

Apathy and Depression in Huntington's Disease: Distinct Longitudinal Trajectories and Clinical Correlates

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Objective: Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease resulting in motor disturbances, dementia, and psychiatric symptoms. Apathy is a common manifestation and rated as one of the most impactful by patients and caregivers. It can often be difficult to distinguish from depression because of shared features and frequent overlap. This study examined the longitudinal trajectories and clinical correlates of apathy and depression.

Methods: Data were drawn from the Cooperative Huntington Observational Research Trial, a prospective, multi-center observational study that recruited 1,082 patients with HD. Measures of cognition, function, neuropsychiatric symptoms, motor function, and medication use were completed annually over 5 years.

Results: Overall, 423 patients (39%) showed evidence of apathy at study baseline, and both the prevalence and overall

severity of apathy increased over time. Depression, by contrast, affected a similar proportion at baseline, although levels remained relatively stable over the study. Apathy was associated with worse cognition, function, neuropsychiatric symptoms, and motor symptoms. Depression was associated with worse neuropsychiatric symptoms, suicidal ideation, and independence but not other outcomes after control for other variables.

Conclusions: Apathy in HD increased over time and was associated with worse clinical outcomes. These associations were independent of depression and other clinical variables. The findings highlight the need to distinguish between apathy and depression given their distinct implications for prognosis and management.

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Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease that is characterized by motor disturbances, dementia, and neuropsychiatric symptoms (1, 2). HD occurs in approximately one in 10,000 people (3), and there is no known prevention or cure. It is caused by an unstable expansion of the cytosine-adenine-guanine (CAG) repeat in the *Huntingtin* gene (4). Onset is typically in midlife, although it can occur at any age and is inversely proportional to the number of CAG repeats (5). Progression of the disease is similarly related to the number of CAG repeats (6). Motor disturbances are a defining characteristic and are required for clinical diagnosis. These disturbances can include chorea (involuntary, jerky movements), dystonia (involuntary co-contraction of muscles leading to abnormal posturing), bradykinesia, imbalance, and rigidity (2, 7, 8). Despite the prominence of motor symptoms, cognitive deficits and psychiatric symptoms may precede the diagnosis by

many years (9) and often emerge over the course of the disease as the most clinically significant and disabling (10).

Apathy—defined as an absence of motivation and goal-directed behavior—is a common feature, affecting around a quarter of premanifest patients (11) and half or more of manifest HD patients (10–17). It is rated as one of most impactful symptoms of the disease by both patients and caregivers (10). It is also associated with greater impairments in cognition (17–20), function (16–22), and movement (16, 18, 19) and greater frequency of other neuropsychiatric symptoms (16, 19) in cross-sectional studies. In addition, apathy predicts the onset of HD in gene carriers and subsequent functional decline in early HD (9).

Apathy in HD has been associated with deficits in specific components of goal-directed behavior, including executive function and planning (19, 23), and insensitivity to reinforcement learning after loss (24). Neurobiological mechanisms underlying apathy remain unclear but appear largely

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unrelated to inheritance (25) or number of CAG repeats (16, 26). One possibility is that apathy results from the degeneration of prefrontal-subcortical circuits underlying motivation and planning (27, 28). In support of this, research has found apathy to be associated with smaller thalamic volumes (29); smaller gray matter volumes in temporal and subcortical regions (17); and lower glucose metabolism in the frontal, temporal, and parietal areas (17).

Despite its prevalence and impact, comparatively little research has examined apathy longitudinally, and most research is based on cross-sectional studies. A further challenge is the fact that apathy often co-occurs with depression, making it difficult to disentangle their relative effects (30). From the available research, apathy appears to increase in frequency and severity over time (9, 11, 31). The timeline for this, however, appears slightly unclear, with evidence that apathy may be reversible in some patients (26) and that levels may be stable over 2 years (32). Mixed findings have also been reported in terms of apathy's relationship to clinical outcomes. One recent study, for example, found that apathy predicted cognitive decline 2 years later in pre-manifest HD gene carriers but not in manifest HD patients and only when controlling for depression (33). Another study found that apathy predicted functional decline over 3 years in early HD but did not control for depression (9).

