Neuropsychiatric phenomena in Huntington's disease

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Chapter 1

Introduction

General introduction

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder characterized by neuropsychiatric symptoms, movement disorders, and cognitive deterioration. The familial pattern of the disease was described by George Huntington in his original report in the Medical and Surgical Reporter in 1872,[1] and the genetic defect causing HD was identified in 1993. This genetic defect concerns a mutation in the *HTT* gene and is located on the short arm of chromosome 4.[2] The *HTT* gene normally directs the cell to produce non-mutant huntingtin protein, but HD mutation carriers have an expanded trinucleotide (CAG) repeat in this gene, which leads to the production of mutant huntingtin which is associated with intracellular protein aggregation. The precise mechanisms leading to cell dysfunction and cell death are still unknown.[3] Persons with >36 repeats are considered mutation carriers, whereas a repeat length of 36-39 repeats is called 'incomplete penetrance'.

Over the years, cerebral atrophy develops in HD which is particularly present in the caudate nucleus and putamen, but other brain regions such as the frontal and temporal lobes are also affected.[4] The caudate nucleus and putamen belong to the basal ganglia that play a key role in movement and behavior control. Their functions are complex, and atrophy of these structures appeared to be directly related to movement,[5] cognitive,[6] and neuropsychiatric disturbances.[7]

The age of onset of motor symptoms is mostly in midlife, but the manifestation of neuropsychiatric and cognitive symptoms may precede the motor symptoms by many years.[8] The mean disease duration is about 20 years after the onset of motor symptoms.[9] The most common cause of death is pneumonia, followed by suicide.[10;11] In the Netherlands, the estimated number of HD patients is about 1,700 and approximately 6,000-9,000 are at risk.

Clinical presentation

Motor symptoms are the most obvious and distinguishing characteristics of HD, and may include chorea, dystonia, bradykinesia, dysarthria, and abnormal ocular movements.[3] During the course of the disease, cognitive symptoms may appear, although subtle cognitive impairments may already be present before the onset of the more noticeable motor symptoms. Frequently encountered cognitive impairments in HD are poor attention, cognitive slowing, mental inflexibility, problems with planning, and memory impairments.[6]

Both formal psychiatric disorders such as depressive and anxiety disorders, and typical neuropsychiatric features such as apathy and irritability are frequently present in HD mutation carriers.[8;12] The presence of psychopathology has an important negative impact on daily functioning and quality of life for patients and their caregivers.[13] Reported prevalences of the different psychiatric disorders in HD mutation carriers vary widely depending on the methodology,

assessment tools, and disease stages examined. The prevalence of depression varies between 33 and 69%,[8;12;14-17] and of anxiety disorders between 34 and 61%,[8;12;14;15;17], with lower prevalences in studies using formal DSM-IV criteria. The prevalence of obsessive compulsive disorder (OCD) is mildly increased in HD mutation carriers compared to non-carriers, with prevalences between 10 and 16%,[12;17] whereas other studies described an increased frequency of obsessive compulsive behaviors and perseverations but did not find an increased prevalence of OCD.[18] The prevalence of psychotic symptoms is lower: 3 to 11%.[8;12;14;17]

