Journal of Huntington's Disease 4 (2015) 49–59
DOI 10.3233/JHD-140133
IOS Press

Rating Apathy in Huntington's Disease: Patients and Companions Agree

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Abstract.
Background: Apathy is a common feature of Huntington's disease (HD), even from early disease. However, patients are believed to lack insight into their own apathy and therefore clinicians and/or companions are relied upon to estimate the extent of a patient's apathy. In addition, the evolution of apathy over time in HD has not been unequivocally established.
Objectives: The purpose of this study was to determine whether HD patient's self-rated apathy scores were consistent with the scores given by companions who were also asked to rate the patients apathy. Furthermore, the clinical correlates of apathy and its stability over time were examined for both self-rated and companion-rated scores.
Methods: Apathy was measured in a large cross-sectional population of HD patients ranging from early to late stage disease ($n = 106$) using the Apathy Evaluation Scale; a subgroup of whom were followed longitudinally ($n = 62$) on average 18.7 (1.2 SD) months later. Comparisons were made between self-rated and companion-rated apathy and the relationship between apathy and motor, cognitive and functional performance was explored.
Results: Analysis of the cross-sectional data revealed that self-rated and companion-rated apathy were highly correlated, establishing the validity of using self-rated instead of, or in combination with, companion-rated assessments of apathy in future studies. Both self-rated and companion-rated scores had a relationship with motor and functional impairment, but had a complex relationship with cognition. The results of the longitudinal comparison revealed that apathy did not change over time in this cohort.
Conclusions: Apathy can be equally well assessed by either patients or companions and does not change significantly over an 18 month period. These findings have implications in the design of studies looking at treating this important aspect of HD.

Keywords: Huntington's disease, apathy, cognition, depression, companion, self-rated, longitudinal

INTRODUCTION

Huntington's disease (HD) is an incurable, inherited, progressive neurodegenerative disorder that is characterised by a triad of motor, cognitive and psychiatric problems [1]. The psychiatric disturbances experienced in HD are the least well understood of the three cardinal features of the disease in terms of both their pathology and etiology. Depression, irritability, anxiety and apathy are commonly reported by HD patients and their companions [2], with both gene carriers and manifest patients showing an increased risk of suicide [3, 4]. However, in general the incidence of psychiatric disturbances in HD is both variable and transient and in most cases does not closely map to disease progression [5].

Prior to the 1990s psychiatric changes in HD were grouped together with problems such as apathy, irritability and social withdrawal collectively termed "personality change". Historically, it has not always been possible to distinguish apathy from other psychiatric syndromes such as depression. This is because apathy is a ***symptom*** in many mental disorders but is less frequently considered as a syndrome itself [6].

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ISSN 1879-6397/15/$35.00

There is now particular interest in defining the etiology and clinical impact of individual syndromes such as depression, irritability and more recently apathy in HD. This is because currently, there are no effective treatments to ameliorate the symptoms of apathy therefore treating apathy as a distinct syndrome may help identify novel targets for future therapeutic trials. It should be acknowledged however, that the syndromal approach to studying the behavioural disturbances in HD may actually hinder research by artificially simplifying what is a complex element of the clinical phenotype of HD with many concurrent, intertwined neuropsychiatric elements.

Apathy can be a particularly problematic feature of HD; the behavior is often poorly understood by those around the patient with apathetic behavior commonly misinterpreted as awkwardness or stubbornness, leading to hostility and putting a strain on social relationships. The prevalence in HD is believed to be high, with between 50%–99% of patients experiencing apathetic symptoms at some point during their disease [7, 8]. It has been shown to be dissociable from depression [9], to be present from the early stages of the disease [10] and unlike other neuropsychiatric features, to become more severe as the disease advances [11–14]. Apathy correlates with both cognitive performance [13, 15] and functional decline [16–18] and is predictive of future functional capabilities in early HD, although this relationship is not necessarily causal [10].

Measuring apathy accurately in HD can be problematic. Historically, clinician administered behavioural inventories such as the UHDRS Behavioural Scale [19] or the Problem Behaviour Assessment (PBA) [12] have been used in HD. These semi-structured interviews, conducted with the patient and/or companion, measure apathy in conjunction with 10 other behavioural problems, and record the frequency and severity of symptoms using a 0 to 4 (for the UHDRS Behavioural Scale) or 5 (PBA) likert scale with 0 indicating NO apathy.

Such scales require the administering clinician to be suitably trained and appropriately skilled which limits the utility of the scales in many settings. Furthermore, while both scales provide data on a range of behavioural problems in HD, the depth of information about any one individual condition is limited. Therefore, detecting subtle but clinically meaningful changes using either the UHDRS Behavioural Scale or the PBA can be difficult, increasing the chances of a type II error.

The Apathy Scale (AS) [20] is the only self-rated measure dedicated exclusively to apathy that has been used in HD to date. Other self-rated scales such as the Frontal Systems Behaviour Scale (FrSBe) have been used which contain a separate subscale on apathy [21] but cover the issue in less detail. The AS requires the patient's companion to rate the extent of apathetic symptoms experienced by the patient. This is due to the assumed lack of insight of HD patients into their psychiatric problems. However, there is little evidence that HD patients do in fact lack insight into their apathy, although previous research has shown that they may lack insight into their cognitive abilities [22, 23] and motor signs of disease [24]. One previous study has reported poor agreement between patient-rated and companion-rated apathy in patients with low cognitive scores but beyond this the agreement is considered as "fair" or better [25]. This reliance on the presence of a companion can be problematic when designing a clinical trial as it restricts the cohort of eligible patients to those who have a reliable companion willing to accompany them for study visits. What is more, it creates a potential recruitment bias as patients with a good support network tend to fare better psychiatrically than those without.

The current study therefore sought to identify whether patients and their companions evaluated apathy in the same way. To do this apathy was measured using the Apathy Evaluation Scale (AES) [26] which is a well validated likert style assessment scale [26–29] that exists in parallel versions for the participant and companion allowing for direct comparison between the two groups. Furthermore, we looked at the relationship between both self-rated and companion-rated apathy with disease stage, depression and measures of cognition. Finally, patients were re-evaluated after approximately 18 months to evaluate the stability of apathy measures over time and to identify whether this changed depending upon who provided the rating.