Given these inconsistent findings, we attempted to characterize the longitudinal outcomes of HD patients with apathy. We drew upon data from the Cooperative Huntington Observational Research Trial (COHORT) (34), which assessed cognition, function, motor disturbances, and neuropsychiatric symptoms in a large sample of patients over a five-year period. Within these domains, we also examined occupational functioning, suicidal ideation, and psychosis separately given their potential specific relationships with apathy and depression. We likewise examined different types of motor disturbances given evidence of distinct trajectories over time (2, 7, 8, 35) and a recent report that apathy may be associated with more severe bradykinesia but less chorea (36). Based on previous research, we hypothesized that apathy would increase over time and be associated with worse clinical outcomes.

METHODS

Design

Participants were drawn from COHORT (34, 35), a prospective observational study conducted across 44 separate testing sites in Australia (N=2), Canada (N=4), and the United States (N=38). The study recruited four types of participants: individuals with a clinical diagnosis of HD; individuals at high risk of HD based on genetic testing prior to the study who did not have a clinical diagnosis of HD; first- and second-degree relatives of individuals from the first two groups (around one-third of whom underwent genetic testing for the study); and spouses or caregivers of individuals from the first two groups who had no genetic risk

for HD. Genetic analyses were completed on blood collected at enrollment. Measures of clinical outcomes were administered annually for 5 years. All participants provided written informed consent. Ethics approval was obtained from ethics committees from individual testing centers (National Institutes of Health clinical trials registry number NCT00313495).

Participants

Our analyses focused on patients with a clinical diagnosis of HD at baseline or who received this diagnosis during the study. This diagnosis was based on the motor subscale of the Unified Huntington Disease Rating Scale (UHDRS) (37), which requires clinicians to rate whether they believe that the subject has manifest HD with a confidence level of $\geq 99\%$. All patients were also required to have a CAG count greater than 35.

Measures and Procedure

Participants provided a medical history and a blood sample for DNA testing and *Huntingtin* CAG repeat genotyping at baseline. At each visit, participants completed a detailed clinical assessment and neurological examination. Function was assessed using the UHDRS measures of independence (range 0–100; higher scores indicate better function) and total functional capacity (TFC; range 0–13; higher scores indicate better function). Occupational functioning was assessed using the occupation item in the TFC measure (range 0–3; higher scores indicate better functioning). Cognition was assessed using the Mini-Mental State Examination (MMSE; range 0–30) (38) and the UHDRS measures: Symbol Digit Modalities Test (SDMT; range 0–110) (39); Verbal Fluency Test (number of words generated in one minute) (40); and Stroop Interference Test (number correct, range 0–100) (41); for all these cognitive measures, higher scores indicate better cognition.

Neuropsychiatric symptoms were assessed using the revised UHDRS scale for behavioral symptoms (37). This scale requires clinicians to rate 11 symptoms in terms of their frequency (range 0–4) and severity (range 0–4). These two ratings can be multiplied to provide a total score for each symptom (range 0–16). A total score of all neuropsychiatric symptoms can be calculated by adding the scores of individual symptoms. Apathy, depression, and suicidal ideation were each assessed using their individual item scores (range 0–16; higher scores indicate more severe and frequent symptoms). For the purpose of this study, a total score of neuropsychiatric symptoms was calculated excluding apathy and depression (range 0–144). Psychosis was defined dichotomously by the presence of delusions or hallucinations on the UHDRS scale; a continuous score for psychosis was also calculated by adding scores for these two items.

Motor disturbance was assessed using the UHDRS (37). This provides a total score of motor disturbance (range 0–124; higher scores indicate more severe symptoms) and subscores for chorea (range 0–28), dystonia (range 0–20),

rigidity (range 0–8), balance (combining scores for gait, tandem gait, and postural stability; range 0–12), and bradykinesia (range 0–4). A list of patients' medications was collected, including antipsychotics (typically prescribed for neuropsychiatric symptoms and chorea), tetrabenazine (typically prescribed for chorea), antidepressants, and stimulants.

