

Relationships Among Apathy, Health-Related Quality of Life, and Function in Huntington's Disease

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Up to 90% of individuals with Huntington's disease (HD)—a progressive, inherited neurodegenerative disorder—experience apathy. Apathy is particularly debilitating because it is marked by a reduction in goal-directed behaviors, including self-care, social interactions, and mobility. The objective of this study was to examine relationships between variables of apathy, functional status, physical function, cognitive function, behavioral status/emotional function, and health-related quality of life. Clinician-rated measures of physical, cognitive, and behavioral function, including one clinician-rated item on apathy, and self-reported measures of physical function, health-related quality of life, and emotional, cognitive, and social function were collected in a single session from 487 persons with the HD mutation (prodromal, N=193; early-stage manifest, N=186; late-stage manifest, N=108). Multiple linear regression models were used to examine which outcomes best predicted clinician-rated apathy after controlling for

disease stage. Greater apathy related to less independence, increased motor impairment, and more clinician-rated behavioral problems (i.e., anger, irritability, depression). Similarly, poorer self-reported health-related quality of life; greater chorea; greater upper- and lower-extremity dysfunction; greater speech and swallowing dysfunction; worse anxiety, depression, and behavioral dyscontrol; worse cognitive function; and less satisfaction with social roles related to greater apathy. In conclusion, apathy related to physical, cognitive, and behavioral dysfunction across disease stages. Future work should explore whether clinical interventions targeting different functional domains may have the potential to reduce apathy in this patient population.

J Neuropsychiatry Clin Neurosci 2018; 30:194–201;
doi: 10.1176/appi.neuropsych.17080173

Huntington's disease (HD) is a genetic, neurodegenerative disease characterized by motor, cognitive, and behavioral changes. The behavioral changes with HD are particularly debilitating and relate to increased caregiver burden and reduced health-related quality of life (HRQOL).^{1,2} Apathy is one of the most disabling behavioral symptoms for patients and caregivers.^{3,4} Apathy affects up to 90% of individuals with HD^{4–6} and includes a marked lack of motivation, as well as reduced goal-directed behavior and action initiation, including self-care and mobility.^{7,8}

Although the diagnosis for manifest HD relies heavily on motor manifestations, apathy may either precede motor difficulties or occur early in the course of the disease,^{9,10} thereby potentially providing an informative clinical marker of disease pathophysiology. Apathy may predict disease onset,¹¹ and it correlates negatively with age at disease onset,⁹ and positively with the number of CAG repeats among those who are at risk for HD. Apathy increased in premanifest individuals over a 3-year period,^{10,11} suggesting that it may be useful for marking progression over time even prior to clinical diagnosis. In manifest disease, higher levels of apathy independently predict disability¹² and

correlate with longer disease duration,¹³ greater functional impairment^{14,15} and increased cognitive difficulty in attention, set shifting, memory, and sequencing.¹⁶ Apathy also relates to depression³ and irritability¹⁷ in HD, although its association to other behavioral symptoms remains to be clarified. Given the link between apathy and disability, as well as the presence of apathy across disease stages, apathy may be an important measure for tracking and monitoring disease progression in both early and late stages of HD.

Although evidence suggests that higher levels of apathy relate to poorer functional, motor, cognitive, and behavioral outcomes, as well as lower HRQOL in HD, a more comprehensive analysis of these associations is needed. Evidence from other neurodegenerative diseases shows that apathy aligns with a greater caregiver burden, greater disability, and less rehabilitation success.¹⁸ Additionally, apathy is linked to poorer cognitive performance on executive function tasks, more severe motor impairments, and communication difficulties,¹⁹ factors that have not yet been examined in HD. A better understanding of the associations among apathy and other measures in HD may provide insights into therapeutics or rehabilitation strategies to target apathy, which is

especially important given the lack of existing recommendations or treatments for apathy.²⁰ Therefore, the objective of this study was to examine associations among apathy, functional status, physical function, cognitive function, behavioral status/emotional function, and HRQOL. We hypothesized that apathy would increase across disease stages and that greater apathy would be related to worse motor, cognitive, and behavioral dysfunction and poorer HRQOL in persons with HD.