MATERIALS AND METHODS

Participants

108 HD patients at baseline and 72 patients at follow up (on average 18.7 months later) ranging from premanifest HD gene carriers to patients with advanced disease were recruited into this study. Participants were identified through the HD service clinic at the John Van Geest Centre for Brain Repair, UK and had previously received genetic confirmation of their HD gene status with a CAG repeat length of greater than 38 repeats.

Participants without a companion also were included in the study.

Participants were tested as part of their routine clinic appointment therefore ethical approval was not obtained prior to testing but permission was granted to analysis of the data by Addenbrooke's Hospital Research & Development (R&D) department.

Procedure

Data was collected at baseline and follow-up in one of two ways:

1. During clinic: Patients due for their annual neuropsychological assessment completed the AES-Participant version (AES-P) at the end of cognitive battery. If accompanied by a companion, the companion was asked to complete the AES-Companion version (AES-C).
2. At home: Those participants who attended clinic outside of their annual appointment due to clinical need were given the AES-P and AES-C to take home. A pre-paid envelope in which to return the completed forms was provided. Where participants had completed the cognitive battery within 6 months of the AES this clinic information was associated with the AES assessment. Data was recorded as missing if the clinic assessment was greater than 6 months from the date of the AES.

Assessments

Apathy

Apathy was assessed using the self-report version of the Apathy Evaluation Scale (AES-P), and the parallel companion version of the same instrument (AES-C) [26]. The AES [26] is an 18 item rating Likert scale where responders are asked to rate the extent to which they agree with a specific statement with responses consisting of not at all, slightly, somewhat, and very. The internal consistency of both the self-report and companion versions of the AES is good with Cronbach alpha scores of 0.94 and 0.86 respectively, and test-retest reliability of 0.94 and 0.76 respectively [26].

HD clinical features

A comprehensive assessment of the motor signs and functional symptoms of HD was completed by an experienced neurologist using the widely validated, standardized, clinical rating scale the Unified Huntington's Disease Rating Scale (UHDRS) [19]. Only the total motor score, functional assessment (FA) and total functional capacity (TFC) sections of the UHDRS were used. Manifest patients were staged according to previously published criteria based on the Total Functional Capacity (TFC) score: scores of between 11 and 13 were classified as early disease, between 7 and 10 as moderate disease and scores of 6 and less as late disease [30].

Cognition

For patients who participated during their routine clinic appointment the neuropsychological data was collected at the same time. For those who participated via post the neuropsychological assessment was completed within one year of their completion of the AES.

Global cognitive function was assessed with the Mini Mental State Exam (MMSE) [31]. Verbal fluency capabilities were evaluated by tests of phonemic (letter) and semantic (category) fluency. Phonemic fluency is thought to be sensitive to frontostriatal deficits [32, 33] and category fluency is sensitive to more temporal lobe deficits [34–36].

Memory was measured using the CANTAB computerized pattern recognition memory (PRM) and spatial recognition memory (SRM) tasks [37]. PRM measures the ability to recognize visual patterns following a short delay as indexed by the percent of patterns correctly recognized from novel distractors and is thought to be sensitive to temporal lobe and hippocampal damage [38]. SRM measures the ability to recognize spatial orientation of visual stimuli following a short delay, as indexed by the percent of placements recognized correctly from distractors with novel placements and is thought to be sensitive to frontal lobe abnormalities [38, 39].

Depression

Depression was assessed using the Beck Depression Inventory (BDI), a 21 item self-report scale [40] used widely worldwide [41] as it provides a robust measure of depression without requiring the presence of a clinician.

Data analysis

Shapiro-Wilk tests revealed that the AES data was not normally distributed therefore non-parametric analyses were used. Between-group differences were calculated using a Kruskal-Wallis test with AES scores as the dependent variable and the value of interest as the independent variable. Spearman's Rho correlations

Table 1
Baseline demographic characteristics and clinical data for all participants completing the Apathy Evaluation Form

	All patients				Patients with companions			
	Pre-HD	Early	Moderate	Late	Pre-HD	Early	Moderate	Late
N	20	24	29	35	15	15	17	25
Gender (m:f)	8:8	21:7	10:19	16:19	4:11	4:11	7:10	10:15
Age	46.8 (15.1)	53.8 (13.6)	54.2 (7.3)	56.7 (12.3)*	46.7 (16.6)	57.7 (13.9)	51.5 (7.7)	58.0 (13.4)
CAG	42.5 (2.8)	42.9 (3.3)	42.4 (1.7)	43.1 (3.1)	42.4 (2.9)	42.6 (3.6)	42.8 (1.6)	43.7 (4.4)
Disease duration	−9.5 (7.9)	6.7 (6.5)	12.0 (5.5)*	11.1 (4.9)*	−9.9 (8.0)	6.1 (7.1)*	11.4 (5.2)*	11.6 (5.1)*
UHDRS	1.7 (1.9)	16.0 (7.3)*	26.4 (13.1)*	42.5 (12.0)	1.5 (1.7)	15.1 (8.0)*	26.6 (14.3)	42.6 (12.6)
FA	24.6 (1.1)	23.8 (1.2)	20.0 (3.2)*	13.9 (7.1)*	24.5 (1.1)	23.8 (1.1)	19.8 (3.8)	13.6 (7.7)
MMSE	28.4 (2.6)	27.0 (2.2)	26.5 (3.0)	22.4 (4.4)*	28.2 (2.7)	26.8 (2.5)	26.3 (3.1)	21.7 (4.5)
BDI	6.5 (6.1)	4.6 (4.9)	13.8 (10.6)	11.7 (9.6)	6.8 (6.2)	5.4 (5.1)	16.3 (11.2)*	13.2 (10.2)
Phonemic fluency	37.1 (13.8)	28.5 (12.8)	26.8 (13.2)	14.0 (7.5)*	37.2 (14.6)	29.2 (15.6)	27.6 (12.9)	11.3 (6.6)*
Semantic fluency	20.0 (5.4)	14.7 (4.4)	13.4 (5.4)*	8.3 (3.5)*	20.7 (5.6)	15.5 (4.4)	12.3 (5.8)*	7.5 (3.8)
CANTAB PRM	18.2 (5.1)	16.8 (2.7)	16.7 (3.6)	14.2 (4.2)	17.6 (5.5)	16.5 (2.9)	16.7 (3.8)	15.4 (2.2)
CANTAB SRM	13.4 (4.4)	13.5 (2.8)	13.4 (2.7)	12.0 (3.4)	13.4 (4.4)	13.5 (2.7)	12.9 (3.1)	12.9 (2.5)