Statistical Analyses

The characteristics of all patients at study baseline (including those with HD at baseline and those subsequently diagnosed) were compared according to whether they experienced apathy at baseline assessment. Data were compared using logistic regression to control for time since clinical diagnosis. The main analyses treated apathy and depression as continuous variables. For the purpose of estimating prevalence, dichotomous scores were calculated for each symptom using both their presence (score ≥ 1) and clinically significant levels (score ≥ 4). The latter score was based on cut-offs used in studies of neuropsychiatric symptoms in other dementias using analogous scales (42) and evidence of thalamic involvement in association with apathy at scores > 2 (29).

Longitudinal data were analyzed using linear mixed models with normally distributed random intercepts and random effects for time. Time was measured from when patients received their clinical diagnosis. Analyses were restricted to the first 4 years of data due to the small number of patients returning for the five-year follow-up (Appendix 1 in the online supplement). Only patients with a current motor diagnosis of HD were included (patients diagnosed with HD during the study were included once they received their diagnosis). To assess the trajectory of apathy over time, a model examined apathy score as outcome and time since clinical diagnosis, age at baseline, sex, and number of CAG repeats as predictors. This was repeated to control for depression and antipsychotic, antidepressant, and stimulant medications. Separate analyses examined the trajectory of depression score as an outcome in a similar manner.

Other longitudinal analyses examined the clinical correlates of apathy. Outcome measures were function (independence, TFC), cognition (MMSE, SDMT, Verbal Fluency, Stroop Interference), neuropsychiatric symptoms (total behavioral score excluding apathy and depression), and motor disturbances (total score). For each outcome, separate models included the following predictors: age, sex, number of CAG repeats, apathy, and depression (both apathy and depression were treated as continuous variables). For neuropsychiatric symptoms, use of antipsychotic medications was included as a dichotomous time-varying variable. Likewise, for motor disturbances, use of antipsychotic medication and tetrabenazine were included as dichotomous time-varying variables. For all outcomes, interactions between apathy and time were included in the model to check if the effect varied over time and were retained in the model if $p < 0.10$. Models were selected based on the Akaike information criterion. Statistical significance

was set at $p < 0.05$ for all statistical tests of main effects given the exploratory nature of the analyses.

Separate analyses examined occupational functioning, suicidal ideation, the presence of psychosis, and different types of motor disturbances (chorea, dystonia, rigidity, balance, bradykinesia) as outcomes. These analyses included the same predictors as the main analyses. For the presence of psychosis, antipsychotic medications were controlled for. For suicidal ideation, function (independence), cognition (MMSE), motor disturbances (total score), and antidepressants were controlled for.

Three further sensitivity analyses were conducted. First, to examine apathy as a trait marker of overall disease course, apathy was defined dichotomously as a time-varying covariate such that patients were categorized as having apathy once they showed active symptoms or if they had previously shown symptoms. Second, to examine the ability of a cross-sectional assessment to predict overall disease course, the main analyses were repeated, taking apathy scores at the study baseline as the predictor of outcome measures. Finally, given previous findings suggesting that findings might be affected by controlling for depression (33), all analyses were repeated without depression as a covariate. All analyses were completed using SPSS, version 25.

RESULTS

Sample Characteristics

Over the course of the study, 1,082 patients with HD were recruited (994 patients had HD at baseline, whereas a further 88 were diagnosed with HD during the study). Of these, 423 (39.2%) exhibited apathy at the baseline assessment and 712 (65.8%) exhibited apathy at some point over the course of their disease.

The characteristics of patients at enrollment—including both those with HD at the baseline visit and those subsequently diagnosed—are shown in Table 1. Patients with apathy at enrollment did not differ from those without apathy in terms of age, sex, education, CAG repeats, or time since diagnosis. Patients experiencing apathy, however, exhibited worse function, depression, and neuropsychiatric symptoms than patients without apathy. Patients experiencing apathy also had less chorea and more bradykinesia than patients without apathy. The sample size across the study is shown in Appendix 1 in the online supplement.