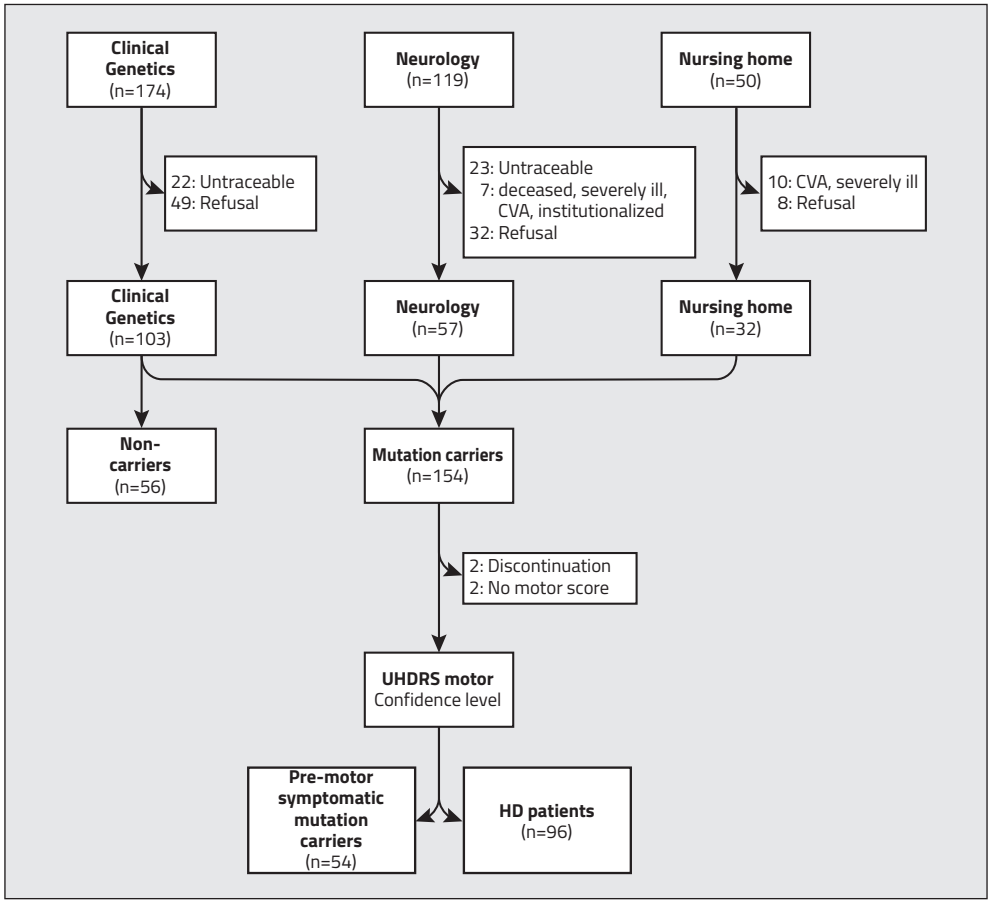
Apathy and irritability are neuropsychiatric features that frequently occur in HD mutation carriers. Apathy is defined as a disorder of motivation in various domains of daily living. Reported prevalences vary between 34 and 76%.[19] Apathy is the only neuropsychiatric symptom in HD that increases with disease progression, both in presence and severity.[20] Since apathy may also be one of the symptoms of a depressive disorder, diagnostic assessment may be complicated. Irritability is best defined as a temporary mood state, characterized by impatience, intolerance, and reduced control over temper which usually results in verbal or behavioral outbursts,[21;22] and reported prevalences of irritability vary between 38 and 73%.[8;12;14;17]

Most of the earlier studies reporting on psychiatric disorders and neuropsychiatric symptoms in HD were done in small populations, and only recently several large multinational studies have been started among both pre-symptomatic and symptomatic mutation carriers. In these observational studies motor, cognitive, and neuropsychiatric symptoms are being assessed, and underlying biological changes are investigated.[23-25]

Assessment tools

The use of traditional psychiatric classifications such as the DSM-IV for the assessment of psychiatric disorders in an HD population is hindered by the frequently present comorbid physical problems, like weight loss and sleep disturbances, thereby making the formal diagnoses less applicable in this population. Furthermore, dysarthria, cognitive disabilities and a lack of insight add to diagnostic difficulties. In most studies, the behavioral section of the Unified Huntington's Disease Rating Scale (UHDRS) is used to assess behavioral symptoms.[26] Next to the UHDRS, we used the Problem Behaviors Assessment (PBA) scale for Huntington's disease that was especially developed to measure a variety of neuropsychiatric symptoms which can be present in HD.[12] We additionally used two symptom-specific instruments: the Apathy Scale,[27] and the Irritability Scale.[28] Since HD patients may suffer from a lack of insight, we made use of information of both the mutation carriers themselves and their caregivers, to increase the reliability.

