Chapter 4

Incidence, course, and predictors of apathy in Huntington's disease: a two-year prospective study

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Abstract

This study examined the incidence and course of apathy in subjects with HD. Our results showed that at follow-up 14% of the subjects free of apathy at baseline had developed apathy. In these subjects, a lower baseline MMSE score predicted incidence of apathy. Of the 34 subjects with apathy at baseline, 14 subjects were no longer apathetic at follow-up. Twenty subjects had persistent apathy, with a low baseline Symbol Digits Modalities Test as the only predictor. These results showed that apathy in HD is most closely linked to global and executive cognitive performance.

Introduction

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disorder caused by an expanded trinucleotide CAG repeat on the *HTT* gene on chromosome 4. Clinical features include motor, neuropsychiatric and cognitive symptoms. Neuropsychiatric and cognitive symptoms often precede the motor symptoms of HD.[1,2] Particularly the presence of psychopathology has an important negative impact on daily functioning and quality of life for patients and caregivers, and increases the risk of institutionalization.[3,4]

Apathy is a common neuropsychiatric symptom in neurodegenerative disorders such as HD, Parkinson's disease (PD) and Alzheimer's disease (AD). It is defined as a disorder of motivation with diminished goal-directed behavior, cognition and emotion.[5-7] Reported prevalences of apathy in HD range from 34-76% depending on the disease stages examined and assessment methods used.[8] Prevalence and severity of apathy in HD increase with disease progression.[9]
Cross-sectional studies in HD have found a correlation between apathy and cognitive impairment as well as with functional decline.[9,10] Furthermore, we earlier demonstrated that in HD mutation carriers apathy was cross-sectionally associated with male sex, presence of depression and use of psychotropic medication.[11] However, longitudinal studies that may identify temporal relationships between apathy and possible predictors for apathy in HD are lacking.[12]
The present study investigates the incidence, course and predictors of apathy in HD mutation carriers with and without apathy at baseline.

Method

Subjects

In this longitudinal study, subjects were recruited between May 2004 and August 2006. A total of 343 genetically tested subjects at initial 50% risk of HD were contacted via the departments of Neurology and Clinical Genetics of the Leiden University Medical Centre and the long-term care facility 'Overduin' (the Netherlands). Of these, 192 subjects were willing and able to participate in the study. Subjects with a neurological condition other than HD or with juvenile HD were excluded. An additional 18 subjects were recruited through other means (such as the Dutch HD Association). In total, two subjects were lost to follow-up. The remaining 208 subjects were divided into three groups based on i) their genetic test result, which was obtained from their medical records, and ii) on their Unified Huntington's Disease Rating Scale (UHDRS) confidence level (CL) into pre-motor symptomatic mutation carriers (n=55) and HD patients (n=97). Non-carriers (n=56) were excluded from further analysis.

The present study includes 152 HD mutation carriers comprising 55 pre-motor symptomatic mutation carriers and 97 motor symptomatic HD patients. Two years after their initial visit, all subjects were approached for a second measurement. Of the 152 baseline subjects, three were deceased and 27 subjects refused to participate or were excluded because of severe dysarthria. This resulted in 122 subjects for the present analysis.
The study was approved by the Medical Ethical Committee of the LUMC and all subjects gave written informed consent.

Instruments

Socio-demographic and clinical characteristics

Information on socio-demographic and clinical characteristics of mutation carriers was collected in a standardized manner. Use of medication was specified into use of antidepressants, neuroleptics, benzodiazepines, and otherwise. Neurological examination was performed according to the motor section of the Unified Huntington's Disease Rating Scale (UHDRS-m) by a neurologist with extensive experience in HD. Global functioning was assessed with the Total Functional Capacity (TFC) scale of the UHDRS. The estimated duration of disease was calculated with the Vassos formula (ln[age of onset] = 6.18 - 0.054 · [CAGrepeats]), in accordance to earlier research.[13]

Assessment of apathy

Apathy was assessed using the semi-structured Apathy Scale (AS).[14] The AS is a modified version of the Apathy Evaluation Scale (AES)[5] and consists of 14 questions, measuring different features of apathy in the two weeks prior to the interview. Since patients with apathy may lack insight into their behavior, we also included caregivers' information and judgment of the interviewer. The total score of the AS ranges from 0-42 points, with higher scores indicating more apathy. The AS has shown good interrater reliability, good test-retest reliability, as well as high internal consistency in patients with PD with a score of ≥14 points being indicative for the presence of apathy.[15] Therefore, in the present study a total score of ≥14 points was used to characterize subjects as apathetic, and those scoring below this cut-off score as non-apathetic.[11,15]