Longitudinal Trajectories of Apathy and Depression

The prevalence of apathy gradually increased over the course of the study. Apathy was evident in 39.2% of patients at baseline, 39.6% at 1 year, 38.9% at 2 years, 44.0% at 3 years, and 46.0% at 4 years. Clinically significant apathy—indicated by a cut-off of 4 or more—was present in 23.8% of patients at baseline, 26.5% at 1 year, 25.7% at 2 years, 31.0% at 3 years, and 34.2% at 4 years. By contrast, the prevalence of depression appeared to be relatively constant, affecting 42.5%, 42.4%, 40.4%, 43.9%, and 39.1% at the respective

TABLE 1. Characteristics of patients at baseline (including both patients with Huntington's disease at baseline and patients who were subsequently diagnosed during the study)^a

| Characteristic | Overall (N=1,082) | | Apathy ^b (N=423) | | No apathy (N=659) | | Statistical comparison ^c | |
|-------------------------------------|-------------------|-------|-----------------------------|-------|-------------------|-------|-------------------------------------|------------------|
| | Mean/number | SD/% | Mean/number | SD/% | Mean/number | SD/% | OR | p |
| Demographic | | | | | | | | |
| Age | 51.64 | 11.75 | 51.16 | 11.53 | 51.94 | 11.90 | 0.99 | 0.181 |
| Sex (female) | 572 | 52.9% | 219 | 51.8% | 353 | 53.6% | 1.09 | 0.509 |
| CAG | 44.30 | 4.12 | 44.30 | 4.42 | 44.30 | 3.92 | 1.00 | 0.998 |
| Education (tertiary) | 444 | 41.1 | 169 | 40.0% | 275 | 41.9% | 0.94 | 0.621 |
| Time since diagnosis (years) | 4.13 | 4.05 | 4.38 | 4.23 | 3.98 | 3.94 | 1.02 | 0.117 |
| Function | | | | | | | | |
| Independence scale | 79.79 | 16.34 | 77.09 | 15.85 | 81.60 | 16.34 | 0.98 | <0.001 |
| Total functional capacity | 8.23 | 3.40 | 7.67 | 3.33 | 8.61 | 3.39 | 0.92 | <0.001 |
| Occupational functioning | 0.92 | 1.10 | 0.75 | 0.98 | 1.03 | 1.15 | 0.79 | <0.001 |
| Cognition | | | | | | | | |
| MMSE | 25.12 | 4.45 | 24.89 | 4.44 | 25.29 | 4.42 | 0.98 | 0.238 |
| SDMT | 24.20 | 11.77 | 24.89 | 11.34 | 24.30 | 12.03 | 1.00 | 0.754 |
| Verbal Fluency Test | 22.33 | 13.11 | 21.67 | 12.59 | 22.78 | 13.40 | 1.00 | 0.272 |
| Stroop Interference Test | 25.70 | 12.18 | 24.86 | 11.99 | 26.22 | 12.28 | 0.99 | 0.183 |
| Neuropsychiatric symptoms | | | | | | | | |
| Behavioral total score ^d | 11.70 | 13.76 | 17.72 | 15.39 | 7.83 | 11.00 | 1.06 | <0.001 |
| Depression score | 1.71 | 2.95 | 2.90 | 3.58 | 0.93 | 2.12 | 1.31 | <0.001 |
| Suicidal ideation score | 0.14 | 0.86 | 0.30 | 1.27 | 0.04 | 0.40 | 1.59 | <0.001 |
| Psychosis present | 138 | 12.8% | 77 | 18.2% | 60 | 9.1% | 2.20 | <0.001 |
| Motor symptoms | | | | | | | | |
| Total motor score | 38.64 | 18.76 | 38.84 | 18.49 | 38.42 | 18.86 | 1.00 | 0.725 |
| Chorea | 9.99 | 5.14 | 9.50 | 4.89 | 10.28 | 5.26 | 0.97 | 0.006 |
| Dystonia | 3.46 | 3.81 | 3.33 | 3.69 | 3.52 | 3.87 | 0.98 | 0.183 |
| Rigidity | 1.36 | 1.59 | 1.42 | 1.63 | 1.31 | 1.56 | 1.03 | 0.473 |
| Balance | 3.90 | 2.76 | 4.06 | 2.81 | 3.79 | 2.73 | 1.03 | 0.260 |
| Bradykinesia | 1.12 | 1.07 | 1.23 | 1.11 | 1.05 | 1.04 | 1.14 | 0.027 |
| Medications | | | | | | | | |
| Antipsychotics | 376 | 34.8% | 170 | 40.2% | 204 | 31.1% | 1.48 | 0.084 |
| Tetrabenazine | 58 | 5.4% | 21 | 5.0% | 37 | 5.6% | 1.50 | 0.338 |
| Antidepressants | 674 | 62.3% | 311 | 73.5% | 361 | 54.9% | 2.17 | <0.001 |
| Stimulants | 23 | 2.1% | 12 | 2.8% | 11 | 1.7% | 1.54 | 0.308 |

