An Item Response Analysis of the Motor and Behavioral Subscales of the Unified Huntington's Disease Rating Scale in Huntington Disease Gene Expansion Carriers

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Abstract

Although the Unified Huntington's Disease Rating Scale (UHDRS) is widely used in the assessment of Huntington disease (HD), the ability of individual items to discriminate individual differences in motor or behavioral manifestations has not been extensively studied in HD gene expansion carriers without a motor-defined clinical diagnosis (i.e., prodromal-HD or prHD). To elucidate the relationship between scores on individual motor and behavioral UHDRS items and total score for each subscale, a non-parametric item response analysis was performed on retrospective data from two multicentre, longitudinal studies. Motor and Behavioral assessments were supplied for 737 prHD individuals with data from 2114 visits (PREDICT-HD) and 686 HD individuals with data from 1482 visits (REGISTRY). Option characteristic curves were generated for UHDRS subscale items in relation to their subscale score. In prHD, overall severity of motor signs was low and participants had scores of 2 or above on very few items. In HD, motor items that assessed ocular pursuit, saccade initiation, finger tapping, tandem walking, and to a lesser extent saccade velocity, dysarthia, tongue protrusion, pronation/supination, Luria, bradykinesia,

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choreas, gait and balance on the retropulsion test were found to discriminate individual differences across a broad range of motor severity. In prHD, depressed mood, anxiety, and irritable behavior demonstrated good discriminative properties. In HD, depressed mood demonstrated a good relationship with the overall behavioral score. These data suggest that at least some UHDRS items appear to have utility across a broad range of severity, although many items demonstrate problematic features.

Keywords

UHDRS; Item Response Theory; Huntington disease

INTRODUCTION

Huntington disease (HD) is an autosomal dominant neurodegenerative disease associated with severe motor, psychiatric and cognitive impairment.[1] Although the gene expansion responsible for HD is present at birth, the onset of clinical motor manifestations normally occurs in mid-life. Non-motor manifestations of HD, including mood and cognitive disturbances, are often present in carriers of the HD gene expansion many years before motor onset.[2–6] Unfortunately, the relationship between these changes, their latency to onset and aetiology are poorly understood, resulting in challenges when developing new rating scales that measure efficacy of both pharmacological and non-pharmacological interventions.

The Unified Huntington's Disease Rating Scale (UHDRS) was developed for the clinical assessment of HD[7], and is the current 'gold-standard' outcome measure used in clinical trials of HD. The UHDRS is divided into multiple subscales, assessing motor and cognitive function, behavioral (i.e., psychiatric) symptoms, and functional capacity. The scale was developed and tested in gene expansion carriers who had manifest motor symptoms of HD,[7] and may not be sensitive to changes in the earlier stages of the disease.[8–10]

The Functional Rating Scale Taskforce for pre-Huntington Disease (FuRST-pHD) is a multinational, multidisciplinary initiative with the goal of developing a data-driven, comprehensive, psychometrically sound, rating scale for assessing symptoms and functional ability in HD gene expansion carriers who have not yet met the motor-defined diagnostic criteria for HD (i.e., prodromal HD). Such a scale is essential in order to develop early interventions that may alter the course of HD in individuals with the CAG expansion. FuRST-pHD has established a collaborative approach for identifying which relevant changes should be assessed, and for developing rating scale items best able to measure severity.[11]

PREDICT-HD is an ongoing NIH- and CHDI-funded multi-centre, longitudinal study in pre-HD gene expansion carriers in the United States, Canada, Europe and Australia.[5] REGISTRY is funded by the CHDI Foundation and managed by the European Huntington's Disease Network (EHDN) and is an ongoing, multi-centre, longitudinal observational study collecting data in HD and pre-HD gene expansion carriers in Europe.[12] The current study used item response theory (IRT) analysis of UHDRS data collected from prodromal HD (prHD) and HD individuals (from PREDICT-HD and REGISTY, respectively) to explore the relationship between scores on individual UHDRS motor and behavioral items and the respective subscale total score. IRT analyses are useful in evaluating the performance of individual items on rating scales by assessing the relationship between scores assigned to an item in the target population and the underlying disease severity measure (e.g., severity of motor signs in HD).[13] The fundamental premise of IRT is that the probability of a particular

score for an item of a rating scale is a function of the underlying trait or condition that is being measured.[13] In this respect, IRT has been used in the evaluation of various rating scales, including the Hamilton Depression[14–17] and Anxiety Rating[15] Scales, Montgomery-Asberg Depression Rating Scale,[17] Beck Depression Inventory,[18] Somatic Symptoms Inventory,[19] and Sexual Interest and Desire Inventory.[20]

METHODS

Participants

Retrospective de-identified data from two ongoing multicentre, longitudinal observational research studies conducted in United States, Canada, Europe and Australia were used in the analyses. Demographic data obtained from the PREDICT-HD and REGISTRY studies included age and gender, as well as group means for CAG repeated length and disease burden scores (Table 1). The dataset used in the present analyses included UHDRS Motor and Behavioral assessments that were supplied for 737 prHD gene expansion carriers (CAG repeat length > 36; UHDRS Diagnostic Confidence Level ≤ 3) with data from 2114 visits (PREDICT-HD) and 686 HD gene expansion carriers (CAG repeat length ≥ 36; UHDRS Diagnostic Confidence Level = 4, possessing motor abnormalities that are unequivocal signs of HD)[7] with data from 1482 visits (REGISTRY). All data collection sites had IRB/EC approval and all participants provided informed consent.