The Composite International Diagnostic Interview (CIDI) was used to assess Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnosis of depressive disorder [Major Depressive Disorder (MDD) or dysthymia] using a computerized questionnaire, version 2.1.[16] The CIDI was not administered in subjects with a Mini-Mental State Examination (MMSE) score <18 points, since it cannot be reliably administered to patients with severe cognitive dysfunction.

Neuropsychological assessment

The MMSE, Symbol Digit Modalities Test (SDMT), Verbal Fluency Test (VFT) and Stroop Color-Word Test were administered to assess cognitive functioning. The MMSE was used to assess

global cognitive functioning.[17] The SDMT examines attention, working memory, and visuoverbal substitution speed.[18] The VFT is sensitive to frontal executive dysfunction and subtle degrees of semantic memory impairment.[19] The Stroop Color-Word Test was used to measure a person's sustained attention in three conditions: color naming, word reading and naming the color of the ink of an incongruous color name (interference).[20]

Statistical analysis

SPSS 17.0 for Windows package was used for the statistical analysis. Data are presented as n (%), or mean (standard deviation; SD) when appropriate. Because of substantial withdrawal of participants between the two measurements, selection bias could not be excluded. Therefore, drop-outs at the second wave were compared with the participants for baseline characteristics. Because of non-normal distribution of number of CAG repeats, TFC score, UHDRS motor score, AS score, and MMSE score these data were dichotomized in order to reduce potential bias caused by outliers (the cut-off scores of the variables are mentioned in the legend of table 1). A composite variable for executive cognitive functioning (ExCog) was computed because of a strong collinearity between the SDMT, VFT and Stroop Color-Word Test ($r > 0.80$). The variable was computed by averaging the standard z-scores of the 5 tests (i.e. subtracting the mean from an individual raw score and then dividing the difference by the SD).

In subjects without apathy at baseline, univariate and multivariate logistic regression analyses were performed with the presence or absence of incident apathy as the dependent variable, and baseline characteristics as the independent variables, to determine the predictive variables. In subjects with apathy at baseline, univariate and multivariate logistic regression analyses were used to analyze potential predictors of persistent apathy at follow-up. Subsequently, we repeated all logistic regression analyses using the continuous independent variables to examine potential effects of dichotomization.

In both multivariate logistic regression analyses, all variables from the univariate analysis with $p < 0.10$ were entered and the model was adjusted for sex and age. Diagnostic statistics were calculated using the Hosmer and Lemeshow goodness-of-fit tests (H&L). For these analyses, the independent variable ExCog was inverted in order to make results better interpretable, i.e. the odds ratios (ORs) correspond to a drop of one SD in ExCog. Additionally, in subjects with apathy at baseline, multivariate regression analysis was repeated after multiple imputations (5 times) for the 15 missing data of the drop-outs, to account for potential selection bias (i.e., bias caused by attrition due to loss of participants who may have been more apathetic). Imputation of the missing variables was based on the distribution of the apathy score and cognitive variables at baseline.

Table 1. *Socio-demographic and clinical characteristics of HD subjects with (n=34) and without (n=88) apathy at baseline for comparison of baseline characteristics between subjects with and without apathy at follow-up*