^a Continuous variables are summarized as means and SDs; categorical variables are summarized as number and percentage. Function, motor, and neuropsychiatric symptoms were measured with the Unified Huntington Disease Rating Scale (UHDRS). CAG, number of cytosine-adenine-guanine repeats; MMSE, Mini-Mental State Examination; SDMT, Symbol Digit Modalities Test. Values in bold indicate $p < 0.05$.

^b Apathy at baseline.

^c Statistical comparison between patients with apathy and patients without apathy, adjusted for time since clinical diagnosis. OR, odds ratio; p, p value.

^d Excluding apathy and depression.

visits (for clinically significant depression, 21.4%, 20.4%, 19.6%, 24.1%, and 23% were affected at the respective visits). Between 25.1% and 27.3% of patients had both symptoms across visits (between 9.8% and 12.3% had both at clinically significant levels).

Across all patients, average apathy scores increased by 0.10 points each year after diagnosis ($p < 0.001$), with controls for age, sex, and number of CAG repeats (Appendix 2 in the online supplement). There was no relationship between apathy scores and number of CAG repeats, age, or sex. Including depression and medications in the model did not change these findings, although depression itself was associated with greater apathy—each point increase in depression score was associated with an increase of 0.42 points in apathy ($p < 0.001$). Antidepressant (effect estimate=0.33, $p < 0.001$) and antipsychotic medication (effect estimate=0.84, $p < 0.001$) were also associated with greater apathy. By contrast, average

depression scores appeared to decrease slightly by 0.01 points each year after diagnosis, although the statistical significance of the effect varied depending on which variables were controlled for (Appendix 2 in the online supplement). Females had greater depression than males; higher CAG count and older age were associated with lower depression. Antidepressants, but not antipsychotics, were associated with greater depression.

Unadjusted mean levels of apathy and depression are shown in Appendix 3 in the online supplement. For patients with data across subsequent annual visits, between 60.5% and 74.6% of those with apathy at the earlier visit still had apathy 1 year later. Likewise, between 59.7% and 72.2% of those with depression at the earlier visit still had depression at the later visit.

Longitudinal Correlates and Outcomes

In linear mixed model analyses, apathy as a continuous variable was associated with worse function, cognition,

TABLE 2. Linear mixed models for measures of function^a

| Parameter | Estimate | 95% CI | p |
|---------------------------|----------|----------------|------------------|
| Independence | | | |
| Intercept ^b | 166.70 | 151.37, 182.04 | <0.001 |
| Time effect ^c | -2.62 | -2.80, -2.44 | <0.001 |
| Apathy | -0.47 | -0.62, -0.31 | <0.001 |
| Apathy×time | 0.02 | 0.00, 0.04 | 0.025 |
| Depression | -0.18 | -0.31, -0.06 | 0.004 |
| CAG | -1.27 | -1.54, -1.01 | <0.001 |
| Age | -0.36 | -0.45, -0.27 | <0.001 |
| Sex (female) | -2.61 | -4.15, -1.06 | 0.001 |
| Total functional capacity | | | |
| Intercept ^d | 26.31 | 22.98, 29.64 | <0.001 |
| Time effect ^e | -0.50 | -0.53, -0.46 | <0.001 |
| Apathy | -0.11 | -0.14, -0.08 | <0.001 |
| Apathy×time | 0.01 | 0.00, 0.01 | 0.002 |
| Depression | -0.01 | -0.04, 0.01 | 0.400 |
| CAG | -0.27 | -0.33, -0.21 | <0.001 |
| Age | -0.07 | -0.09, -0.05 | <0.001 |
| Sex (female) | -0.61 | -0.95, -0.28 | <0.001 |

^a Function and neuropsychiatric symptoms were measured with the Unified Huntington Disease Rating Scale (UHDRS). CAG, number of cytosine-adenine-guanine repeats. Numbers in bold indicate $p < 0.05$.

^b Random effect with mean 166.70 and SD=10.46.