Clinical Assessments

The UHDRS Motor Subscale has 15 items measuring eye movements (ocular pursuit, saccade initiation and velocity), speech (dysarthia), motor coordination (tongue protrusion, finger taps, pronate/supinate, Luria-manual sequencing), rigidity, bradykinesia, dystonia, chorea, and gait/balance. The UHDRS Behavioral Subscale includes 11 items that independently assess frequency and severity of psychiatric-related symptoms, including depressed mood, apathy, low self-esteem/guilt, suicidal thoughts, anxiety, irritable behavior, aggressive behavior, obsessional thinking, compulsive behavior, delusions, and hallucinations. Each UHDRS item is rated on a 5-point scale, with each item contributing 0–4 points to the total score. The UHDRS'99 Motor and Behavioral Subscales were administered to each patient at each visit by a qualified rater. A total score was separately calculated for the Motor and Behavioral Subscales by summing up all the individual motor and behavioral items (separately for frequency and severity), respectively, with higher scores representing more severe manifestations.[7]

Analyses

Non-parametric IRT analyses of the UHDRS Motor and Behavioral Subscales were performed to determine the relationship between scores on the individual UHDRS items and total score on the relevant UHDRS subscale (i.e., Motor and Behavioral subscales). IRT software (TESTGRAF)[21,22] was used to generate Option Characteristic Curves (OCCs) that display the probability of a particular option score (i.e., a score of 0, 1, 2, 3, 4) on each UHDRS item as a function of overall level of severity (i.e., total Motor or Behavioral score). As such, OCCs provide a graphical representation of how informative a particular item (or symptom) is as a measure of illness. The item is effective if the options discriminate differences in severity; as there is an increase in severity of the underlying trait (increased total score on the scale) the probability of low scores on the individual item decrease and the probability of higher scores increase. Highly discriminating items are characterized by (1) OCCs that rise and fall quickly, indicating good discrimination across the range of severity, and (2) OCCs whose weights correspond to the ordinal position in which they are most likely to be endorsed. In the present study, we used retrospective data from PREDICT-HD and REGISTRY to generated OCCs from the UHDRS Motor and Behavioral Subscales to

illustrate the relationship between scoring patterns for each item and the range of total UHDRS subscale score in prHD and HD. It should be noted that multiple scores were included from each participant, yet no corrections for repeated assessments were employed in the analysis. This is justified because Item Response Theory assumes local independence (i.e., independence among item responses at any given level of severity), and so the analyses are not invalidated by virtue of covariance among an individual's item scores. In addition, given that multiple observations were obtained from individuals with scores throughout the continuum of severity, it is unlikely that any systematic biased would have occurred. A thorough description of the TESTGRAF software may be obtained at www.psych.mcgill.ca/faculty/ramsay/ramsay.html.

RESULTS

UHDRS Motor Subscale in prHD Participants

prHD participants had scores of 2 or more on very few items, and the overall severity of motor signs was significantly lower than that observed in HD participants (prHD = 5.58 ± 0.13; HD = 43.06 ± 0.55, $p<0.01$, Table 1). There were indications that some items performed better than others (Figure 1), including saccade initiation (Figure 1A) in which the option with the highest probability of being scored increased from 0 to 2 as motor symptom severity increased; however, neither Option 3 nor Option 4 had a high probability of being scored even at high levels of overall severity of motor signs. For the other items in the UHDRS motor subscale, scores of '0' (Luria, rigidity, dystonia, tongue protrusion, Figure 1B) or at the most scores of '1' (occular pursuit, dysarthria, saccade velocity, bradykinesia, chorea, finger taps, pronation/supination, Figure 1C,D) had the highest probability of being scored across the full range of severity. These items appear to have limited usefulness in assessing motor manifestations in the prHD population.

UHDRS Motor Subscale in HD Participants

In HD participants (Figure 2), UHDRS motor items assessing ocular pursuit, saccade initiation, tandem walking and finger taps (Figure 2A) showed reasonable approximation of the "ideal" OCC, where the trait level is represented by the total UHDRS Motor Subscale Score. That is, as total Motor Subscale scores increase the probability of low scores on the individual item decrease and the probability of higher scores increase. From an IRT perspective, these items demonstrate desirable psychometric features including a clear identification of the range of severity scores over which each option is most likely scored, rapid changes in the curves which correspond to changes in severity, and an orderly relation between the weight assigned to the option and the region of severity over which an item had the highest probability of being scored.[13]

Figure 2 also shows items that display some discrimination across motor severity, but were less successful in their ability to discriminate over the full range of severity. For example, in items assessing saccade velocity, tongue protrusion and Luria (Figure 2B), the middle options had a lower probability of being scored as compared to options '0' or '4' across the severity range. For items assessing chorea, gait, and rigidity (Figure 2C), the probability of Options 3 and 4 (i.e., the most severe level of these signs) being scored was very low. As a result, at the higher severity range, the sensitivity of these items to detect changes in motor severity is reduced. It is possible that not enough participants in the population exhibited these levels of manifestation, and that these options may be endorsed with a greater frequency in a more affected population. Conversely, dystonia (Figure 2D) showed poor discriminative properties, which were manifested primarily at the highest levels of motor severity and did not discriminate well at lower motor scores.

UHDRS Behavioral Subscale in prHD Participants

Figure 3 shows the performance of UHDRS behavioral items in relation to total Behavioral Subscale score in prHD participants. Depressed mood, anxiety, irritable behavior (Figure 3A), and to a lesser extent guilt and apathy (Figure 3B) demonstrated good discriminative properties across a broad range of severity. By contrast, aggressive behavior, compulsive behavior and obsessional thinking (Figure 3C) did not discriminate well at lower levels of severity and scores greater than '0' were only observed at higher levels of severity, indicating that these symptoms are of relevance in patients that exhibit higher levels of psychiatric disturbances. For the remaining items (suicidal thoughts, delusions, hallucinations; Figure 3D), the '0' option had the highest probability of being scored across the entire severity range, indicating that that these may not manifest in a prHD population.