	No apathy at baseline					Apathy at baseline				
	No apathy at follow-up (n=75)	Incident apathy (n=13)	OR	(95% CI)	*p*-value	Remittent apathy (n=14)	Persistent apathy (n=20)	OR	(95% CI)	*p*-value
Socio-demographic characteristics										
Male sex	28 (37)	6 (46)	1.44	0.44-4.71	0.55	9 (64)	13 (65)	0.97	0.23-4.04	0.97
Age	45 ± 11	45 ± 11	0.99	0.95-1.05	0.94	44 ±11	57 ±12	1.11	1.03-1.20	**0.006**
Higher level of education[a]	49 (65)	6 (46)	0.47	0.14-1.55	0.22	10 (71)	9 (45)	0.33	0.08-1.40	0.13
Married or with partner	60 (79)	7 (54)	0.31	0.09-1.06	**0.06**	7 (50)	11 (55)	1.67	0.38-7.39	0.50
Clinical characteristics										
High number of CAG repeats[b]	39 (51)	8 (62)	1.02	0.86-1.20	0.85	8 (62)	39 (51)	0.82	0.62-1.09	0.18
Disease duration (yrs)[c]	0.50 ± 11	0.01 ± 14	1.00	0.95-1.05	0.89	-0.58 ± 12	9.63 ± 10	1.09	1.01-1.18	**0.02**
Lower TFC[d]	35 (46)	11 (85)	6.44	1.34-31.1	**0.02**	3 (21)	13 (65)	6.81	1.41-32.8	**0.02**
Higher motor score[e]	36 (48)	10 (77)	3.61	0.92-14.2	**0.07**	5 (36)	12 (60)	2.70	0.66-11.1	0.17
Use of psychotropic medication	19 (25)	6 (46)	2.53	0.76-8.46	0.13	6 (43)	16 (80)	5.33	1.16-24.5	**0.03**
Antidepressants	12 (16)	5 (39)	3.33	0.93-11.9	**0.06**	5 (36)	12 (60)	2.70	0.66-11.1	0.17
Antipsychotics	3 (4)	1 (8)	2.03	0.20-21.1	0.55	1 (7)	7 (35)	7.00	0.75-65.2	**0.09**
Benzodiazepines	10 (13)	2 (15)	1.20	0.23-6.23	0.83	5 (36)	10 (50)	1.80	0.44-7.31	0.41
Neuropsychiatric characteristics										
Higher apathy score[f]	32 (42)	9 (69)	3.09	0.88-10.9	**0.08**	3 (21)	14 (70)	8.56	1.74-42.2	**0.008**
DSM-IV depression[g]	1 (1)	0 (0)			0.26	3 (21)	5 (25)	1.22	0.24-6.23	0.81
Lower MMSE[h]	31 (41)	11 (85)	7.98	1.65-38.6	**0.01**	6 (43)	13 (65)	2.48	0.61-10.1	0.21
Lower SDMT[i]	37 (49)	8 (62)	1.69	0.51-5.63	0.40	3 (21)	14 (70)	8.56	1.74-42.2	**0.008**
Lower Stroop color[j]	36 (47)	9 (69)	2.50	0.71-8.82	0.15	5 (36)	12 (60)	2.70	0.66-11.1	0.17
Lower Stroop word[k]	37 (49)	8 (62)	1.69	0.51 -5.63	0.40	4 (29)	13 (65)	4.64	1.06-20.4	**0.04**
Lower Stroop interference[l]	36 (47)	8 (62)	1.79	0.53 -5.93	0.35	5 (36)	12 (60)	2.70	0.66-11.1	0.17
Lower VFT[m]	36 (47)	9 (69)	2.50	0.71-8.82	0.15	5 (36)	12 (60)	2.70	0.66-11.1	0.17
ExCog[n]	36 (47)	9 (69)	2.50	0.71-8.82	0.15	5 (36)	12 (60)	2.70	0.66-11.1	0.17

Data are means (standard deviations), or numbers (percentages) where appropriate using univariate logistic regression analysis with odd ratios (OR) and 95% CI Apathy is defined as apathy score >13 on the Apathy Scale. Cut-off scores were based on median scores, which are different for the group without (NA) and the group with apathy (A) at baseline. These two cut-off scores for several covariates are:

[a] > 12 years of education;
[b] NA >44 repeats, A >45 repeats;
[c] Disease duration is an estimation computed by age minus estimated age of onset (Vassos formula);
[d] Total functioning capacity (TFC) score ranging from 0–13, lower score indicating worse performance NA <12, A <11;
[e] range 0–28, with higher score indicating more neurological symptoms, NA >10, A >17;
[f] range 0–42, with higher score indicating more apathy, NA >0, A >19;
[g] MDD or dysthymia according to the CIDI;
[h] Mini Mental State Examination (MMSE), range 0–30 points, NA <28, A <25;
[i] Symbol Digit Motor Test (SDMT) ranges from 0–110, NA <40, A <24;
[j] Stroop tests range from 0–100, NA <60, A <35;
[k] NA <80, A <58;
[l] NA <35, A <23;
[m] Verbal Fluency Test (VFT) counts the number of words the patient can come up with, NA <22, A <16. All cognitive tests show lower scores with worse performance.
[n] Executive cognitive function (ExCog) is defined by 5 index *z*-scores derived from SDMT, VFT and Stroop tests, NA <0.14, A ≤0.26.