Figure 1. *Flow chart showing inclusion of the 96 study subjects.*



Earlier results

Between May 2004 and August 2006, 206 persons were recruited from the Departments of Neurology and Clinical Genetics of the Leiden University Medical Centre, and from a specialized long-term care facility. They were divided into two groups based on their genetic status (mutation carriers and non-carriers), and mutation carriers were divided in two subgroups based on the presence of motor symptoms using the UHDRS confidence level (pre-motor symptomatic and motor symptomatic mutation carriers) (Figure1). Persons with juvenile onset, concurrent diseases of the central nervous system, inability to speak (mutism or severe dysarthria), or lack of sufficient command of the Dutch language were excluded. Of the initial 206 participants, 122 HD mutation carriers and 41 non-carriers were willing to participate in the follow-up assessment after two years.[29]

Baseline results showed that of the 140 HD mutation carriers, 26% (n=36) had at least one formal DSM-IV diagnosis in the past 12 months.[29] Major depressive disorder (18%) was the most frequent psychiatric disorder in these mutation carriers, next to social phobia (6%), generalized anxiety disorder (5%), and obsessive compulsive disorder (4%). No significant differences were found in the 12-months prevalence of formal psychiatric disorders between pre-motor symptomatic and motor symptomatic mutation carriers, but pre-motor and motor symptomatic mutation carriers had significantly higher prevalences of depressive disorders, generalized anxiety disorder, and obsessive compulsive disorder than the general population.[28] Besides formal DSM-IV diagnoses, neuropsychiatric symptoms were assessed with the Problem Behaviors Assessment (PBA) scale. Using Principal Component Analysis, three different factors were extracted from the PBA: a depression factor, an apathy factor, and an irritability factor.[20] According to these underlying factors of the PBA, mutation carriers, including pre-motor symptomatic persons, showed more depression, apathy, and irritability compared to non-carriers,[29] which is consistent with the findings of a larger study on mutation carriers versus age-matched controls.[24] Although controls, being family members with an a priori 50% risk of HD, had a shared environment during a significant period of their lives, they were not more susceptible to psychopathology than the general population.[20]

Aims of this thesis

The primary aim of this thesis was to assess the presence and course of both formal psychiatric disorders and neuropsychiatric symptoms in HD mutation carriers, and their correlates and predictors, in comparison with non-carriers, at baseline and at two years follow-up.

First, we assessed the course of formal psychiatric diagnoses in a two year follow-up study (chapter 2). Furthermore, we investigated the course of the symptom clusters depression, apathy, and irritability according to the PBA over time (chapter 3). We hypothesized that the scores on the different symptom clusters would increase over time. Using the Apathy Scale, we examined characteristics of apathy in HD mutation carriers (chapter 4), and predictors of apathy at two-year follow-up (chapter 5). Also, we assessed the psychometric qualities of the Irritability Scale and assessed the prevalence of irritability and its clinical correlates in HD (chapter 6). Finally, we analyzed whether motor rigidity co-occurs with rigidity of behavior, in particular with apathy, in HD mutation carriers (chapter 7).

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Chapter 2

Hypokinesia in Huntington's disease co-occurs with executive cognitive dysfunction and adversely affects global functioning

W. Reedeker, R.C. van der Mast, E.J. Giltay, E. van Duijn, R.A.C. Roos.
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Abstract

Besides chorea, hypokinesia is an important motor disturbance in Huntington's disease (HD) but its clinical, neuropsychiatric, and cognitive functioning correlates are largely unknown. This cross-sectional study investigates correlates of hypokinesia in HD and its effect on global functioning. Among 150 HD mutation carriers, 96 patients were clinically motor symptomatic. Hypokinesia was assessed using the motor section of the Unified Huntington's Disease Rating Scale and global functioning was measured using the Total Functioning Capacity (TFC) scale. Neuropsychiatric measures included the Apathy Scale and the Composite International Diagnostic Interview for diagnosis of depression. The Mini Mental State Examination (MMSE) and a composite executive cognitive measure were used to assess global and executive cognitive functioning, respectively. Compared with 45 patients with no or mild hypokinesia, 51 patients with moderate to severe hypokinesia showed a significant difference in most clinical and neuropsychiatric variables and had worse cognitive functioning scores. However, using forward logistic regression analysis, poor executive cognitive functioning was the only independent correlate of hypokinesia (OR 7.33; 95% CI: 2.82–19.0; $p < 0.001$). Hypokinesia score was inversely associated with the TFC score ($p < 0.001$), also after adjusting for chorea, use of antipsychotics, apathy, and global and executive cognitive functioning. In conclusion, the presence of moderate to severe hypokinesia in HD patients co-occurs with executive cognitive dysfunction and adversely affects global functioning.