*Significant difference compared to pre-HD ($p < 0.05$). ***Abbreviations***: BDI: Beck Depression Inventory, CAG: cytonsine-adenine-guanine, CANTAB PRM: Cambridge Neuropsychological Test Automated Battery Pattern Recognition Memory, CANTAB SRM: Cambridge Neuropsychological Test Automated Battery Spatial Recognition Memory, MMSE: Mini Mental State Exam, pre-HD: pre-manifest HD gene carriers, UHDRS: Unified Huntington's Disease Rating Scale, FA: UHDRS Functional Assessment.

were used to measure the association between variables and change over time was evaluated using the Mann-Whitney U test. Where possible data was categorized according to published guidelines (BDI [40] and AES [27] and between group comparisons were made. Finally, principal component analysis was used to identify the items of the AES which accounted for the greatest variance in both the self-rated and companion rated scores.

All analysis was performed using Predictive Analytic SoftWare (PASW) Statistics, version 21.

RESULTS

Demographic and clinical information

Baseline participant demographic and clinical data is summarised in Table 1. Patients with and without a companion did not differ from one another in the degree of self-rated apathy they reported ($p = 0.598$) nor in their UHDRS motor score ($p = 0.257$), age ($p = 0.853$) or disease duration ($p = 0.14$), although patients without a companion were significantly less depressed (with companion, mean BDI: 10.99, S.D: 9.8, without companion, mean BDI: 6.74, S.D: 6.9; $p < 0.05$)).

Over the 18.7 months (S.D. 1.2 months) follow up, 37.9% of patients were lost to follow-up (see Fig. 5) which also meant that the population of companion raters was reduced by 57.5%. Of those patients not followed up 8 (7.6%) withdrew because of advancing disease, 4 (3.8%) patients died and the remaining 25 (25.6%) did not return to clinic or respond to attempts to contact them. The baseline characteristics of patients who completed the AES at both time points are shown in Table 2.

Table 2
Baseline demographic characteristics for all patients who completed the AES at both baseline and follow up. * indicates a significant difference compared to pre-manifest HD group at the $p = 0.05$ level

	Pre-HD	Early	Moderate	Late
N	11	17	19	20
Gender (m/f)	4:7	11:6	8:8	11:9
Age	50.6 (15.1)	52.5 (14.2)	524 (7.7)	55.5 (13.5)
CAG	42.0 (1.8)	42.8 (3.6)	41.8 (1.5)	44.9 (4.4)
Disease duration	−7.2 (6.8)	6.2 (7.2)*	10.3 (5.9)	10.4 (4.1)
UHDRS	1.9 (1.8)	14.5 (7.2)	23.6 (14.8)*	44.3 (10.6)*
FA	24.4 (1.3)	23.9 (1.1)	20.1 (3.6)*	13.4 (4.9)*
MMSE	28.2 (3.0)	26.9 (2.3)	26.4 (2.9)	22.1 (3.8)*
BDI	7.0 (6.3)	5.6 (5.6)	13.1 (10.2)	10.6 (10.4)
Phonemic fluency	38.6 (15.0)	28.9 (14.7)	25.2 (15.3)	26.7 (15.0)*
Semantic fluency	20.8 (6.0)	14.6 (4.7)	13.3 (5.2)	8.4 (3.4)*
CANTAB PRM	17.5 (6.5)	16.2 (2.6)	16.3 (3.4)	13.8 (4.3)
CANTAB SRM	11.3 (4.7)	13.3 (2.9)	14.1 (2.5)	12.1 (3.7)

Abbreviations: BDI: Beck Depression Inventory, CAG: cytosine-adenine-guanine, CANTAB PRM: Cambridge Neuropsychological Test Automated Battery Pattern Recognition memory, CANTAB SRM: Cambridge Neuropsychological Test Automated Battery Spatial Recognition memory, FA: UHDRS Functional Assessment, UHDRS: Unified Huntington's Disease Rating Scale.

Inter-rater reliability

Self-rated and companion rated AES scores correlated significantly with one another ($r^2 = 0.76$, $p < 0.001$) indicating a high degree of rater agreement between these two measures and demonstrating evidence of high construct validity supporting the use of the self-rated AES in HD. Furthermore, a

related-samples Wilcoxon Signed Rank Test showed that there was no statistical difference between individual participants self-rated apathy and their companions rating of the patients apathy ($Z = -1.02$, $p = 0.307$,ns).

The prevalence of apathy in HD was estimated using published cut-off scores [27] originally generated for use with patients following traumatic brain injury (TBI) [42] (scores of >41 for the patient rated AES scale and >39 for the companion rated AES scale are considered to be indicative of apathy). Based on this, 26.9% (29/108) of HD patients were classified as apathetic according to patient rated AES scores whereas, 50.6% (40/79) of patients met the criteria for apathy based upon the companion rated AES scores. When the patient rate cut-off criteria were applied to the companion rated scores the prevalence of apathy based upon the companion AES scores fell to 37.9% (30/79). Given that there is no statistical difference between a patient's ratings of their own apathy and their companion's rating of the patient's apathy these results suggest that the published criteria need to be adapted for use in HD.

Relationship to disease stage

There was a significant main effect of disease stage for both self-rated ($X^2(3) = 11.98$, $p < 0.01$) and companion rated apathy ($X^2(3) = 28.87$, $p < 0.001$). *Post-hoc* analysis revealed that, for self-rated apathy, both pre-manifest HD gene carriers and early HD patients had significantly less self-rated apathy than those with late disease ($p < 0.05$); moderate and late HD groups did not differ significantly from one another (Fig. 1). For companion-rated apathy, pre-manifest HD gene carriers and early stage patients differed significantly from moderate stage patients ($p < 0.05$) as well as those with late disease ($p < 0.005$).