METHODS

Data for the current analysis were collected from the baseline visit of a large cohort study that examined HRQOL in individuals with prodromal HD (positive gene test but no clinical diagnosis of HD), early-stage HD, or late-stage HD (clinical diagnosis plus score of 7–13 for early-stage HD and 0–6 for late-stage HD on the Total Functional Capacity [TFC], described below).²¹ Data collection occurred in conjunction with the PREDICT-HD study,²² a global cohort study assessing early symptoms of HD in prodromal participants.

Participant Visits

Participants were recruited through eight established HD clinics (in California, Iowa, Indiana, Maryland, Michigan, Minnesota, Missouri, and New Jersey), the National Research Roster for Huntington's Disease, online medical record data capture systems,²³ and articles/advertisements in HD-specific newsletters and websites. Recruitment also included HD support groups and specialized nursing home units throughout the United States. Participants completed an in-person assessment and a computer-based self-report survey regarding HRQOL. Study visits lasted approximately 2 hours, and participants were compensated with \$40.00. All data were collected in accordance with local institutional review boards, and participants provided informed consent prior to their participation in study activities.

Clinician-Rated Assessments

Functional status. Three measures from the Unified Huntington Disease Rating Scale (UHDRS) were administered to assess functional status: the TFC,²⁴ the Functional Assessment (FA) scale, and the Independence Scale. The TFC²⁴ provides a clinician-rated assessment of ability to engage in work, manage finances, complete activities of daily living (ADLs), complete chores, and live independently. Scores range from 0 to 13, with higher scores indicating better functioning. This measure was also used to determine HD staging (criteria highlighted above). The FA consists of 25 yes/no questions that assess the participant's ability to perform tasks such as ADLs, to engage in gainful employment, to manage finances, or to complete chores. Total scores range from 0 to 25, with higher scores indicating better functioning. The Independence Scale evaluates functional independence. Scores range from 0 to 100, with higher scores indicating better independence. All

functional status measures were based on clinical interviews with the patient and an informant (when possible).

Physical limitations. The total motor score (TMS) from the UHDRS was used to assess motor impairment across 15 different domains, including chorea, dystonia, rigidity, oculomotor function, and bradykinesia. Total scores range from 0 to 124, with higher scores indicating more motor impairment.

Cognition. Three measures of cognition from the UHDRS were also administered: Verbal Fluency, Symbol Digit Modalities Test (SDMT), and Stroop (color naming, word reading, and interference). Verbal Fluency provides a measure of executive function and language and requires participants to name as many words as they can that start with a particular letter within one minute. Scores reflect the total number of named words across three different letters. The SDMT provides a measure of psychomotor processing speed and working memory and requires participants to match symbols with numbers according to a key that is provided at the top of the page. Total scores reflect the number of correctly matched symbols provided in 90 seconds. Scores range from 0 to 120, with higher scores indicating better psychomotor processing speed. The Stroop is an executive functioning task that involves selective attention, cognitive flexibility, cognitive inhibition, and information-processing speed. In this three-part task, participants are required to name patches of colored ink (color naming), to read words (i.e., red, green, or blue; Word Reading), or to name the color of written words that are written in the wrong color ink (i.e., the word "red" written in green ink; Interference). For each Stroop task, total scores reflect the number of correct responses provided in 45 seconds; higher scores indicate better executive function.

Behavioral status. The Problem Behaviors Assessment short version (PBA-s)²⁵ was administered to evaluate 11 different behavioral problems and psychiatric symptoms (depression, suicidal ideation, anxiety, anger/aggression, irritability, apathy, obsessive-compulsive behavior, perseverative thinking, delusions, hallucinations, and disoriented behavior). Severity scores for each behavior are rated from 0 (normal) to 4 (causing significant distress), and frequency scores are rated from 0 (never/almost never) to 4 (every day/at least once a day). The product of severity and frequency scores is calculated to create a final score for each behavior, which can range from 0 to 16, with higher scores indicating worse behavioral problems for each domain. Total scores reflect the sum of the scores across all 11 behaviors; however, given that apathy is our dependent variable of interest in the current analysis, the total PBA-s scores included only the other 10 behaviors.

Self-Reported Measures

Generic measures of HRQOL. The EuroQol 5D (EQ-5D)²⁶ is a standardized instrument that measures health status across five domains of HRQOL: mobility, pain, ability to perform regular activities, ability to care for oneself, and

anxiety/depression. The EQ-5D includes both an Index scores (which ranges from 0 to 25, with higher scores indicating worse health outcomes) and a Health Scale score (which ranges from 0 to 100, with lower scores indicating worse overall health).