Results

At baseline, the 88 HD subjects without apathy did not differ in their education level, marital status, number of CAG repeats, and estimated duration of disease from the 34 subjects with apathy. However, the apathetic subjects performed worse on all clinical and neuropsychiatric characteristics (data not shown).

At 2-year follow-up, 13 (14%) of the 88 subjects without apathy at baseline had developed apathy. Of the 34 subjects with apathy at baseline, 14 (41%) no longer met the criteria for apathy two years later, whereas 20 (59%) subjects remained apathetic.

Table 1 shows that, of the 88 subjects without apathy at baseline, the 13 subjects with incident apathy differed significantly from the 75 subjects without apathy at follow-up in more often having a lower TFC score (OR=6.44, 95% confidence interval [CI]: 1.34-31.1, *p*=0.02) and a lower MMSE score (OR=7.98, 95% CI: 1.65-38.6, *p*=0.01). Using forward logistic regression, with adjustment for sex and age, a lower MMSE score at baseline remained the only predictor for incident apathy (OR=9.78, 95% CI: 1.90-50.3, *p*=0.006, the Hosmer and Lemeshow test =0.72) (Table 2). When we repeated this logistic regression analysis with continuous UHDRS-M, TFC, and MMSE scores, the MMSE score remained the only independent predictor (OR per 1 point decrease in MMSE: 1.34; 95% CI: 1.09-1.65; *p*=0.006). The influence of a depressive disorder on apathy in subjects without apathy at baseline was not analyzed, since only one of the baseline subjects versus none at follow-up had a depressive disorder.

Of the 34 subjects with apathy at baseline (Table 1), the 20 subjects with persistent apathy at follow-up were older (OR=1.11, 95%CI 1.03-1.20, *p*=0.006), had a longer disease duration (OR=1.09, 95%CI 1.01-1.18, *p*=0.02), and showed a significantly decreased TFC score (OR=6.81, 95% CI 1.41-32.8, *p*=0.02), SDMT score (OR=8.56, 95%CI 1.74-42.2, *p*=0.008) and Stroop Word Test score (OR=4.64, 95%CI 1.06-20.4, *p*=0.04) at baseline, compared to subjects with remittent apathy. No difference was found in the number of depressions between subjects with persistent and remittent apathy (OR=1.22, 95% CI 0.24-6.23, *p*=0.81), although all three subjects with reversible apathy and

Table 2. *Predictors of incident apathy at two-years follow-up in 88 subjects without apathy at baseline*

	No apathy at follow-up (n=75)	Apathy at follow-up (n=13)	*p*-value
Male sex	1.00	0.41 (0.11-1.57)	0.19
Age	1.00	0.99 (0.93-1.05)	0.73
Lower MMSE score	1.00	9.78 (1.90-50.3)	0.006

Data were analyzed using multivariate logistic regression analysis. Data are presented as ORs (95% confidence intervals). Variables in the model are Mini Mental State Examination (MMSE) score, Unified Huntington's Disease Rating Scale motor score, Apathy Score, marital status, Total Functional Capacity score, and use of antidepressants.

Table 3a. *Predictors of persistent apathy at two-years follow-up in 34 subjects with apathy at baseline*

	Apathy at follow-up (n=20)	No apathy at follow-up (n=14)	*p*-value
Male sex	1.00	1.43 (0.27-7.65)	0.68
Age	1.00	0.68 (0.10-4.76)	0.70
Lower SDMT score	1.00	7.13 (0.95-53.5)	0.06