By definition, apathy is associated with reduced levels of daily functioning therefore to ensure that this association was not a circular construct (e.g. great levels of apathy led to a reduced total functional capacity score and therefore a higher disease stage) AES scores were correlated with UHDRS scores. Total UHDRS scores correlated with self-rated apathy ($r^2 = 0.21$, $p < 0.05$) and companion-rated apathy scores ($r^2 = 0.56$, $p < 0.001$) (Fig. 2).

In addition, there was a negative correlation between rater agreement and UHDRS scores ($r^2 = -0.42$, $p < 0.001$) indicating that this relationship changes with advancing disease. When presented graphically it becomes apparent that in pre-manifest and early disease patients tend to rate themselves as more apathetic than their companion does however, by late stage disease this relationship has switched so that it is companions who are rating the apathy more severely than the patients (Fig. 3).

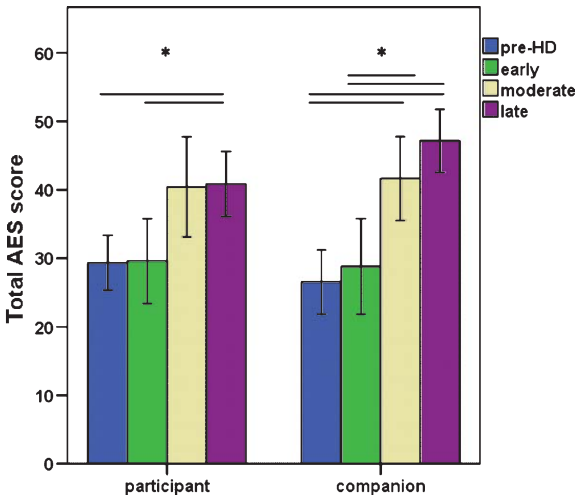

Fig. 1. Mean response on the Apathy Evaluation Scale for both participants and companions stratified by disease stage. *indicates a significant difference at the $p = 0.05$ level. Bars represent means 95% confidence intervals of the mean.

Relationship to depression

Both self-rated and companion rated apathy correlated with depression ($r^2 = 0.50$, $p < 0.001$; $r^2 = 0.48$, $p < 0.01$ respectively). A main effect of depression was found for both self-rated ($X^2(3) = 21.87$, $p < 0.001$) and companion rated scores ($X^2(3) = 7.79$, $p = 0.05$) when patients were grouped according to symptom severity according to published criteria [40] (no depression [BDI < 10], patient $n = 55$, companion $n = 38$; mild depression [BDI 10–15], patient $n = 21$, companion $n = 14$; moderate depression [BDI 16–30], patient $n = 15$, companion $n = 12$; severe depression [BDI > 30], patient $n = 4$, companion $n = 4$). *Post-hoc* analysis revealed that patients with no depression rated themselves as significantly less apathetic than those with either mild ($p < 0.01$) or moderate ($p < 0.001$) depression but not different from those with severe depression (although our sample size was only 4). Patients with mild, moderate or severe depression did not differ significantly from one another in terms of their degree of apathy. For companion ratings the total AES score was significantly different when comparing patients classified as having no depression compared to those with moderate depression only ($p < 0.05$), (Fig. 4).

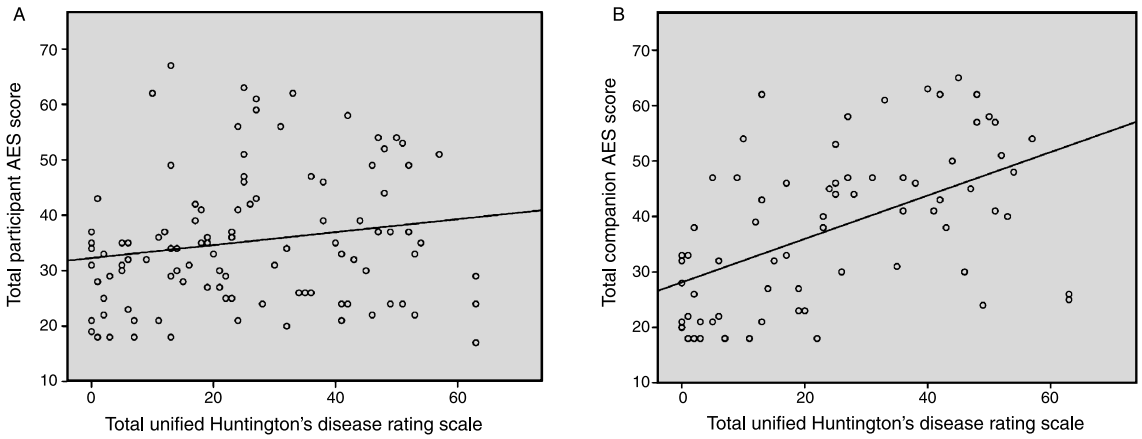

Fig. 2. Mean response on the Apathy Evaluation Scale correlated with total motor performance for (A) participant responses and (B) companion responses.

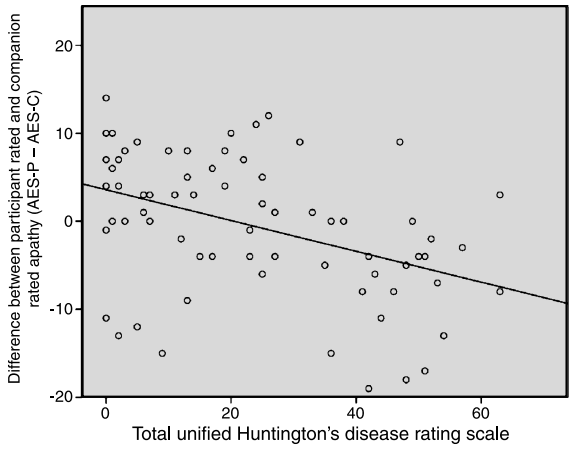

Fig. 3. Difference between patient's self-rated apathy and companions ratings of the patients apathy (calculated as AES-P – AES-C), correlated with total motor performance.