Rand-12²⁷ is an HRQOL measure that asks about limitations in activities in relation to physical (pain, disability) and mental (depression, apathy, anxiety) health within the past month. Separate scores are calculated for physical and mental sections of the RAND-12, for which raw scores range from 0 to 100. Final scores are calculated by subtracting the participant's score from the average for their age group, resulting in positive and negative difference scores.²⁸ Positive scores reflect above-average health for an individual's age group, and negative scores reflect below-average health for the participant's age group.²⁸

The World Health Organization Disability Assessment Schedule (WHODAS) 2.0²⁹ is a 12-item generic assessment of health and disability; it assesses mobility, cognition, self-care, participation, and activities. Total scores range from 0 to 48, with higher scores indicating more functional limitations.

Physical ability measures. Several physical ability measures from the Quality of Life in Neurological Disorders (Neuro-QoL)³⁰ and the Huntington Disease Quality of Life (HDQLIFE) measurement system²¹ were also completed. The Neuro-QoL is designed to evaluate HRQOL in individuals with neurological conditions,³⁰ whereas HDQLIFE was developed to examine HRQOL domains specific to those living with HD. We administered the Neuro-QoL subscale for lower-extremity functioning (mobility), Neuro-QoL subscale for upper-extremity functioning (ability to use hands and arms to perform tasks of ADL and fine-motor movements), HDQLIFE subscale for speech difficulties³¹ (ability to speak and be understood in a variety of social situations), HDQLIFE subscale for swallowing difficulties³¹ (ability to swallow and fears related to choking), and HDQLIFE subscale for chorea³² (effects of chorea on task completion). Each item bank is scaled on a T metric with a mean of 50 and a standard deviation of 10 (the referent group for Neuro-QoL consists of other individuals with neurological conditions, whereas the referent group for HDQLIFE consists of other individuals with HD), with higher scores on Neuro-QoL domains indicating better functioning and higher scores on HDQLIFE measures indicating poorer physical functioning.

Emotional status measures. Study participants also completed several measures of emotional function on the Neuro-QoL,³⁰ HDQLIFE,²¹ and the Patient Reported Outcomes Measurement Information System (PROMIS).³³ Participants completed the Neuro-QoL subscale for emotional/behavioral dyscontrol (irritability, impatience, and impulsiveness), Neuro-QoL subscale for positive affect and well-being (perceived sense of purpose and meaning), Neuro-QoL subscale for stigma (perceived negativity of others toward the participant as a result of his or her symptoms); the HDQLIFE

subscale for concern with death and dying³⁴ (end-of-life issues, including fear of death and end-of-life planning), HDQLIFE subscale for meaning and purpose³⁴ (sense of meaning and making the most of the time the patient has left to live); the PROMIS subscale for anger, PROMIS subscale for anxiety, and PROMIS subscale for depression. Each item bank is scaled on a T metric with a mean of 50 and a standard deviation of 10 (the referent group for Neuro-QoL consists of other individuals with neurological conditions, whereas the referent group for HDQLIFE consists of other individuals with HD; the referent group for PROMIS consists of individuals in the general population), with higher scores indicating worse emotional functioning (except for the Neuro-QoL subscale for positive affect and well-being and the HDQLIFE subscale for meaning and purpose, for which higher scores indicate better functioning).

Cognitive ability measures. Two measures of cognition were administered from the Neuro-QoL³⁰: the Neuro-QoL subscale for applied cognition-executive function (cognitive planning and organizing) and the Neuro-QoL subscale for applied-cognition general concerns (perceived difficulty in concentration and memory). Measures are scored on a T metric with a mean of 50 and a standard deviation of 10 (the referent group for these measures consists of other individuals with neurological conditions), with higher scores indicating better cognitive function.

Social function measures. Two measures of social function were administered from the Neuro-QoL²⁰: satisfaction with social roles and activities (one's contentment in obligations pertaining to family, friends, and work) and ability to participate in social roles and activities (one's involvement in obligations pertaining to family, friends, and work). These item banks are scaled on a T metric with a mean of 50 and a standard deviation of 10 (the referent group consists of other individuals with neurological conditions), with higher scores indicating better social function.