UHDRS Behavioral Subscale in HD Participants

Figure 4 shows the performance of UHDRS behavioral items in relation to total Behavioral Subscale scores in HD participants. In line with previous studies, psychiatric symptoms were present in HD.[2–6] There are clear differences in items of the UHDRS Behavioral Subscale with respect to their performance in discriminating different levels of severity, with depressed mood (Figure 4A) showing the best discriminative properties. The remaining items did not discriminate across levels of severity, including: items that had scoring above '0' only at the highest levels of severity (aggressive behavior, apathy; Figure 4B); items that poorly discriminated in the mid-range of scoring (guilt, anxiety, irritable behavior; Figure 4C); and items that had no scoring across most of the severity range (suicidal thought, obsessional thinking, compulsive behavior, delusions; Figure 4D).

DISCUSSION

The present study assessed how well items on the UHDRS Motor and Behavioral Subscales captured scoring across disease severity in two populations: HD gene expansion carriers with and without a motor diagnosis. The total score on the Motor Subscale was significantly lower in the prHD population as compared to the HD population. This is not surprising as the classification of "prHD" is defined as the absence of sufficient motor signs to meet conventional diagnostic criteria for manifest disease.[23] Examination of the UHDRS Motor Subscale in the prHD population (Figure 1) showed modest scoring on the majority items; that is, scores above 2 were rare, with a score of '0' often being the one with the highest probability across the full range of motor severity. An obvious interpretation of these results is that the prHD population exhibit less severe motor manifestations than the HD population. Since the UHDRS was designed to measure motor signs in a manifest HD population, it is sub-optimal for the assessment of milder motor signs prevalent in the prHD population. It may be necessary to design new scales or develop quantitative motor devices that are more sensitive to detecting subtle changes in a prHD population that exhibit mild motor signs.[24,25,26] It is important to note that although prHD and HD stratifications in the present analyses were based on UHDRS Diagnostic Confidence Level scores, the groups may also have differed with respect to CAG repeat length and disease burden scores (see Table 1). However, because only group means were provided for CAG repeat length, the contribution of CAG repeat length to differences between prHD and HD could not be determined.

Examination of the UHDRS Motor Subscale in the HD population (Figure 2) revealed that a number of items (e.g., ocular pursuit, saccade initiation, finger taps, tandem walking and to a lesser extent saccade velocity, dysarthria, tongue protrusion, pronation/supination, Luria, bradykinesia, chorea, gait, and retropulsion) showed favorable item response characteristics, thus supporting their utility in assessing motor signs in HD. Other items (e.g., dystonias and rigidity of the arms), however, did not discriminate individual differences over the full range

of severity and contain options that do not track with changes in overall motor severity. Although the UHDRS appears to provide useful information about the status of a given HD patient, the scale could nevertheless be improved to address these issues. It may be possible to alter the wording and scoring options of these items to improve item performance. There were, however, some items (e.g., the dystonia items) where the '0' option had the highest probability of being scored across almost the full range of severity, indicating that these items are not sensitive to changes in disease and appear to be less relevant for motor assessment in HD. This latter issue suggests that the UHDRS itself could be refined by removing irrelevant or redundant items resulting in increased sensitivity and reduced noise.[26,27] It is also important to note that the motor phenotype in HD is not homogenous and, although the phenotype that is characterized by prominent dystonia may be present in only a subset of participants,[28] it is none-the-less an important feature to assess when this phenotype needs to be captured.

It is well-established that in addition to motor manifestations, mood and other psychiatric disturbances are also present in HD[2–6] and reported to be functionally debilitating.[29,30] In the present study, the total Behavioral Frequency Subscale score did not vary substantially between the prHD and HD population (prHD = 6.67 ± 0.13; HD = 6.32 ± 0.18; n.s.), whereas the total Behavioral Severity Subscale score was higher in HD than prHD (prHD = 4.81 ± 0.12; HD = 5.97 ± 0.16; $p<0.01$) (Table 1). It is possible, therefore, that while motor signs progress from prHD to HD, the frequency of behavioral manifestations do not progress or may in fact be under-reported due to decreased self-awareness of behavioral manifestations.[31] On the other hand, the severity of the behavioral manifestations are greater in HD than prHD; indications that the functional impact of these manifestations are more pronounced in HD than in prHD. Interestingly, when comparing prHD and HD participants, some items on the UHDRS Behavioral Subscale were generally less problematic in prHD in discriminating across ranges of severity. The reason for these discrepancies are not clear but may be related to the presence of motor manifestations in HD which could overshadow the ability to assess behavioral symptoms and thus does not adequately capture the mood and psychiatric disturbances that may occur in HD.

It is important to note that even though some items may not perform well from an IRT perspective, their assessment from a clinical perspective is none-the-less important and may provide critical clinical information. For example, although a high proportion of participants did not endorse the UHDRS Suicidal Thoughts Item and the '0' option had the highest probability of being scored, 8.3% of prHD and 9.4% of HD participants reported frequency of Suicidal Thoughts with scores of 2 or more (i.e., thoughts about suicide at least once a month or more often). Indeed, elevated rates of suicidal behavior in HD is a significant concern[32,33] and thus it is important to be aware of those that may be at an increased risk; including regulatory requirements that suicidality be closely monitored during clinical trials.[34]

To examine motor and behavioral manifestations in gene expansion carriers, we used an IRT approach to assess the discriminative properties of individual items on the UHDRS Motor and Behavioral Subscales in prHD and HD participants using retrospective data from two ongoing multicentre, longitudinal observational research studies. Although there is the possibility that some (albeit relatively few) of the participants may have participated in both PREDICT-HD and REGISTRY or where from the same families that may have similar behavioral and motoric profiles, there was no way of identifying those subjects based on the de-indentified data that was provided. However, given the large sample sizes used in the analyses it is unlikely that these individuals would have systematically biased the results. Further, it is important to note that comparisons were made between scores generated and

stratified based on UHDRS Diagnostic Confidence Level scores. As such, none of the scores that contributed to the data were duplicates and were treated as independent data points.