Introduction

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disorder resulting from an expanded trinucleotide cytosine-adenine-guanine (CAG) repeat (≥36 glutamines) in the *HTT* gene on chromosome 4, coding for the mutant protein huntingtin.[1] The classic phenotype of HD is characterized by motor disturbances, including both hyperkinetic and hypokinetic movements, and a more general but nonspecific impairment of skilled movements.[2] Besides movement disturbances, clinical features of HD include neuropsychiatric symptoms and cognitive dysfunction. The onset of clinical symptoms is usually in the fourth or fifth decade of life, with a mean illness duration of 16 years. The phenomenology and course of HD are remarkably heterogeneous and may show large variations between patients.[3] Whereas chorea is the major motor disturbance in HD, patients may display a decrease in overall daytime motor activity that is suggestive of hypokinesia or paucity of movements.[4] Hypokinesia seems to occur mainly in an advanced disease stage.[5] Predominant neuropsychiatric psychopathology in HD includes depression and apathy. Depression occurs in all disease stages, whereas apathy shows a clear relation with disease progression.[6–8] It is unclear whether specific neuropsychiatric symptoms in HD co-occur with particular motor disturbances. Furthermore, executive cognitive deficits (such as decreased abstract thinking, problem solving, planning, and cognitive speed and flexibility) increase with the progression of HD.[9] It is also unknown whether cognitive dysfunction in HD is associated with the presence of particular motor disturbances.
It is expected that the presence of motor disturbances, such as chorea and hypokinesia, may have a significant effect on global functioning in HD. For example, in 82 HD patients, a strong correlation was found between increased motor disturbances and decreased global functioning;[10] in another study the presence of chorea appeared to correlate with decreased global functioning.[11] However, it is unknown whether the presence of hypokinesia independently contributes to poor global functioning. Therefore, this study investigated clinical, neuropsychiatric, and cognitive correlates of hypokinesia in HD patients who were motor symptomatic. In line with earlier studies, we hypothesized that apathy and executive cognitive dysfunction would be independent correlates of hypokinesia. Furthermore, based on the hypothesis that poor global functioning is an important consequence of hypokinesia, we tested whether hypokinesia is independently associated with global functioning.

Methods

Subjects

In this cross-sectional study, subjects were recruited (May 2004 to August 2006) from the outpatient departments of Neurology and Clinical Genetics of the Leiden University Medical Center (LUMC), and from a regional nursing home (Overduin in Katwijk) with a specialized ward for HD patients. Details of the study design have been reported earlier.[6] Patients with juvenile HD were

not included. This study included 150 HD mutation carriers, comprising 54 premotor symptomatic mutation carriers and 96 motor symptomatic HD patients (Fig. 1). All subjects gave written informed consent. The study was approved by the Medical Ethical Committee of the LUMC.