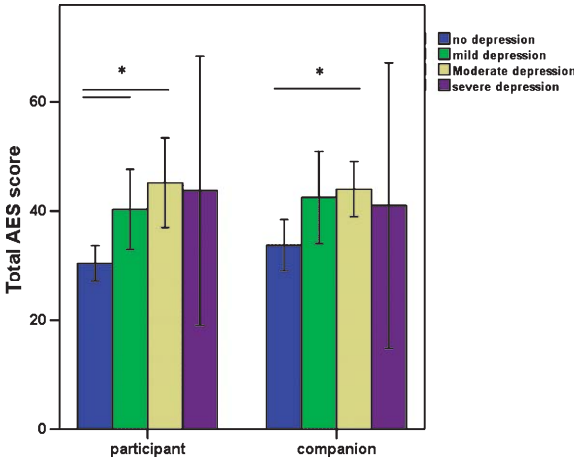

Fig. 4. Mean response on the Apathy Evaluation Scale for both participants and companions stratified by depression score. *indicates a significant difference at the $p = 0.05$ level. Bars represent means 95% confidence intervals of the mean.

Relationship to cognitive performance

Self-rated apathy scores correlated with performance on the MMSE ($r^2 = -0.24$, $p < 0.05$) and CANTAB SRM ($r^2 = -0.35, p < 0.01$), whereas performance on the MMSE ($r^2 = -0.51, p < 0.001$) phonemic ($r^2 = -0.55$, $p < 0.001$), semantic fluency ($r^2 = -0.51$, $p < 0.001$) and CANTAB SRM ($r^2 = -0.46, p < 0.001$) tasks correlated with companion-rated apathy.

Inter-rater reliability between the AES-P and AES-C did not correlate with the MMSE ($r^2 = 0.19$, $p < 0.20$ ns) but did correlate with phonemic fluency ($r^2 = -0.37$, $p < 0.01$), semantic fluency ($r^2 = -0.32$, $p < 0.038$) and CANTAB SRM ($r^2 = -0.34, p < 0.044$). This suggests that the extent of rater agreement did not relate to global cognitive performance but may have a relationship with the extent of executive dysfunction in HD. However, similar to the UHDRS, the correlation between cognitive performance and rater agreement represents a switch from higher participant ratings in pre-manifest and early disease to higher companion ratings by late stage disease.

Medications effects

The impact of dopamine blocking/depleting drugs commonly used to treat HD (sulpiride, amisulpiride, olanzapine, tetrabenazine or haloperidol) on AES scores was examined. As the likelihood of being pre-

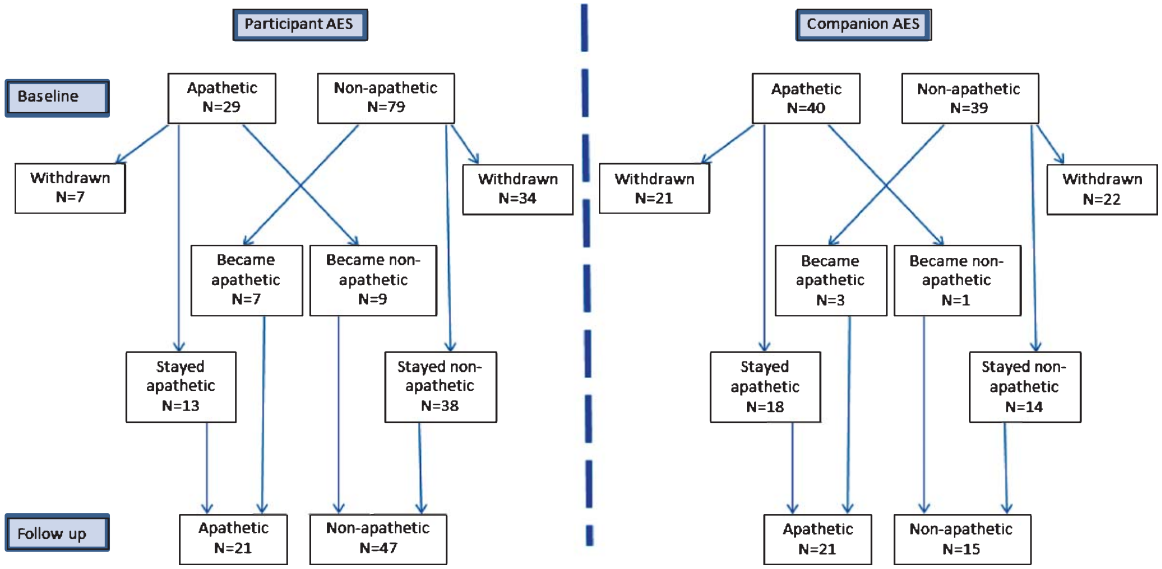

Fig. 5. Flow-chart summarizing the re-classification of apathy in a cross-sectional sample of 108 HD patients with motor signs of disease ranging from mild to advanced stages followed up on average for 18.7 (1.2) months from their first visit. Apathy was defined based upon published criteria [27].

scribed antidopaminergic medication increases with advancing disease only the late-HD group were evaluated (due to insufficient numbers of patients taking antidopaminergic medication in the mild and moderate HD groups). Patients prescribed antidopaminergic medication had higher self-reported apathy ($U = 97.0$, $p = 0.043$) and companion rated apathy ($U = 25.0$, $p = 0.013$).

Change over time

The prevalence of apathy at follow up was estimated as 30.9% (21/68) and 56.9% (29/51) for self-rated and companion-rated apathy respectively. Of the 29 patients classified as apathetic according to the self-ratings at baseline, 13 remained apathetic, 9 were no longer classified as apathetic at follow up and 7 were lost to follow up. Of the 79 patients classified as non-apathetic according to patient ratings at baseline, 38 remained non-apathetic at follow up, 34 were lost to follow up and 7 Patients who were not classified as apathetic at baseline became apathetic by follow up.

Of the 40 patients classified as apathetic according to the companion ratings at baseline, 18 remained apathetic, 1 was no longer classified as apathetic at follow up and 21 were lost to follow up. Of the 39 patients classified as non-apathetic at baseline, 14 remained non-apathetic, 3 became apathetic and 22 were lost to follow up (Fig. 5).