The cohorts used these analyses are out-patient ambulatory participants and thus limiting conclusions with respect to more advanced disease and/or higher severity of motor signs. These participants, however, are likely representative of those that would participate in clinical trials. Also worth noting is that that some pharmacological treatments are effective in treatment of psychiatric and motor problems in HD[35] and thus may mask the prevalence of these manifestations in the PREDICT and REGISTRY participants. Nevertheless, the present results suggest that the UHDRS will likely perform sub-optimally in the measurement of treatment-induced changes in this population and provide useful information about the performance of specific UHDRS items in prHD and how their assessment might be improved. The results suggest that some UHDRS items appear to have utility across a broad range of disease severity; although many items demonstrate problematic features and some issues remain with regard to the use of individual UHDRS items as measures of severity in these populations. In addition, these analyses highlight the advantages of using existing data bases to improve assessment and measurement. As part of the FuRST-pHD, we are using this approach to help identify and develop items to better assess changes experienced in HD.

Acknowledgments

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APPENDIX

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1a. OCULAR PURSUIT (Horizonal)

1b. OCULAR PURSUIT (Vertical)

2a. SACCADE INITIATION (Horizional)

2b. SACCADE INITIATION (Vertical)

3a. SACCADE VELOCITY (Horizional)

3b. SACCADE VELOCITY (Vertical)

4. DYSARTHRIA

5. TONGUE PROTRUSION

6a. FINGER TAPS (Right)

6b. FINGER TAPS (Left)

7a. PRONATE/SUPINATE-HANDS (Right)

7b. PRONATE/SUPINATE-HANDS (Left)

8. LURIA

9a. RIGIDITY-ARMS (Right)

9b. RIGIDITY-ARMS (Left)

10. BRADYKINESIA-BODY

11a. MAXIMAL DYSTONIA (TRUNK)

11b. MAXIMAL DYSTONIA (RUE)

11c. MAXIMAL DYSTONIA (LUE)

11d. MAXIMAL DYSTONIA (RLE)

11e. MAXIMAL DYSTONIA (LLE)

12a. MAXIMAL CHOREA (FACE)

12b. MAXIMAL CHOREA (BOL)

12c. MAXIMAL CHOREA (TRUNK)

12d. MAXIMAL CHOREA (RUE)

12e. MAXIMAL CHOREA (LUE)

12f. MAXIMAL CHOREA (RLE)

12g. MAXIMAL CHOREA (LLE)

13. GAIT

14. TANDEM WALKING

15. RETROPULSION PULL TEST

FIGURE 1.
OCCs for representative UHDRS motor items in relation to UHDRS Motor Subscale Score
in prHD participants. The remaining OCCs are available as supplemental material online.

1a. OCULAR PURSUIT (Horizonal)

1b. OCULAR PURSUIT (Vertical)

2a. SACCADE INITIATION (Horizional)

2b. SACCADE INITIATION (Vertical)

3a. SACCADE VELOCITY (Horizional)

3b. SACCADE VELOCITY (Vertical)

4. DYSARTHRIA

5. TONGUE PROTRUSION

6a. FINGER TAPS (Right)

6b. FINGER TAPS (Left)

7a. PRONATE/SUPINATE-HANDS (Right)

7b. PRONATE/SUPINATE-HANDS (Left)

8. LURIA

9a. RIGIDITY-ARMS (Right)

9b. RIGIDITY-ARMS (Left)

10. BRADYKINESIA-BODY

11a. MAXIMAL DYSTONIA (TRUNK)

11b. MAXIMAL DYSTONIA (RUE)

11c. MAXIMAL DYSTONIA (LUE)

11d. MAXIMAL DYSTONIA (RLE)

11e. MAXIMAL DYSTONIA (LLE)

12a. MAXIMAL CHOREA (FACE)

12b. MAXIMAL CHOREA (BOL)

12c. MAXIMAL CHOREA (TRUNK)

12d. MAXIMAL CHOREA (RUE)

12e. MAXIMAL CHOREA (LUE)

12f. MAXIMAL CHOREA (RLE)

12g. MAXIMAL CHOREA (LLE)

13. GAIT

14. TANDEM WALKING

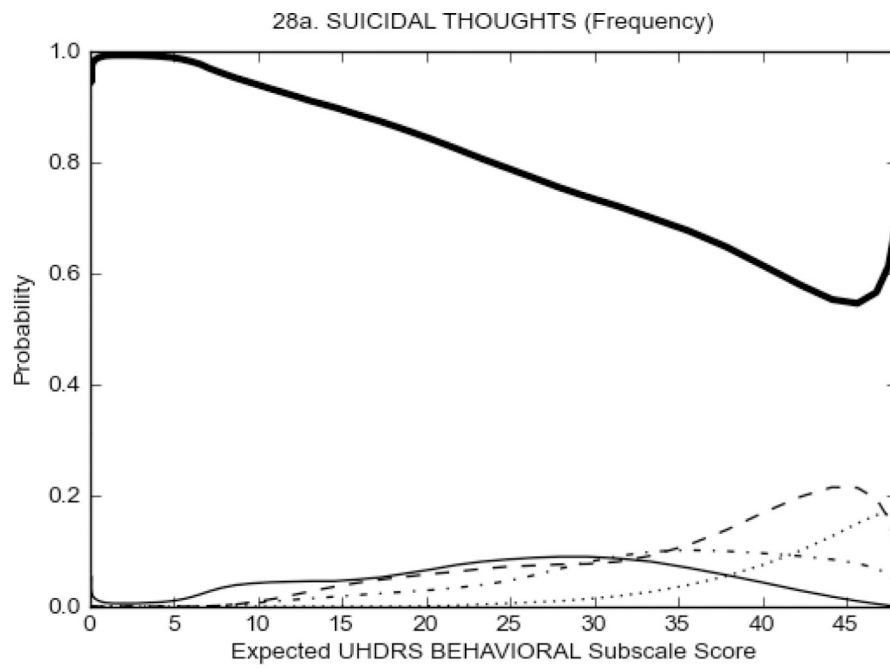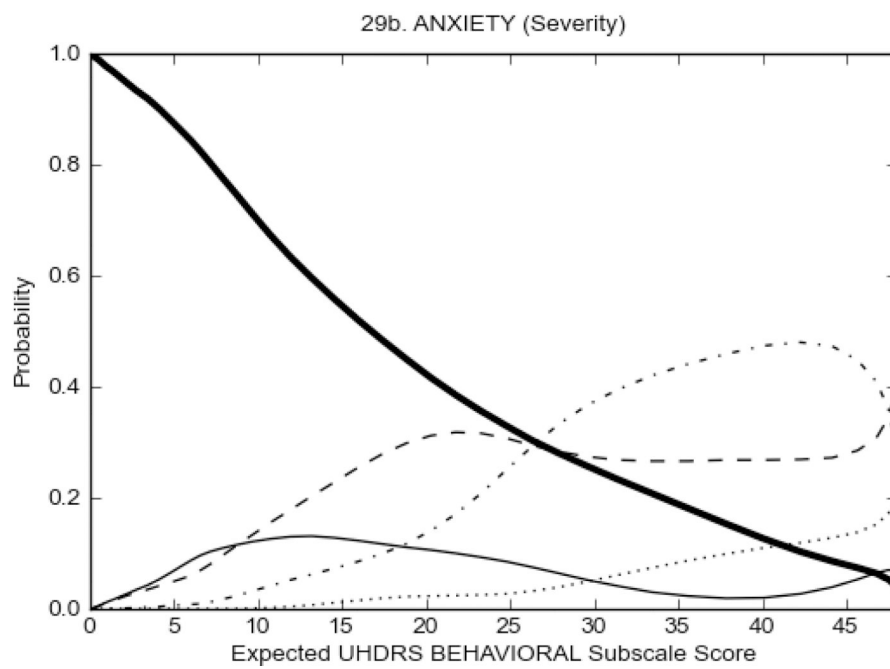## 15. RETROPULSION PULL TEST