^c Random effect with mean -2.62 and SD=1.28.

^d Random effect with mean 26.31 and SD=2.40.

^e Random effect with mean -0.50 and SD=0.22.

neuropsychiatric symptoms, and motor symptoms. For measures of function, there were significant interactions between apathy and time (Table 2). At time of diagnosis, each point on the apathy scale was associated with scoring 0.47 points lower on the independence scale ($p < 0.001$) and 0.11 points lower on the TFC scale ($p < 0.001$), with analyses adjusting for depression, age, sex, and number of CAG repeats. Thereafter, each point on the apathy scale was associated with a slightly slower rate of decline on functional measures (0.02 each year on the independence scale; 0.01 each year on the TFC scale). Apathy, but not depression, was also specifically associated with reduced occupational functioning: each point on the apathy scale was associated with 0.03 reduced function ($p < 0.001$; Appendix 4 in the online supplement). Depression was associated with slightly reduced independence, but not TFC (Table 2).

For cognition, each point on the apathy scale was associated with scoring 0.09 points lower on the MMSE ($p < 0.001$), 0.13 points lower on the SDMT ($p = 0.001$), and 0.18 lower in verbal fluency ($p < 0.001$), with adjustment for other variables (Table 3; Appendix 2 in the online supplement). There were no interactions with time, indicating these associations were stable over time. For the Stroop Interference Test, there was a significant interaction: at time of diagnosis, each point on the apathy scale was associated with scoring 0.39 points lower on the Stroop Interference Test ($p < 0.001$); thereafter, each point on the apathy scale was associated with a slightly slower rate of decline (0.03 points; $p = 0.003$; Appendix 2 in the online supplement). Depression was unrelated to MMSE, SDMT, and Stroop

TABLE 3. Linear mixed models for measures of cognition and neuropsychiatric symptoms^a

| Parameter | Estimate | 95% CI | p |
|---------------------------|----------|--------------|------------------|
| Cognition (MMSE) | | | |
| Intercept ^b | 45.58 | 41.06, 50.09 | <0.001 |
| Time effect ^c | -0.43 | -0.49, -0.38 | <0.001 |
| Apathy | -0.09 | -0.12, -0.06 | <0.001 |
| Depression | 0.00 | -0.04, 0.04 | 0.905 |
| CAG | -0.32 | -0.40, -0.24 | <0.001 |
| Age | -0.08 | -0.11, -0.06 | <0.001 |
| Sex (female) | -0.41 | -0.85, 0.04 | 0.076 |
| Neuropsychiatric symptoms | | | |
| Intercept ^d | 3.41 | -6.77, 13.60 | 0.511 |
| Time effect ^e | 0.03 | -0.10, 0.15 | 0.688 |
| Apathy | 0.89 | 0.72, 1.07 | <0.001 |
| Apathy×time | -0.04 | -0.06, -0.02 | 0.001 |
| Depression | 1.68 | 1.55, 1.82 | <0.001 |
| CAG | 0.08 | -0.09, 0.26 | 0.352 |
| Age | -0.03 | -0.10, 0.03 | 0.285 |
| Sex (female) | -0.17 | -1.16, 0.83 | 0.740 |
| Antipsychotic | 1.61 | 0.69, 2.54 | 0.001 |

^a Neuropsychiatric symptoms were measured with the Unified Huntington Disease Rating Scale. Cognition was measured with the Mini-Mental State Examination (MMSE). CAG, number of cytosine-adenine-guanine repeats. Numbers in bold indicate $p < 0.05$.

^b Random effect with mean 45.58 and SD=2.77.

^c Random effect with mean -0.43 and SD=0.45.

^d Random effect with mean 3.41 and SD=6.48.

^e Random effect with mean 0.03 and SD=0.00.

Interference Tests, but was related to slightly better verbal fluency, after analyses controlled for apathy and other clinical variables.

For neuropsychiatric symptoms, there was an interaction with time such that each point on the apathy scale at the time of diagnosis was associated with 0.89 points greater overall neuropsychiatric symptoms, but thereafter was associated with a slightly slower rate of increase over time (0.04 points each year; Table 3). Depression was similarly associated with greater neuropsychiatric symptoms. Both apathy and depression were associated with psychotic symptoms (Appendix 4 in the online supplement). By contrast, depression, but not apathy, was associated with suicidal ideation.