Statistical Analyses

Prior to examining the associations between clinician-rated and self-report variables and PBA-s apathy scores, we first compared the levels of PBA-s apathy scores across the three staging groups (prodromal, early-stage HD, or late-stage HD) using one-way, two-tailed, analysis of variance (ANOVA). Next, we computed a series of multiple linear regressions using PBA-s apathy as the outcome and each of the clinician-rated and self-report variables as independent measures.

Clinician-rated apathy. A one-way, two-tailed ANOVA was conducted to determine differences in PBA-s apathy scores among the three HD staging groups.

Creating composite scores. To minimize the number of regression models used, we created composite scores for each of the nine aforementioned domains (clinician-rated

physical ability [TMS], clinician-rated functioning, clinician-rated cognition, clinician-rated behavioral status, generic HRQOL, self-report physical ability, self-report emotional status, self-report cognition, and self-report social function) for participants with complete data. Scores on each individual measure (i.e., verbal fluency, Stroop, and Symbol Digits Modalities Test for clinician-rated cognition; UHDRS independence subscale, UHDRS functional assessment subscale, and UHDRS total functional capacity subscale for clinician-rated functioning; the 11 behaviors on the PBA-s for clinician-rated mental health; UHDRS total motor score for clinician-rated physical ability; Neuro-QoL subscale for emotional and behavioral dyscontrol, Neuro-QoL subscale for positive affect and well-being, Neuro-QoL subscale for stigma, HDQLIFE subscale for concern with death and dying, HDQLIFE subscale for meaning and purpose, PROMIS subscale for depression, PROMIS subscale for anxiety, and PROMIS subscales for anger and self-reported emotional status; HDQLIFE subscale for chorea, HDQLIFE subscale for speech difficulties, HDQLIFE subscale for swallowing difficulties, Neuro-QoL subscale for lower extremities, and Neuro-QoL subscale for upper extremities for self-reported physical ability; Neuro-QoL subscale for ability to participate in social roles and activities and Neuro-QoL subscale for satisfaction with social roles and activities for social functioning; Neuro-QoL subscale for executive functioning and Neuro-QoL subscale for general concerns for self-reported cognition; and the WHODAS, RAND-12, and EQ-5D measures for generic HRQOL) were first recoded to ensure that higher scores indicated better outcomes. Next, these individual scores were then standardized to have a mean of 0 and standard deviation of 1. Then, these standardized scores were summed for each respective composite score (i.e., clinician-rated cognition, clinician-rated functioning, clinician-rated behavioral status, self-report emotional status, and clinician-rated physical ability, self-reported emotional status, self-report physical ability, self-report social function, self-reported cognition, and generic HRQOL). The sum scores within each of the nine composite groups were then scaled with a mean of 0 and standard deviation of 1 so that each composite score was on the same scale.

Multiple Linear Regression Models

Each of the nine composite scores was entered into separate multiple linear regression models (significance was set at a p value <0.05 , two-tailed tests), in which the composite measure was the predictor, staging and clinician-rated depression were covariates (except when depression was included as part of the composite score, i.e., analysis examining Clinician Mental Health), and apathy was the outcome. R^2 values were used to determine which variables accounted for the most variance in apathy scores. We considered R^2 values between 0.01 and 0.08 to be small or minimal effect sizes, values between 0.09 and 0.24 were considered moderate, and effect sizes greater than 0.25 were considered large. These R^2 values were then compared using Fisher's

R-to-Z transformation,³⁶ which sets correlation coefficient values onto a normal distribution scale with confidence intervals that can be statistically evaluated (though similar, this is not to be confused with the Fisher's Z distribution). Finally, the root-mean-square error, which is the standard deviation of the residuals, was calculated as an additional assessment of model fit.

RESULTS

One hundred and ninety-three prodromal, 187 early-stage, and 91 late-stage manifest HD participants were assessed (Table 1). The three groups differed by age ($F=43.3$, $df=2$, 468, $p<0.0001$), which was expected given the progressive nature of HD. The prodromal participants were approximately 8 years younger than those in the early-stage group and 13 years younger than those in the late-stage group. The prodromal participants also had significantly more years of education ($F=15.6$, $df=2$, 434, $p<0.0001$) than either the early- or late-stage group. The groups did not significantly differ for gender ($\chi^2=3.60$, $p=0.17$). The groups did significantly differ for race (Fisher's exact test: $p<0.0001$); the prodromal group did not include African Americans, whereas the early- and late-stage groups did. The groups also differed for marital status (Fisher's exact test: $p<0.0001$); the prodromal group did not include any widowed individuals and had fewer divorced/separated individuals than did the other two groups.