Total AES scores at baseline and follow-up correlated significantly for both the self-rated ($n = 67$, $r^2 = 0.71$, $p < 0.001$) and companion-rated responses ($n = 51$, $r^2 = 0.57$, $p < 0.05$). Furthermore, a Wilcoxon signed-rank tests found no significant difference in self-rated AES scores at baseline (mean = 35.6, S.D. = 12.72) and follow-up (mean = 36.2, S.D. = 12.38); ($Z = -0.141$, $p = 0.21$). Although, companion-rated AES scores were significantly lower at baseline (mean = 37.5, S.D. = 13.98) than at follow up (mean = 40.5, S.D. = 14.81); ($Z = -1.99$, $p < 0.05$).

Further analysis found that patients who remained consistently apathetic had significantly lower baseline FA (apathetic 15.5 (5.9 S.D.) vs non-apathetic 21.5 (4.6 S.D.), ($U = 206.5$, $p < 0.001$)), higher BDI scores (apathetic 16.6 (9.8 S.D.) vs non-apathetic 5.8 (6.1 S.D.), ($U = 157.5$, $p < 0.001$)) and more advanced disease stage (apathetic 2.5 (0.8 S.D.) vs non-apathetic 1.5 (0.8 S.D.), ($U = 237.0$, $p < 0.001$). They were also more likely to be taking anti DA medication at baseline ($U = 281.0$, $p < 0.005$) than those who were consistently non-apathetic. Due to the sample size this was only completed using the self-rated apathy scores.

Factors contributing to apathy score

Principal component analysis (PCA) revealed that the same 11 questions emerged as explaining the majority of the variance in both the self-rated and com-

Table 3
Items from the Apathy Evaluation Scale classified into components according to the results of the principal component analysis. Items written in bold* indicate questions present in the companion but not the self-rated model

Component 1	Component 2	Component 3
Is interested in things	Has an accurate understanding of their problems	Puts little effort into anything
Getting this started on own I important to them	Has friends	Is less concerned about problems than they should be
Is interested in having new experiences	Getting together with friends is important to them	
Is interested in learning new things		
Seeing a job through to the end is important		
Has initiative		
Has motivation		
Getting things done during the day is important		
Gets things done during a day		
Approaches life with intensity		
Spends time doing things that interest them		
Someone has to tell them what to do each day *		

panion rated AES (Table 3), although the model created from the companion-rated scores also contained the additional item "someone has to tell them what to do each day".

DISCUSSION

In this study we used a well validated self-report questionnaire to compare; (1) two independent perspectives on apathy in a large cohort of HD patients and (2) to see how stabile any reported scores of apathy were over an 18 month follow up period. Importantly, the results of the current study confirmed that there is a good inter-rater reliability between the self-rated and companion rated AES. Coupled with this the results of the PCA demonstrated that both patients and companions rated apathy according to the same constructs within the scale. As such it is reasonable to conclude that patients are able to provide a useful evaluation of their level of apathy even in later stages of the disease, endorsing the use of self-rated apathy scales in an HD population. This has implications for the design of future therapeutic trials aimed at treating these features of apathy in HD. The freedom to use self-rating scales, in combination with or instead of companion rated scales means that companion-less patients need no longer be excluded from participating in such trials. Opening up recruitment in this way will help to reduce the bias and increase power of future studies in this clinical area.

However, despite the overall agreement, it does appear that in early disease when cognitive performance is preserved, patients tend to rate their levels of apathy as higher than their companions whilst in later disease, when cognitive performance is worse, this relationship switches so that companions rate apathy as higher than the patients do. Others have reported a relationship between cognition and apathy in HD [15, 25] whereby patients with who perform worse on cognitive task are less accurate at rating their own apathy. The current study does not include an independent rating of the patient's apathy therefore it is impossible to judge whether the patient or companion provides the more "accurate" rating but it is clear that the relationship between the two opinions does change as the disease advances. In light of this, it may still be prudent to consult both the patient and companion where possible.

One advantage of the AES over other methods of rating apathy is the availability of published normative data and clinical cut-off values which can be used to classify an individual as apathetic or not. Using the published cut-off scores from the AES the prevalence of apathy in HD was estimated at between 26.9% and 50.6% depending upon whether the patient or companion reports are used. This is consistent with the previous literature which has cited a prevalence rate in the region of 50% [7] if you consider the companion data, with the lower cut off score (>39 compared to > 41 for patient responses) being more accurate. It is possible that this is an over estimation of the true extent of apathy in the HD population given that patients and carers actually score apathy similarly. In which case it may be more appropriate to abandon the two tier

approach and have one cut-off value that is applicable for both self-rated and companion-rated AES scores in HD.

Beyond this the only area where self-rated and companion rated apathy scores yielded different results was in the relationship between apathy and cognition. Self-rated AES scores were significantly related to performance on the CANTAB SRM, whereas companion rated AES scores yielded differences on both verbal fluency tasks (phonemic and semantic) with non-apathetic patients out-performing their apathetic counterparts. Baudic and colleagues [15] are the only group to date to have studied the impact of apathy on cognitive performance in HD in a systematic way using a comprehensive neuropsychological battery. They concluded that apathy has a detrimental effect on executive function, memory and cognitive efficiency. Although, unlike the results of this study they were unable to find an effect of apathy on either phonemic or semantic verbal fluency. These differences may be linked to the lower cut-off scores provided for the companion rated version of the AES compared to the self-rated cut-off scores, potentially leading to a relative ***overestimation*** of the prevalence of apathy in this population. This could go some way to explaining why the relationship between companion rated apathy and cognitive deficit presented in this study differs from that of self-rated apathy scores and from previous studies.

Despite this, the majority of the findings of our current study are consistent with the existing literature. For example both self-rated and companion rated apathy increases with advancing disease with patients in the pre-manifest and early stages of HD reporting significantly lower AES scores than those at later stages of the illness [8]. However, apathy levels in moderate and late stage patients do not differ significantly from one another.

As this effect is seen both in self-rated and companion rated scores it is unlikely to be an artifact of increasing cognitive impairment which occurs with advancing disease [30] making them unable to accurately evaluate their own apathy. One possible explanation is that the ***expectations*** of both patients and companions change as the disease progresses and therefore the reduced activity is attributed to the progressing motor impairment rather than to motivational factors. Additionally, there appears to be a degree of variability in the AES scores which cannot be explained in the context of disease severity but which may be indicative of different phenotypic subgroups of disease, with some patients being particularly susceptible to experience apathetic symptoms and others not. Further work in this area is needed to ascertain whether this is the case.

