHDRS Diagnostic Confidence Score.

to understand how PwHD are different from people without the HD CAG expansion. Relevant phenotype definition is critical to the success of gene-discovery studies. The atlas will facilitate definition of more detailed and possibly more sensitive CAG-adjusted phenotypes for such studies.[13] For example, variability not well-explained by age and CAG might be used as the phenotypic outcome measure in studies searching for additional HD-modifying genes. The EHDPA may also be a useful tool in assessing whether future therapeutic agents have a differential effect on motor, cognitive, and psychiatric aspects of HD.

Clinicians are often faced with the challenge of providing prognosis for an individual, which could help PwHD and families with their professional and financial plans as well as for future care needs. The EHDPA has been developed to provide a graphical multidimensional representation of the range of HD phenotypes and assist clinicians in tracking disease progression in an individual by identifying phenotypic features most associated with loss of function. It will also assist in determining whether a suspected deviation from the likely course is truly unusual. The work done to develop this atlas has potential as a prototype for initiatives in other trinucleotide repeat disorders if large databases like Enroll-HD can be created.

Acknowledgment

Figure 5 Cross-Domain (Motor, Cognitive, Psychiatric/Behavioral, Functional Independence) Correlations Illustrating the Inter-Relationship Among Assessment Measures for Participants Aged 35–39 Years With a CAG Length of 45
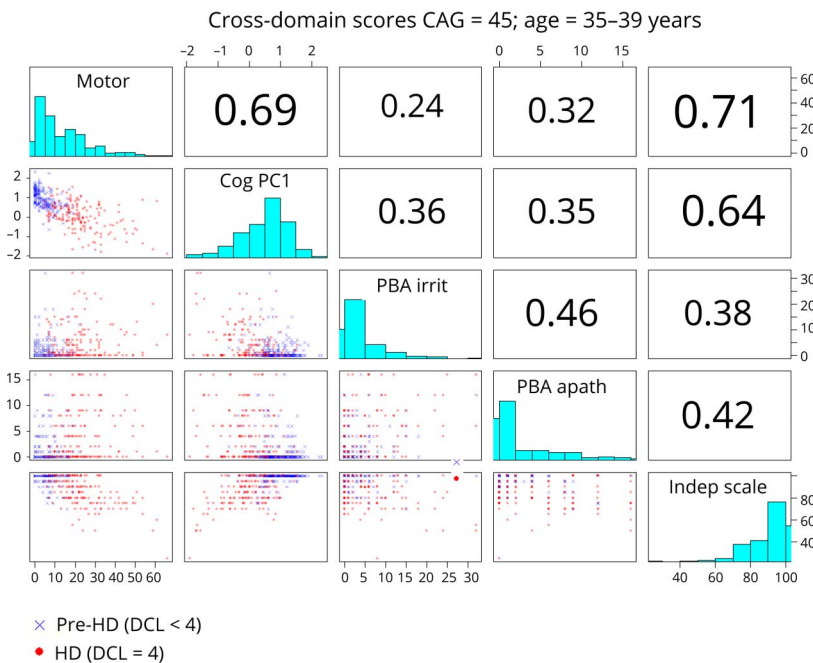
Please see the Figure 4 legend for further details. Motor = UHDRS Total Motor Score, Cog PC1 = Cognitive PC1, PBA Exec = PBA Executive function, PBA Apath = PBA Apathy, Indep Scale = UHDRS Independence Scale, DCL = UHDRS Diagnostic Confidence Score.

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Clement Loy, PhD, FRACP, MBA	Macquarie Medical School, Macquarie University, Sydney, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Cristina Sampaio, MD, PhD	CHDI Management/ CHDI Foundation, Princeton, NJ	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Elizabeth A. Mccusker, MB BS (Hons), MBioeth, FRACP	Department of Neurology (Huntington disease Service), Westmead Hospital, University of Sydney, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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