Across the three HD groups, the average PBA-s apathy score was 2.5 ($SD=4.0$). The prodromal group had an average score of 1.4 ($SD=2.9$), which was significantly lower than that of either the early-stage (mean=3.0, $SD=4.1$) or late-stage (mean=3.9, $SD=5.0$) group ($F=14.9$, $df=2$, 468, $p<0.0001$). Early- and late-stage scores did not significantly differ. Therefore, all models were adjusted for stage of disease.

Multiple Linear Regression Models

Table 2 highlights findings from the multiple linear regression models, after controlling for HD disease stage. For clinician-rated assessments, better behavioral status ($t=-12.77$, $df=1$, $p<0.0001$) was associated with better apathy scores (Table 2). There was no association between apathy and clinician-rated cognition ($t=-0.85$, $df=1$, $p=0.3955$), clinician-rated functioning ($t=-1.15$, $df=1$, $p=0.2504$), or clinician-rated physical ability ($t=-0.86$, $df=1$, $p=0.3928$). The adjusted R^2 value for behavioral status was large at 0.30, whereas the adjusted R^2 values for physical ability, functioning, and cognition were all moderate (0.20, 0.14 and 0.18, respectively).

For self-reported HRQOL, better scores on the generic composite measure ($t=-2.33$, $df=1$, $p=0.0201$), emotional status ($t=-3.74$, $df=1$, $p<0.0001$), cognition ($t=-5.04$, $df=1$, $p<0.0001$), and social functioning ($t=-6.25$, $df=1$, $p<0.0001$) were all significantly associated with better apathy outcomes (Table 2). Self-reported physical ability ($t=-1.46$, $df=1$, $p=0.1445$) was not associated with apathy. Adjusted R^2 values for generic HRQOL (0.21), physical ability (0.19),

TABLE 1. Demographic Characteristics of the Three Staging Groups

Variable	Prodromal (N=193)	Early (N=187)	Late (N=91)	All (N=471)
Age (years); mean (SD) ^a	43.1 (12.1)	51.5 (12.8)	56.2 (10.4)	48.9 (13.1)
Gender (%)				
Female	64.8	55.6	57.1	59.7
Male	35.2	44.4	42.9	40.3
Race (%) ^a				
Caucasian	98.5	95.7	94.5	96.6
African American	0.0	1.6	5.5	1.7
Other	1.0	2.7	0.0	1.5
Not provided	0.5	0.0	0.0	0.2
Ethnicity (%)				
Not Hispanic/Latino	93.3	92.5	97.2	93.8
Hispanic/Latino	1.0	4.3	0.9	2.3
Not provided	5.7	3.2	1.9	3.9
Education (years); mean (SD) ^a	16.0 (2.8)	14.8 (2.8)	14.2 (2.6)	15.2 (2.9)
Marital status (%) ^a				
Single, never married	14.4	15.7	8.2	13.8
Married	69.5	56.2	67.1	63.8
Separated/divorced	13.9	21.4	22.4	18.4
Widowed	0.0	2.8	2.3	1.6
Living with partner	2.2	3.9	0.0	2.4
CAG repeats; mean (SD)	42.1 (2.5)	43.2 (3.9)	43.3 (2.8)	43.0 (3.4)

^a Significant group differences were observed.

emotional status (0.22), cognition (0.24) were moderate, and that for social function (0.26) had a large effect size.

Comparisons of R² Effect Sizes

The Fisher's R-to-Z transformations revealed significant differences between R² values for each of the eight composite measures. The composite score with the highest R² value was clinician-rated problem behaviors (R²=0.30; Table 2). The R² value for clinician-rated problem behaviors did not significantly differ from generic HRQOL (R²=0.21, z=1.79, p=0.0735). The R² value for clinician-rated problem behaviors was, however, significantly higher than that for clinician-rated physical functioning (R²=0.20, z=2.03, p=0.04), clinician-rated functioning (R²=0.14, z=2.99, p=0.0028), clinician-rated cognition (R²=0.18, z=2.18, p=0.0324), and self-reported physical functioning (R²=0.19, z=2.21, p=0.0271). Additionally, self-reported social functioning

(R²=0.26) had a higher adjusted R² value than did clinician-rated functioning (R²=0.14, z=2.26, p=0.0238). Generic HRQOL, self-report emotion, and self-reported cognition had similar adjusted R² values with all other composite measures.