In addition, the results of the current study provide additional evidence that apathy is distinct from depression. Whilst there is evidence of some overlap between apathy and depression scores in these patients, the level of apathy did not change as depressive symptoms increased supporting the independence of the two conditions. Furthermore, the degree of apathy did not change between patients who were or were not, using either antidepressant or dopamine blocking drugs but the numbers of patients in these groups were small and therefore the analysis was potentially underpowered.

Finally and in contrast to the findings of other studies [8, 10] apathy appears to remain relatively constant over time in our study. This may reflect the slow rate of progression experienced by many patients with HD rather than a true "stability" especially given that companion AES scores did deteriorate significantly over the 18 month period. The studies which demonstrated an increase in apathetic symptoms over time studies their cohorts for 3 years [8, 10] whereas the one other study has failed to show a longitudinal change in apathy scores only had a follow-up period of 12 months [43]. A similar effect is seen in the cognitive domain where there is increasing evidence that extended periods of follow-up are needed to detect longitudinal change in performance [44, 45]. In addition, a retrospective power calculation demonstrated that the longitudinal study only had 35% power to detect change. Therefore, the results are insufficient to conclude that apathy is stable over time in HD.

There are limitations with the current study that should be taken into consideration. Firstly, the majority of patients completed the cognitive tasks at the same time as the AES however, for some patients the time difference between completing the two was up to 1 year. Cognitive performance, specifically on the tasks used in this study have been shown to be stable over a 12 month period and greater [46]. It is possible that the increased gap introduced variability into the data and therefore diluted the relationship between apathy and cognition in this study. In which caution should be expressed before concluding that apathy does not have a relationship with individual cognitive measures on the basis of the negative results presented here. Secondly, there was a high attrition rate in the study with 37.9% of patients not completing follow-up after 18 months. Whilst this is unavoidable in studies of this nature it is important to acknowledge that this may have biased the data. At a group level patients who

completed follow-up did not differ from the baseline group in terms of demographic information or clinical characteristics but it is still possible that there was a fundamental difference between the two groups. Finally, while the overall sample size is relatively large, when this is broken down in to smaller sub-groups based upon disease severity the number in each group becomes significantly smaller. Therefore, this work would need replicating in a larger cohort before this data can truly be used to support changes in clinical trial design.

In conclusion, our new study demonstrates that the AES is a credible tool for measuring apathy in HD and may prove to be a valuable measure for use in future clinical trials. It is easy to administer, quick to complete and validated in multiple languages, although caution should be expressed when using the published cut-off scores as this may lead to an overestimation of apathetic symptoms if only the carers score is used. Furthermore, its utility may be limited by the apparent lack of change in scores in the short term although further work is needed to see if this varies as a function of disease stage.

ACKNOWLEDGMENTS

The work included in this manuscript has been partially funded by financial support from the NIHR Cambridge Biomedical Research Centre and the Cambridge University NHS Foundation Trust.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

REFERENCES

[1] Bates G, Harper P, Jones L. Huntington's disease. 3rd. Oxford: New York Oxford University Press (UK); 2002.
[2] van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J Neuropsychiatry Clin Neurosci. 2007;19:441-8.
[3] Schoenfeld M, Myers RH, Cupples LA, Berkman B, Sax DS, Clark E. Increased rate of suicide among patients with Huntington's disease. J Neurol Neurosurg Psychiatry. 1984;47:1283-7.
[4] Fiedorowicz JG, Mills JA, Ruggle A, Langbehn D, Paulsen JS, Group P-HIotHS. Suicidal behavior in prodromal Huntington disease. Neurodegener Dis. 2011;8:483-90.
[5] Zappacosta B, Monza D, Meoni C, Austoni L, Soliveri P, Gellera C, Alberti R, Mantero M, Penati G, Caraceni T, Girotti F. Psychiatric symptoms do not correlate with cognitive decline, motor symptoms, or CAG repeat length in Huntington's disease. Arch Neurol. 1996;53:493-97.
[6] Svenaeus F. Diagnosing mental disorders and saving the normal: American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, 5th ed. American Psychiatric Publishing: Washington, DC. 991 pp., Med Health Care Philos. 2013.
[7] Paulsen JS, Ready RE, Hamilton JM, Mega MS, Cummings JL. Neuropsychiatric aspects of Huntington's disease. J Neurol Neurosurg Psychiatry. 2001;71:310-4.
[8] Thompson JC, Harris J, Sollom AC, Stopford CL, Howard E, Snowden JS, Craufurd D. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. J Neuropsychiatry Clin Neurosci. 2012;24:53-60.
[9] Naarding P, Janzing JG, Eling P, van der Werf S, Kremer B. Apathy is not depression in Huntington's disease. J Neuropsychiatry Clin Neurosci. 2009;21:266-70.
[10] Tabrizi SJ, Scahill RI, Owen G, Durr A, Leavitt BR, Roos RA, Borowsky B, Landwehrmeyer B, Frost C, Johnson H, Craufurd D, Reilmann R, Stout JC, Langbehn DR. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: Analysis of 36-month observational data. Lancet Neurol. 2013;12:637-49.
[11] Levy ML, Cummings JL, Fairbanks LA, Masterman D, Miller BL, Craig AH, Paulsen JS, Litvan I. Apathy is not depression. J Neuropsychiatry Clin Neurosci. 1998;10:314-9.
[12] Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington Disease. Neuropsychiatry Neuropsychol Behav Neurol. 2001;14:219-26.
[13] Thompson JC, Snowden JS, Craufurd D, Neary D. Behavior in Huntington's disease: Dissociating cognition-based and mood-based changes. J Neuropsychiatry Clin Neurosci. 2002;14:37-43.
[14] Kingma EM, van Duijn E, Timman R, van der Mast RC, Roos RA. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. Gen Hosp Psychiatry. 2008;30:155-61.
[15] Baudic S, Maison P, Dolbeau G, Boisse MF, Bartolomeo P, Dalla Barba G, Traykov L, Bachoud-Levi AC. Cognitive impairment related to apathy in early Huntington's disease. Dement Geriatr Cogn Disord. 2006;21:316-21.
[16] Hamilton JM, Salmon DP, Corey-Bloom J, Gamst A, Paulsen JS, Jerkins S, Jacobson MW, Peavy G. Behavioural abnormalities contribute to functional decline in Huntington's disease. J Neurol Neurosurg Psychiatry. 2003;74:120-2.
[17] Banaszkiewicz K, Sitek EJ, Rudzinska M, Soltan W, Slawek J, Szczudlik A. Huntington's disease from the patient, caregiver and physician's perspectives: Three sides of the same coin? J Neural Transm. 2012;119:1361-5.
[18] van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. J Neuropsychiatry Clin Neurosci. 2010;22:287-94.
[19] Huntington Study Group. Unified Huntington's Disease Rating Scale: Reliability and consistency. Huntington Study Group. Mov Disord. 1996;11:136-42.
[20] Marin RS. Apathy: A neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci. 1991;3:243-54.
[21] Read J, Jones R, Owen G, Leavitt BR, Coleman A, Roos RA, Dumas EM, Durr A, Justo D, Say M, Stout JC, Tabrizi SJ, Craufurd D, investigators T-H. Quality of life in Huntington's disease: A comparative study investigating the impact for those with pre-manifest and early manifest disease, and their partners. J Huntingtons Dis. 2013;2:159-75.
[22] Sitek EJ, Soltan W, Robowski P, Schinwelski M, Wieczorek D, Slawek J. Poor insight into memory impairment in patients