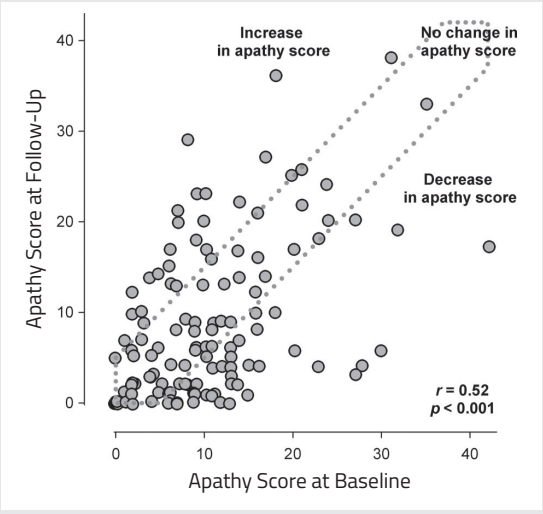
Data were analyzed using multivariate logistic regression analysis. Data are presented as ORs (95% confidence intervals). Sex and age were forced into the model. As potential variables in the model, Total Functional Capacity score, use of antipsychotics, and Symbol Digit Motor Test (SDMT) score were selected. The Stroop Word Test score is excluded because of the high correlation with the SDMT score (r=0.88).

Table 3b. *Predictors of persistent apathy at two-years follow-up in 49 subjects with apathy at baseline with imputed scores on apathy at follow-up**

	Apathy at follow-up (n=35)	No apathy at follow-up (n=14)	*p*-value
Male sex	1.00	1.44	0.70
Age	1.00	0.51	0.41
Lower SDMT score	1.00	3.69	0.21

Data were analyzed using multivariate logistic regression analysis after multiple imputation of the 15 missing apathy scores at follow-up. Data are presented as ORs. Variables in the model are age, sex and Symbol Digit Motor Test (SDMT) score. Multiple imputation of the missing data was based on the baseline Apathy Score, Mini Mental State Examination score and all cognitive variables except the SDMT score. Variables were log transformed when not normally distributed.

Figure 1. *AS score at baseline plotted against AS score at follow-up in 122 HD mutation carriers.*



depression at baseline, no longer had depression at follow-up. Also, no incident depression occurred in this group. In contrast, in the 20 subjects with persistent apathy, five subjects had depression at baseline and four subjects had depression at follow-up, of whom three had persistent depression. In the multivariate logistic regression analysis, age was additionally dichotomized, to put a similar statistical weight on all included variables in the analysis. Using forward logistic regression analysis, a lower SDMT score at baseline was the only independent predictor of persistent apathy at 2-year follow-up (OR=7.13, 95% CI: 0.95-53.5, p=0.06, the Hosmer and Lemeshow test =0.51) (Table 3a), but with a very wide CI. When we repeated this logistic regression analysis with continuous age, SDMT and TFC scores, the SDMT score was not a predictor of persistent apathy at 2-year (OR per 10 numbers decrease in SDMT: 1.21; 95% CI: 0.77-1.89; p=0.41). Similarly, after imputation of apathy scores of the 15 drop-outs, a lower SDMT score did not remain a significant predictor for persistence of apathy (OR=3.69, p=0.21) (Table 3b).

For all 122 mutation carriers, Figure 1 presents the AS scores at baseline versus those at follow-up for the groups with an increasing, equal, and decreasing AS score over time.

To consider possible attrition bias, drop-outs with and without apathy at baseline were compared with the HD subjects with and without apathy who had had two assessments, respectively. Of the 27 drop-outs, 12 (44%) had apathy at baseline. Drop-outs with apathy had worse motor and cognitive functioning as well as higher apathy scores at baseline, compared to the included 34 apathetic subjects (all $p \leq 0.02$). In contrast, drop-outs without apathy showed no significant differences compared to the remaining 88 subjects without apathy at baseline, except for their AS score which was slightly higher in the drop-out group (p=0.05) (data not shown).

Discussion

The present study shows that incident apathy occurred in 13 (14%) of the 88 subjects without apathy at baseline. At the same time, 14 (41%) of the 34 subjects with apathy at baseline showed remittance of apathy at 2-years follow-up. Subjects with incident apathy had decreased TFC and MMSE scores at baseline compared to subjects without apathy at follow-up. In the subjects with apathy at baseline, those with persistent apathy were older and had a longer disease duration. Furthermore, subjects with persistent apathy had decreased TFC, SDMT and Stroop Word Test scores, and also a higher AS score at baseline, compared with subjects with remittent apathy at follow-up. Decreased MMSE score at baseline was the only independent predictor for incident apathy, whereas a lower score on the SDMT predicted persistence of apathy. However, the SDMT score did not remain significant when the analysis was repeated with the continuous variables.