For movement disturbances, each point on the apathy scale was associated with scoring 0.16 points greater on the UHDRS motor disturbance scale ($p = 0.005$), with adjustment for other variables (Table 4). There was no interaction with time, indicating the association was stable over time. Separate analyses for different types of movement disturbances indicated that apathy was associated with greater rigidity, imbalance, and bradykinesia, although not chorea or dystonia (Appendix 4 in the online supplement). Depression was unrelated to movement disturbances.

A sensitivity analysis treating apathy as a dichotomous trait (comparing patients who had experienced apathy to those who had not, rather than as a continuous measure) similarly found that patients with apathy had worse function (0.98 points on the TFC scale at time of diagnosis; 4.03 points on the independence scale, $p < 0.001$); worse

TABLE 4. Linear mixed models for total motor score^a

| Parameter | Estimate | 95% CI | p |
|--------------------------|----------|-----------------|------------------|
| Intercept ^b | -91.51 | -109.31, -73.72 | <0.001 |
| Time effect ^c | 2.45 | 2.24, 2.66 | <0.001 |
| Apathy | 0.16 | 0.05, 0.27 | 0.005 |
| Depression | 0.10 | -0.04, 0.24 | 0.175 |
| CAG | 2.02 | 1.72, 2.33 | <0.001 |
| Age | 0.56 | 0.45, 0.67 | <0.001 |
| Sex (female) | 1.80 | 0.01, 3.59 | 0.049 |
| Antipsychotic | 2.71 | 1.49, 3.92 | <0.001 |
| Tetrabenazine | 1.52 | -0.42, 3.45 | 0.125 |

^a Function and neuropsychiatric symptoms were measured with the Unified Huntington Disease Rating Scale. CAG, number of cytosine-adenine-guanine repeats. Numbers in bold indicate $p < 0.05$.

^b Random effect with mean -91.51 and SD=12.32.

^c Random effect with mean 2.45 and SD=1.41.

cognition (declining more quickly at a rate of 0.44 points on the MMSE each year compared with 0.38 points in patients without apathy, $p < 0.001$); greater neuropsychiatric symptoms (5.21 points on the UHDRS scale, $p < 0.001$); and greater motor symptoms overall (1.44 points on the UHDRS scale, $p = 0.010$), after controlling for other variables (Appendix 5 in the online supplement). A further sensitivity analysis focusing on baseline apathy score as a continuous measure likewise found that it predicted worse function and cognition and greater neuropsychiatric symptoms, but not overall movement disturbances, over the course of the disease (Appendix 6 in the online supplement). The direction, relative magnitude, and statistical significance of effects for apathy were unchanged in all analyses when removing depression as a predictor.

DISCUSSION

Apathy affected a large proportion of HD patients. Approximately 40% showed some evidence of apathy and both the prevalence and severity of apathy increased over time. Apathy was also associated with worse clinical outcomes. Patients with apathy had greater functional and cognitive impairments, neuropsychiatric disturbances, and movement symptoms compared with patients without apathy, after we controlled for depression and other clinical variables. These differences in outcomes were apparent prospectively, with apathy at baseline predicting worse cognition, function, and neuropsychiatric disturbances (although not movement symptoms) over the course of the disease.

The proportion of patients experiencing apathy was comparable with previous studies of manifest HD, which have reported apathy in around 50% of patients (10–13, 15–17). The relationship between apathy and clinical outcomes is likewise consistent with previous cross-sectional research, which has found that apathy is associated with worse cognition (18, 19), function (16, 18, 19, 21, 22), neuropsychiatric disturbances (16, 19), and motor symptoms (16, 18, 19). The current study extends this previous research by confirming that apathy gradually increases from time of

diagnosis (albeit with some fluctuation in whether individual patients exhibit the symptom on consecutive visits) and is associated with globally worse outcomes over time. The current study also highlights the impact of medication; both antidepressants and antipsychotics were associated with greater apathy. Given these medications' established side-effect profiles, it is plausible that antipsychotics may directly increase apathy, whereas antidepressants may be started due to apathy's phenotypic similarity to depression and the limited availability of alternatives.