FIGURE 2.
OCCs for representative UHDRS motor items in relation to UHDRS Motor Subscale Score
in HD participants. The remaining OCCs are available as supplemental material online.

25a. DEPRESSED MOOD (Frequency)

25b. DEPRESSED MOOD (Severity)

26a. APATHY (Frequency)

26b. APATHY (Severity)

27a. LOW SELF-ESTEEM/GUILT (Frequency)

27b. LOW SELF-ESTEEM/GUILT(Severity)

28a. SUICIDAL THOUGHTS (Frequency)

28b. SUICIDAL THOUGHTS (Severity)

29a. ANXIETY (Frequency)

29b. ANXIETY (Severity)

30a. IRRITABLE BEHAVIOR (Frequency)

30b. IRRITABLE BEHAVIOR (Severity)

31a. AGGRESSIVE BEHVIOR (Frequency)

31b. AGGRESSIVE BEHVIOR (Severity)

32a. OBSESSIONAL THINKING (Frequency)

32b. OBSESSIONAL THINKING (Severity)

33a. COMPULSIVE BEHAVIOR (Frequency)

33b. COMPULSIVE BEHAVIOR (Severity)

34a. DELUSIONS (Frequency)

34b. DELUSIONS (Severity)

FIGURE 3.
OCCs for representative UHDRS behavioral items in relation to UHDRS Behavioral Subscale Score in prHD participants. The remaining OCCs are available as supplemental material online.
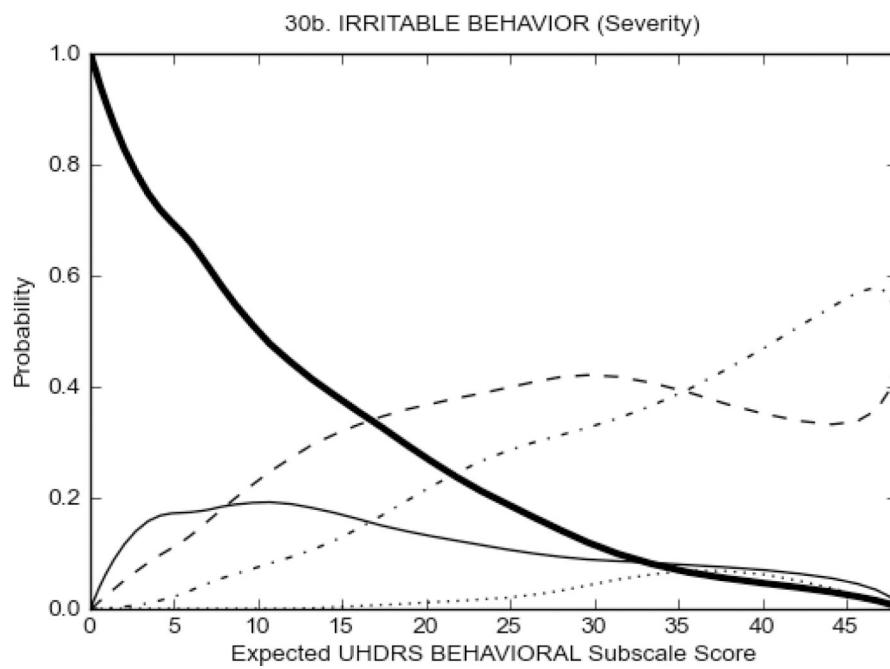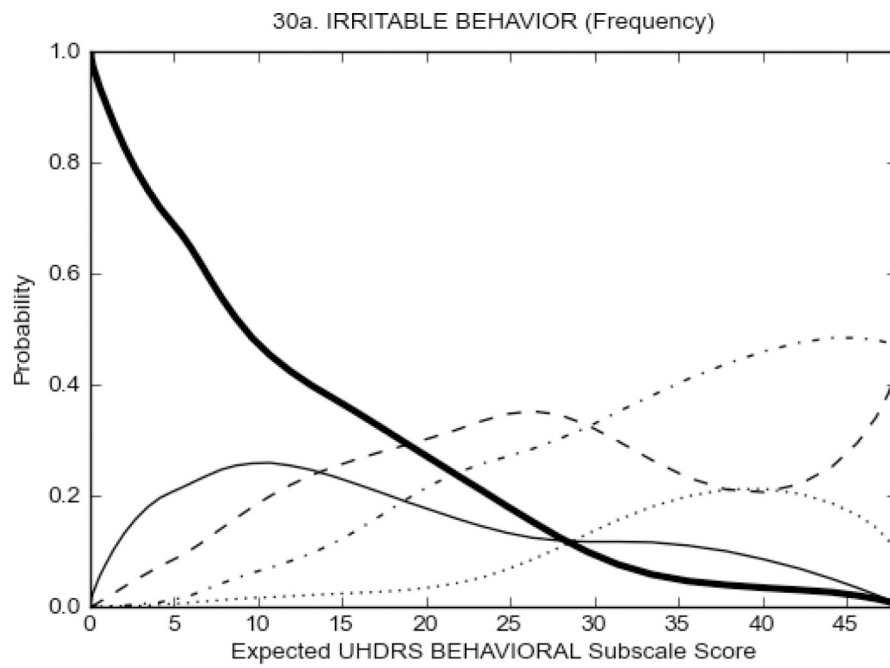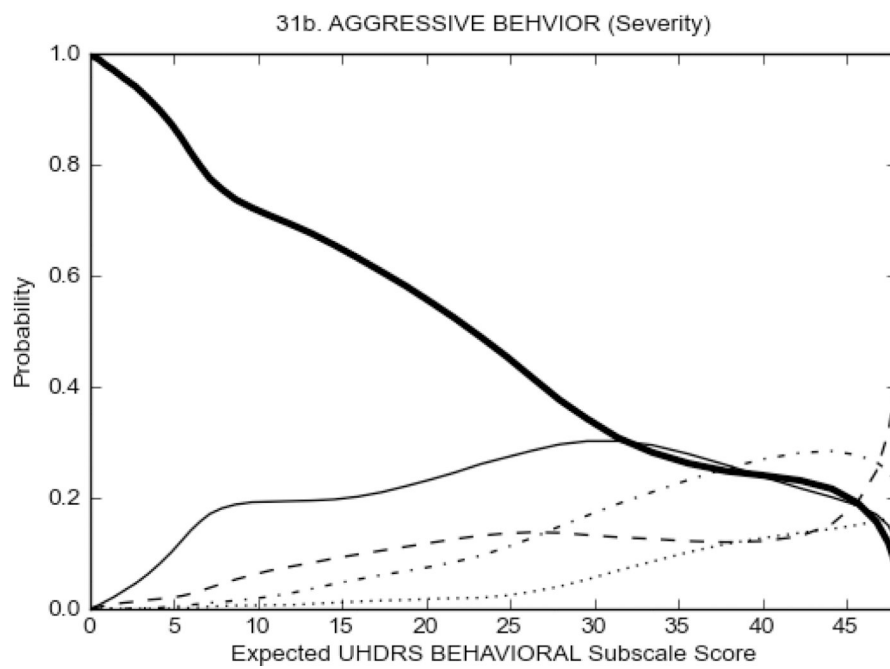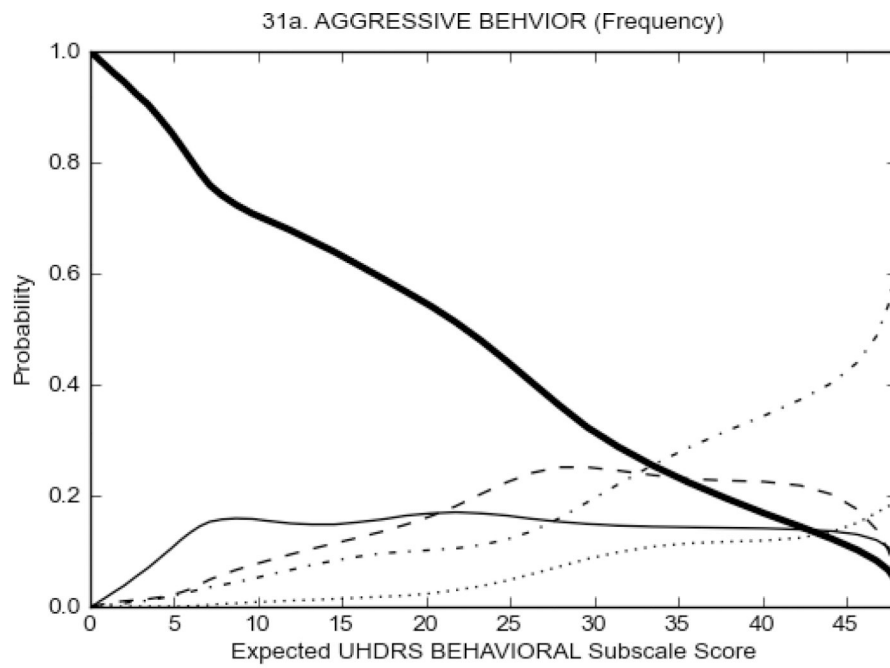
25a. DEPRESSED MOOD (Frequency)

25b. DEPRESSED MOOD (Severity)

26a. APATHY (Frequency)

26b. APATHY (Severity)

27a. LOW SELF-ESTEEM/GUILT (Frequency)

27b. LOW SELF-ESTEEM/GUILT(Severity)

28a. SUICIDAL THOUGHTS (Frequency)

28b. SUICIDAL THOUGHTS (Severity)

29a. ANXIETY (Frequency)

29b. ANXIETY (Severity)

30a. IRRITABLE BEHAVIOR (Frequency)

30b. IRRITABLE BEHAVIOR (Severity)

31a. AGGRESSIVE BEHVIOR (Frequency)

31b. AGGRESSIVE BEHVIOR (Severity)