with Huntington disease. Neurol Neurochir Pol. 2012;46: 318-25.
[23] Ho AK, Robbins AO, Barker RA. Huntington's disease patients have selective problems with insight. Mov Disord. 2006;21:385-9.
[24] Justo D, Charles P, Daunizeau J, Delmaire C, Gargiulo M, Hahn-Barma V, Naccache L, Durr A. Is non-recognition of choreic movements in Huntington disease always pathological? Neuropsychologia. 2013;51:748-59.
[25] Chatterjee A, Anderson KE, Moskowitz CB, Hauser WA, Marder KS. A comparison of self-report and caregiver assessment of depression, apathy, and irritability in Huntington's disease. J Neuropsychiatry Clin Neurosci. 2005;17:378-83.
[26] Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991;38:143-62.
[27] Glenn MB, Burke DT, O'Neil-Pirozzi T, Goldstein R, Jacob L, Kettell J. Cutoff score on the apathy evaluation scale in subjects with traumatic brain injury. Brain Inj. 2002;16: 509-16.
[28] Kirsch-Darrow L, Fernandez HH, Marsiske M, Okun MS, Bowers D. Dissociating apathy and depression in Parkinson disease. Neurology. 2006;67:33-8.
[29] Marin RS, Firinciogullari S, Biedrzycki RC. Group differences in the relationship between apathy and depression. J Nerv Ment Dis. 1994;182:235-9.
[30] Begeti F, Tan AY, Cummins GA, Collins LM, Guzman NV, Mason SL, Barker RA. The Addenbrooke's Cognitive Examination-Revised accurately detects cognitive decline in Huntington's disease. J Neurol. 2013;260:2777-85.
[31] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.
[32] Coslett HB, Bowers D, Verfaellie M, Heilman KM. Frontal verbal amnesia. Phonological amnesia. Arch Neurol. 1991;48:949-55.
[33] Crowe SF. Dissociation of two frontal lobe syndromes by a test of verbal fluency. J Clin Exp Neuropsychol. 1992;14:327-39.
[34] Corcoran R, Upton D. A role for the hippocampus in card sorting? Cortex. 1993;29:293-304.
[35] Cuenod CA, Bookheimer SY, Hertz-Pannier L, Zeffiro TA, Theodore WH, Le Bihan D. Functional MRI during word generation, using conventional equipment: A potential tool for language localization in the clinical environment. Neurology. 1995;45:1821-27.
[36] Martin RC, Loring DW, Meador KJ, Lee GP. The effects of lateralized temporal lobe dysfunction on formal and semantic word fluency. Neuropsychologia. 1990;28:823-29.
[37] Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge Neuropsychological Test Automated Battery (CANTAB): A factor analytic study of a large sample of normal elderly volunteers. Dementia. 1994;5:266-81.
[38] Owen AM, Sahakian BJ, Semple J, Polkey CE, Robbins TW. Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia. 1995;33:1-24.
[39] Rogers RD, Sahakian BJ, Hodges JR, Polkey CE, Kennard C, Robbins TW. Dissociating executive mechanisms of task control following frontal lobe damage and Parkinson's disease. Brain. 1998;121 (Pt 5):815-42.
[40] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561-71.
[41] Richter P, Werner J, Heerlein A, Kraus A, Sauer H. On the validity of the Beck Depression Inventory. A review. Psychopathology. 1998;31:160-8.
[42] Lane-Brown AT, Tate RL. Measuring apathy after traumatic brain injury: Psychometric properties of the Apathy Evaluation Scale and the Frontal Systems Behavior Scale. Brain Inj. 2009;23:999-1007.
[43] van Duijn E, Reedeker N, Giltay EJ, Eindhoven D, Roos RA, van der Mast RC. Course of irritability, depression and apathy in Huntington's disease in relation to motor symptoms during a two-year follow-up period. Neurodegener Dis. 2014;13: 9-16.
[44] Solomon AC, Stout JC, Weaver M, Queller S, Tomusk A, Whitlock KB, Hui SL, Marshall J, Jackson JG, Siemers ER, Beristain X, Wojcieszek J, Foroud T. Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. Mov Disord. 2008;23: 1830-6.
[45] Brandt J, Bylsma FW, Gross R, Stine OC, Ranen N, Ross CA. Trinucleotide repeat length and clinical progression in Huntington's disease. Neurology. 1996;46:527-31.
[46] Mason SL, Wijeyekoon R, Swain R, Ho AK, Smith EL, Sahakian B, Barker RA. Cognitive follow up of a small cohort of Huntington's disease patients over a 5 year period. PLoS Curr. 2010;2:RRN1174.