In the case of function, cognition, and neuropsychiatric symptoms, there was evidence of a floor effect whereby patients with apathy reach more severe levels of impairment earlier in the disease and thereafter progress more slowly. Such an effect could reflect limitations in the scales used or neurobiology, such that patients with apathy experience more pronounced deterioration of brain regions underpinning cognition and function before progression to other areas. Previous longitudinal research found that apathy predicted cognitive decline over 2 years in premanifest HD, but not manifest HD, and only with control for depression (33). Another study found apathy predicted functional decline over 3 years but did not control for depression (9). The current study demonstrates that these longitudinal associations are present in manifest HD across cognitive, functional, neuropsychiatric, and motor domains; are apparent over a longer time period; and are independent of depression and other clinical variables.

The current study found evidence of a relationship between apathy and depression, which has been reported previously (16). This is not surprising given some overlap in features (30), including anhedonia and loss of interest in activities. Importantly, however, the current study demonstrated differences in trajectory between the two symptoms: whereas apathy appeared to increase progressively from time of diagnosis, depression remained relatively constant or decreased slightly. In addition, the current study confirmed that apathy, but not depression, predicts clinical outcomes, including function, cognition, motor disturbances, and overall neuropsychiatric symptoms (15, 18). Apathy, but not depression, was also specifically associated with reduced occupational functioning.

Finally, apathy and depression were associated with different neuropsychiatric symptoms: whereas both were associated with greater risk of psychosis, depression was associated with greater suicidal ideation. Altogether, the findings are consistent with the notion that the symptoms involve distinct mechanisms. Apathy may reflect neurodegeneration, hence its association with poorer clinical outcomes overall. By contrast, depression, which involves aspects of attribution and mood, may also depend on cognition, appraisals, and social factors, hence its weaker association with disease course and more specific association with increased suicidal ideation (42–44). The distinct correlates of apathy and depression highlight the need to carefully screen for associated features if one or both are present.

The study did not replicate a recent report that apathy may be associated with less chorea (36). Although a difference in chorea was apparent in baseline comparisons, the effect disappeared in the longitudinal analyses and after control for other variables. Instead, the study found apathy was related to greater movement disturbances overall, particularly rigidity, balance, and bradykinesia. The current study likewise found no relationship between apathy and age or sex. Other studies reported higher levels of apathy in older patients (15) and in males (16, 19), although without control for time since diagnosis. Females, however, showed higher levels of depression, consistent with previous research (20).

The current study had several limitations. First, the study was limited by its convenience sampling of patients and the fact that patients were volunteers recruited from HD specialists. As a result, patients may have come from higher socioeconomic backgrounds and different disease severity and apathy levels than patients recruited from other clinical settings. Second, data were available for 4 years, which is only a small proportion of disease course. Third, assessment of apathy and other neuropsychiatric symptoms was limited by reliance on the UHDRS scale, rather than Problem Behavior Assessments, which provide for a broader assessment of symptoms (13), or symptom-specific scales of apathy and depression, which allow for more detailed examination of subcomponents. Fourth, assessment of cognition was limited by reliance on the MMSE and UHDRS, rather than a more formal neuropsychological battery, and did not evaluate cognitive subdomains. Fifth, data about specific sites and number of raters were not available due to confidentiality requirements, so it was not possible to control for these variables in the analyses. Finally, analysis of medications was limited and did not include dosage or duration due to the practical and conceptual difficulties in standardizing these variables across different medications.

CONCLUSIONS

Despite these limitations, the study confirms that apathy increases over time and is associated with worse clinical outcomes in HD. The study also suggests that apathy has a different longitudinal trajectory and different clinical correlates to depression. These findings highlight the need to distinguish between these two symptoms given their distinct implications for prognosis and management. Apathy's close relationship to disease progression and antipsychotic medication, for example, may encourage more immediate planning for further deterioration while considering behavioral support strategies and rationalization of antipsychotics. Depression, which appears less closely tied to disease course and medication, could be more amenable to treatment and may prompt consideration of the broader range of factors that underpin it. The frequent overlap of symptoms, however, suggests the need to consider the presence of the other as a differential diagnosis or comorbid condition (30). For both symptoms, clarifying causal mechanisms and identifying effective clinical interventions remain important goals to address the significant impairment they cause.

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