DISCUSSION

This study examined associations among apathy and functional status, physical ability, cognition, behavioral status/emotional health and HRQOL in participants with prodromal and manifest HD. As was expected, apathy levels differed by stage of disease, with individuals in the prodromal group demonstrating less apathy than

did participants in the early- and late-stage groups. These findings support other research that suggests that apathy increases with HD progression.⁹

In our cohort, worsened functional capacity and behavioral status were associated with higher levels of apathy. In addition, apathy related to almost all self-reported assessments of these same constructs, as well as to cognition. These findings are largely consistent with the extant literature in HD, which indicates that greater apathy relates to lower functional status and reduced independence.^{14,15,36,37} Our findings are somewhat discrepant from other research in HD, Parkinson disease (PD), and Alzheimer disease (AD) suggesting that increased apathy relates to worse objectively measured cognitive function.^{16,19} Although previous research shows correlations between objective cognition and apathy, our study did not find such associations. One explanation for this is that our study measured different

domains of cognitive function than did previous studies. The cognitive measures used in this study (Stroop, Verbal Fluency, and SDMT) primarily measure executive functioning, processing speed, attention, and language, whereas other studies have utilized the Mini-Mental State Examination,¹⁹ which measures orientation, registration, calculation, and recall, or the Mattis Dementia Rating Scale,¹⁶ which measures

TABLE 2. Standardized Composite/Aggregate Scores^a

Variable	N	Adjusted R ²	T-value	RMSE	Significant Adjusted R ² Comparisons
A. Clinician-rated physical functioning	462	0.20	-0.86	3.52	A<D
B. Clinician-rated functioning	305	0.14	-1.15	4.03	B<D, I
C. Clinician-rated cognition	270	0.18	-0.85	3.74	C<D
D. Clinician-rated behavioral health	455	0.30	-12.69**	3.33	A, B, C, F<D
E. Generic health-related quality of life measure	429	0.21	-2.33**	3.49	E=A-I
F. Self-reported physical function	438	0.19	-1.46	3.62	F<D
G. Self-reported emotion	433	0.22	-3.74*	3.52	G=A-I
H. Self-reported cognition	434	0.24	-5.04**	3.47	H=A-I
I. Self-reported social function	433	0.26	-6.25**	3.42	B<I

^a All predictors are standardized with a mean of 0 and SD of 1. RMSE=root-mean-square error (smaller=better).

*p<0.05. **p<0.0001.

initiation, construction, conceptualization, and memory. Therefore, it is possible that different domains of objective cognition have different associations with apathy. Although apathy did not correlate with objective assessments of cognition, there was a significant association between apathy and self-reported cognitive function. One explanation for this discrepancy is that subjective measures of memory and cognition are often stronger indicators of overall emotional distress rather than an objective evaluation of cognition.³⁸ Additionally, anosognosia, or symptom unawareness, is common in HD and therefore may play a role in this discrepancy; previous studies have shown that participants with greater cognitive deficits are more likely underreport cognitive symptoms.³⁹

Although little is known about the association between apathy and emotional and behavioral status in HD, our results are consistent with prior work showing associations among apathy, depression, and irritability.^{3,17} In our cohort, clinician-rated behavioral problems, self-reported emotional problems/symptoms, and lower levels of positive affect/well-being and feelings of meaning/purpose were all associated with higher levels of apathy.

With regard to HRQOL, greater apathy related to worse overall HRQOL and less social satisfaction and participation. Such findings support previous work in HD^{40,41} and PD.¹⁹ This study builds on prior work by including five different measures of HRQOL in a large cohort of individuals with HD across stages of disease.

To our knowledge, no existing clinical treatments have targeted the reduction of apathy. Our results, however, identify associations of apathy, such as depression and behavioral dyscontrol, that may be manageable with pharmacological and nonpharmacological interventions. These results align with studies in PD and AD, suggesting that many associations with apathy may be common among neurodegenerative conditions. Because depression and behavioral dyscontrol are quite common in HD, future work is needed to determine whether interventions that target these specific domains may vicariously reduce apathy as a result.