32a. OBSESSIONAL THINKING (Frequency)

32b. OBSESSIONAL THINKING (Severity)

33a. COMPULSIVE BEHAVIOR (Frequency)

33b. COMPULSIVE BEHAVIOR (Severity)

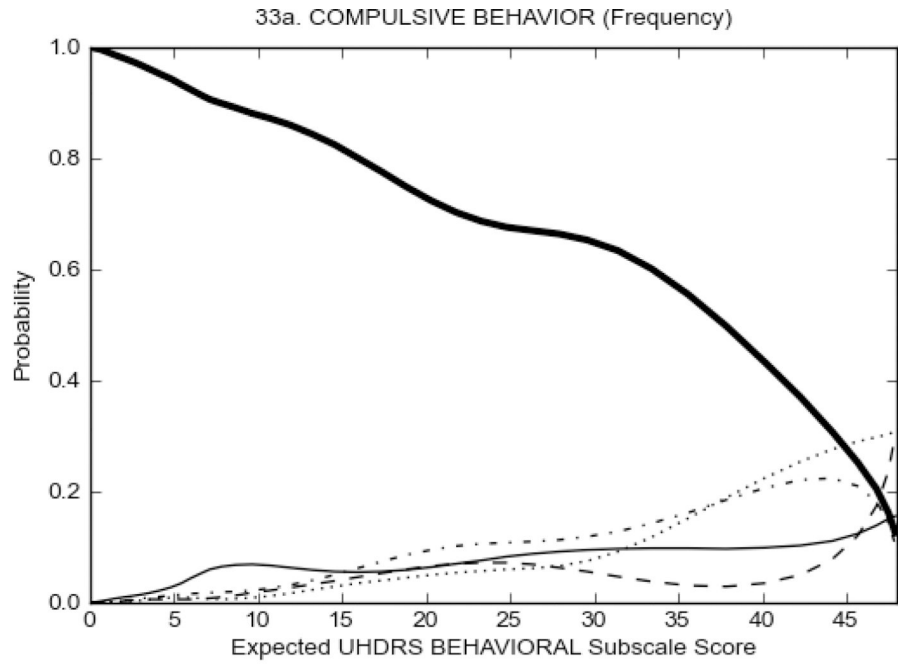34a. DELUSIONS (Frequency)
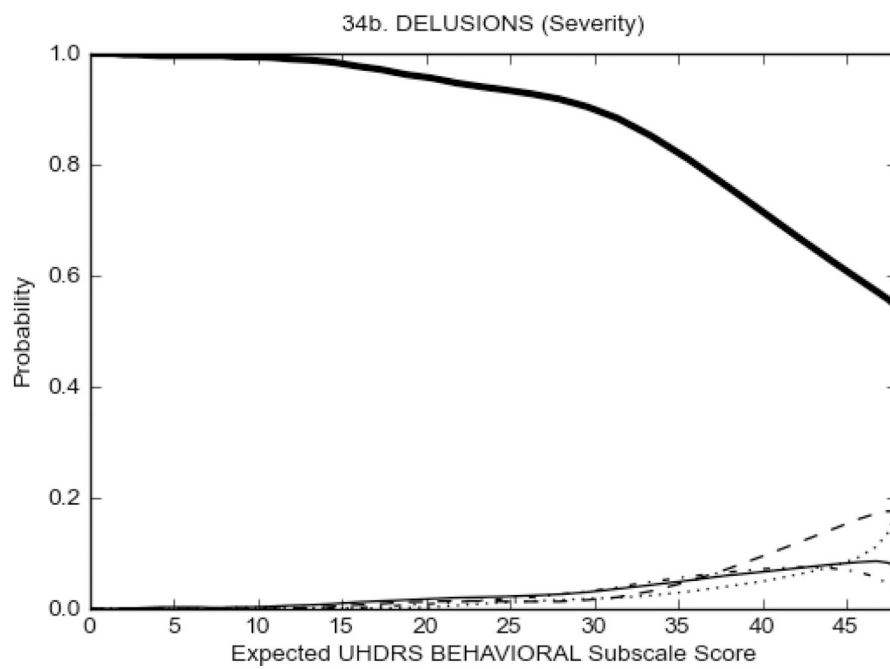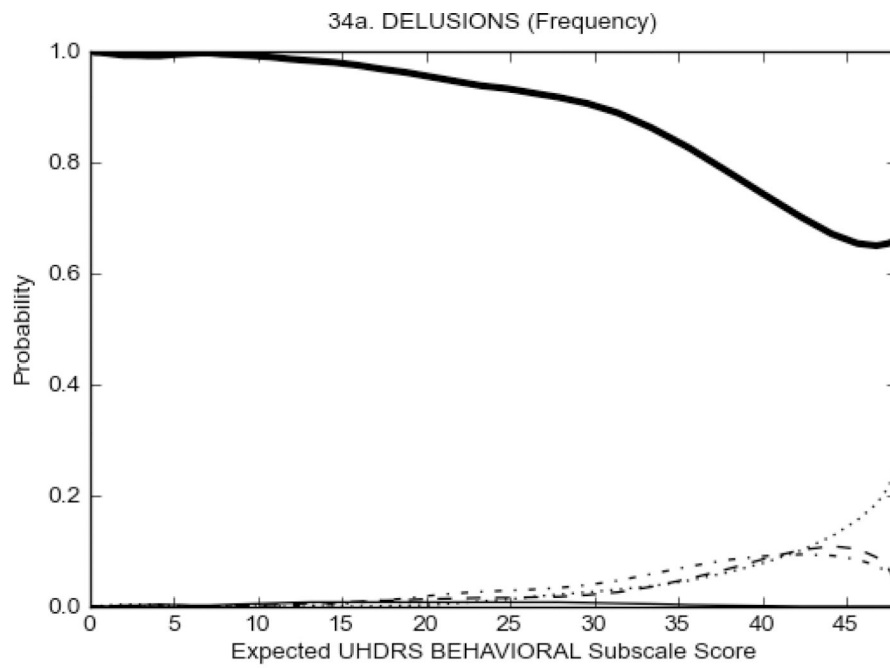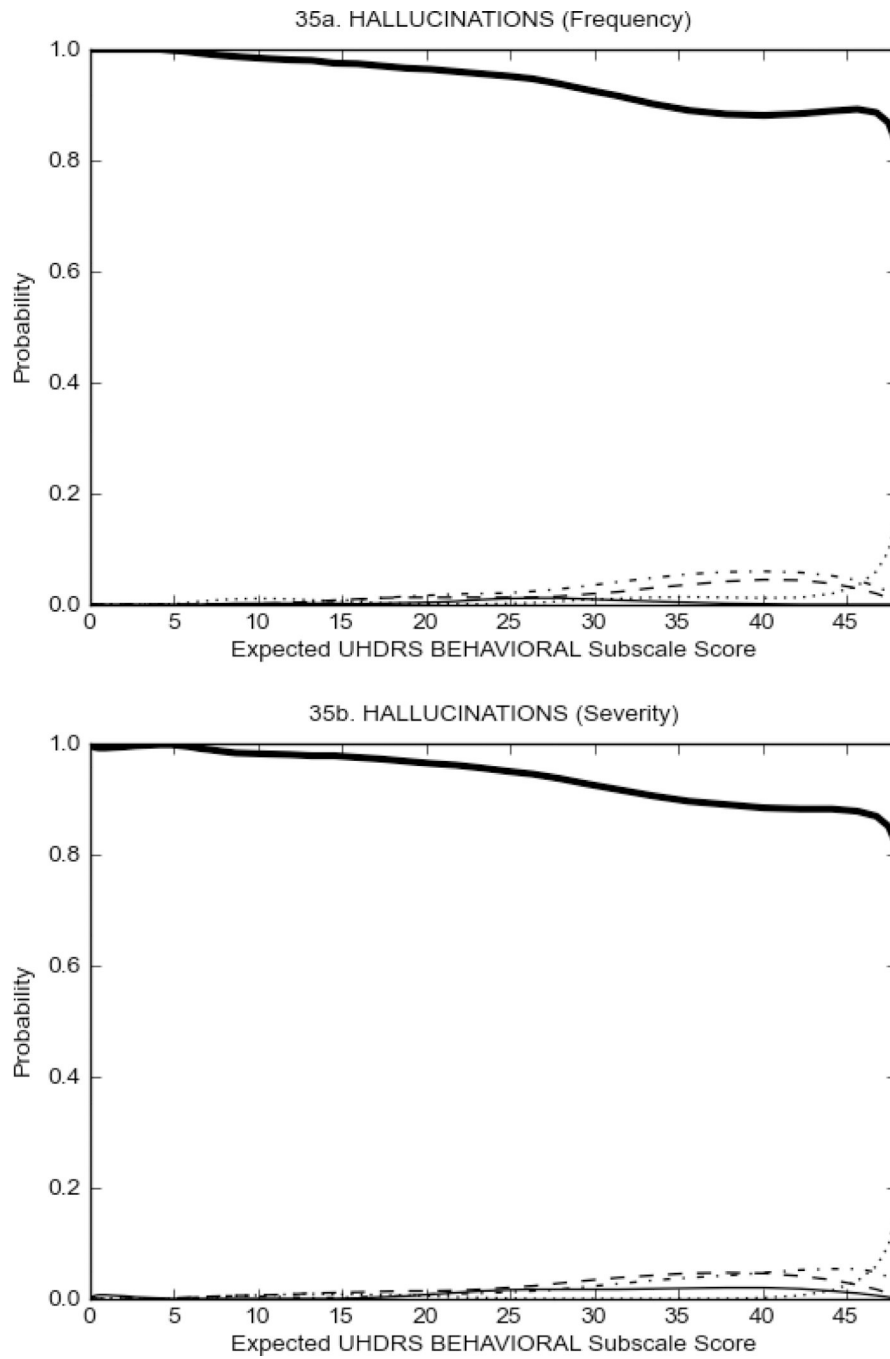