The incidence rate of apathy in HD at 2-years follow-up is 14%, which is relatively low compared with incidence rates reported in other neurodegenerative disorders. For example, in a study on patients with PD, incidence of apathy according to the Neuropsychiatric Inventory over a 4-year follow-up was 57% (39/68 non-apathetic subjects at baseline).[12] An explanation for this high incidence may be that many patients in the latter study were in a more advanced disease stage when apathy occurs more frequently. Also, many PD patients with persistent or incident apathy had a depressive disorder at baseline (6/11=55% and 5/39=13%, respectively)[12], which may also have caused symptoms of apathy. In AD the incidence of apathy during 1-4 years of follow-up was 23% according to the Lille Apathy Rating Scale (41/179 subjects).[21] In this latter study, however, the follow-up visit was not at a fixed moment, which hinders determination of the incidence rate and comparison with our study. Another explanation for the lower incidence rate in our study may be the attrition bias due to differential drop-out of apathetic subjects with worse motor and cognitive functioning, as well as higher AS scores at baseline.

Our results show that global cognitive dysfunctioning precedes the onset of apathy. Although the association has scarcely been studied in patients with HD, these findings are in line with other studies investigating patients with PD and AD.[12, 21-24] Patients with mild cognitive impairment and AD or PD with apathy at baseline were at increased risk of accelerated cognitive decline.[21, 24] In patients with PD, poor cognitive function and dementia at baseline predicted onset of apathy 1.5 to 4 years later.[12] This study therefore showed a similar result as in our study, as we found that cognitive dysfunctioning predicted the occurrence of apathy as well in patients with HD. The previous studies combined with our findings point to a strong link between apathy and cognitive impairment. Future studies should try to elucidate the underlying causal pathways.

Remarkably, in the present study 14 subjects recovered from apathy. A longitudinal study on apathetic patients with AD found a similar phenomenon, but no further information about these AD patients who recovered from apathy is available because they were excluded from further analyses.[21] Since we earlier showed that apathy is cross-sectionally associated with the presence of depression and use of psychotropics,[11] remittance of apathy might be related to recovery from a depressive disorder and/or discontinuation of psychotropic medication between the two measurement points. Remission from apathy was predicted by higher scores on the SDMT, indicating that poor cognitive functioning may decrease the chance of remission from apathy in HD. There may be a substantial construct overlap of depression and apathy, which makes it difficult to differentiate between these two neuropsychiatric disorders. This is supported by the data in the present study, where the subjects with reversible apathy and depression at baseline recovered from both disorders at follow-up. These findings might be of clinical importance because this suggests that apathy is reversible, being a symptom of depression. Also, in the present study, the use of psychotropic medication (especially antipsychotics) was related to a lower chance of

remission, but not in the multivariate analysis possibly due to the relatively low power. It remains to be established whether psychotropic medication can be a cause or effect of apathy.

The strengths of this study are its prospective design, the relatively large group of HD mutation carriers, and the use of specific validated measurement tools in a standardized interview. Some limitations also need addressing. First, the cut-off score for the presence of apathy has been investigated in PD patients but not in HD patients. Also, a gold standard is lacking for the assessment of apathy, thereby hindering the validation of any apathy scale. Second, many of the subjects who were lost to follow-up had apathy at baseline. Similar to the increased chance of depressed participants dropping-out from prospective studies,[25] apathetic HD patients were more likely to withdraw. This probably led to an underestimation of the occurrence of apathy, as well as persistent apathy, at follow-up. Because this attrition bias was probably larger in the analysis for predictors of persistent apathy, we did an additional analysis with multiple imputation of the missing AS scores at follow-up; this indeed supported the idea that the predictive value of a lower SDMT score could partly be ascribed to bias. Third, the strongly skewed distributions of most of the independent variables necessitated the use of categorization, which limits our statistical power. Finally, effects of regression to the mean may have enlarged the changes in apathy found in our subjects, explaining part of the improvement and deterioration of apathy in HD patients.[26]

In conclusion, the results of the present study support the assumption that cognitive dysfunction contributes to the presence of apathy in HD. However, because apathy can be reversible, we recommend that HD patients with apathy undergo clinical evaluation for treatable causes of apathy, including the presence of depression and/or use of pychotropic medication.

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