Although this study highlights a number of important findings with regard to apathy in HD, it is also important to acknowledge several study limitations. First, findings are based on a convenience sample of individuals with HD and thus may not represent the HD population at large. Second, although apathy is considered a multidimensional construct,^{7,8} this study utilized a single clinician-rated item of apathy and did not include a self-report measure of apathy. Future work should include a more comprehensive assessment of apathy that includes multiple aspects of motivation. In addition, participants completed the clinician-rated assessments and self-report measures within a two-week window and not necessarily within the same session, weakening analyses focused on the associations between clinician-rated apathy and self-report assessments for some participants.

CONCLUSIONS

Our data suggest that apathy relates to functional status, physical function, self-report cognitive function, behavioral status/emotional function, and HRQOL in HD. These findings are consistent with work in other neurodegenerative diseases and suggest that clinical interventions should consider targeting apathy, because it appears to be rather pervasive in terms of affecting multiple aspects of functioning and HRQOL. In addition, future work should focus on further characterizing the different aspects of apathy that have been established in other neurological diseases.

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Supported by the National Center for Advancing Translational Sciences (grant UL1TR000433), NIH, and the National Institute of Neurological Disorders and Stroke (grant R01NS077946). A portion of this study sample was assembled in conjunction with the PREDICT-HD study. The PREDICT-HD study was supported by the Center for Inherited Disease Research (which provided support for sample phenotyping), the Cure Huntington's Disease Initiative Foundation (award to the University of Iowa), the National Institute of Neurological Disorders and Stroke (grant R01NS040068), and NIH.

The authors thank the University of Iowa, the investigators and coordinators of this study, the study participants, the National Research Roster for Huntington Disease Patients and Families, the Huntington Study Group, the Huntington's Disease Society of America (HDSA), and the HDSA Center of Excellence at Washington University.

The authors thank HDQLIFE Site Investigators and Coordinators: Noelle Carlozzi, Praveen Dayalu, Anna L. Kratz, Stephen Schilling, Amy Austin, Matthew Canter, Siera Goodnight, Jennifer Miner, Nicholas Migliore (University of Michigan, Ann Arbor, Mich.); Jane S. Paulsen, Nancy Downing, Isabella DeSoriano, Courtney Hobart, Amanda Miller (University of Iowa, Iowa City, Iowa); Kimberly Quaid, Melissa Wesson (Indiana University, Indianapolis, Ind.); Christopher Ross, Gregory Churchill, Mary Jane Ong (Johns Hopkins University, Baltimore); Susan Perlman, Brian Clemente, Aaron Fisher, Gloria Obialisi, Michael Rosco (University of California, Los Angeles); Michael McCormack, Humberto Marin, Allison Dicke, Judy Rokeach (Rutgers University, Piscataway, N.J.); Joel S. Perlmutter, Stacey Barton, Shineeka Smith (Washington University, St. Louis); Martha Nance, Pat Ede (Struthers Parkinson's Center); Stephen Rao, Anwar Ahmed, Michael Lengen, Lyla Mourany, Christine Reece, (Cleveland Clinic Foundation, Cleveland); Michael Geschwind, Joseph Winer (University of California, San Francisco), David Cella, Richard Gershon, Elizabeth Hahn, Jin-Shei Lai (Northwestern University, Chicago).

The authors also thank Jeffrey D. Long, Hans J. Johnson, Jeremy H. Bockholt, and Roland Zschiegner, as well as Roger Albin, Kelvin Chou, and Henry Paulsen for their assistance with participant recruitment.

Dr. Quaid died July 26, 2017.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

Dr. Stout has served on the scientific advisory board for Roche; she has served or presently serves as an expert consultant to Prana Biotechnology and the University of Michigan; she is Director of Stout Neuropsych Pty Ltd, which provides clinical trial services for Ionis, Omeros, Teva, and Vaccinex; and she receives compensation from the Huntington's Study Group for her role as Treasurer on the Board. All other authors report no financial relationships with commercial interests.

Received Aug. 29, 2017; revision received Nov. 9, 2017; accepted Jan. 3, 2018; published online March 21, 2018.

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