34b. DELUSIONS (Severity)

FIGURE 4.
OCCs for representative UHDRS behavioral items in relation to UHDRS Behavioral Subscale Score in HD participants. The remaining OCCs are available as supplemental material online.

TABLE 1

Demographics and clinical characteristics of prHD (PREDICT-HD) and HD (REGISTRY) participants.

Characteristic	PrHD	HD
Male gender	36.8%, N=271	47.7%, N=327
Age	42.50 ± 0.22 (18–79)	52.07 ± 0.30 (19–87)
CAG repeat length	42.51 ± 0.10 (38–61)	44.78 ± 0.15 (37–75)
[a]Disease/genetic burden score	277.54 ± 1.66 (90.75–813.70)	442.25 ± 2.73 (91.5 – 1165.5)
[b]Expected yrs to onset	13.71 ± 0.15 (3.44–42.46)	n/a
UHDRS Total Motor	5.58 ± 0.13 (0–45)	43.06 ± 0.55 (0–106)
UHDRS Total Behavioral-Frequency	6.67 ± 0.13 (0–44)	6.32 ± 0.18 (0–34)
UHDRS Total Behavioral-Severity	4.81 ± 0.12 (0–44)	5.97 ± 0.16 (0–31)

Gender and CAG repeat length were based on first visit data, all remaining variables averaged across all visits. Mean ± SEM, range in parenthesis.

[a]Disease Burden Score = (CAG repeat length – 35.5) × age; Penney JB Jr, Vonsattel JP, MacDonald ME, Gusella JF, Myers RH. Ann Neurol. CAG repeat number governs the development rate of pathology in Huntington's disease. *Ann Neurol.* 1997;41(5):689–692.

[b]Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR; International Huntington's Disease Collaborative Group. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clin Genet.* 2004 Apr;65(4):267–77.