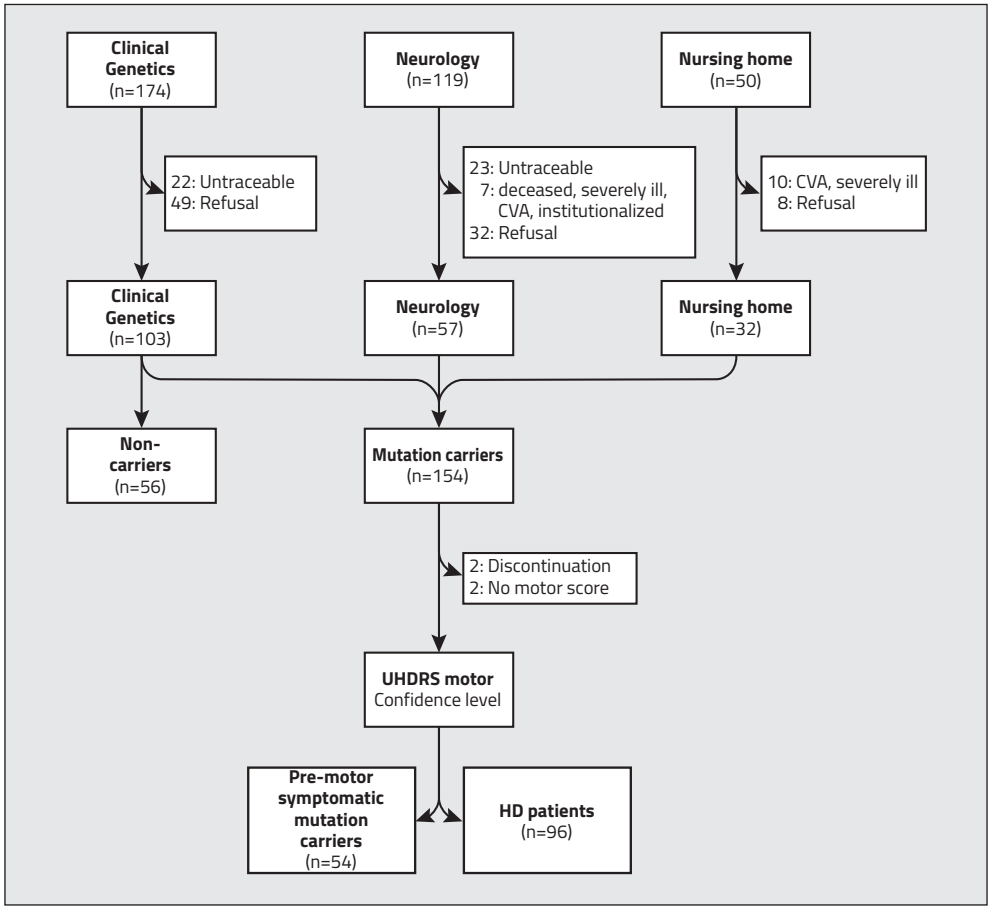
Instruments

Motor assessment was performed by a neurologist with experience in HD, who was blind to the genetic status of each subject. Subjects were rated according to the motor section of the Unified Huntington's Disease Rating Scale (UHDRS-m).[12] The Confidence Level of the UHDRS-m was used to define subjects as premotor symptomatic (Confidence Level score = 0 or 1 points) or motor symptomatic (Confidence Level score = 2–4 points) in agreement with our earlier reports on this study population, although other studies used a confidence level of 4 as being indicative of motor symptomatic mutation carriers.[13] Severity of hypokinesia was rated using eight items of the UHDRS-m that assess reduced movement speed, including: two items for finger tapping (left and right), two items for pronation/supination of the hands (left and right), bradykinesia, presence of rigidity of the left and right arm, and gait abnormalities. The total score ranges from 0–32 points, with higher scores indicating more hypokinesia. Severity of chorea (being a possible confounder for the relation between hypokinesia and clinical, neuropsychiatric and cognitive variables) was rated using the seven items of the UHDRS-m section that assess choreatic movements (face, buccal-oral-lingual region, trunk, and left/right upper and lower extremities), with a total score ranging from 0–28 points, with higher scores indicating more chorea. The presence of depression (major depressive disorder or dysthymia) was assessed with the computerized version of the *Composite International Diagnostic Interview (CIDI, Version 2.1*, Dutch translation),[14] that measures the presence of depression according to the criteria of the *Diagnostic Statistical Manual (DSM)* of mental disorders, *version IV*.[15] Because the CIDI cannot be reliably administered to patients with severe cognitive impairments, the CIDI was not administered to subjects with a score <18 points on the Mini Mental State Examination (MMSE). In these latter subjects, the presence of a depression was assessed clinically, based on the combined information from psychiatric examination, medical reports, and caregivers.

Apathy was assessed using the semistructured Apathy Scale (AS).[16] The AS consists of 14 questions, measuring different features of apathy in the two weeks before the interview. As patients with apathy often lack insight into their own behavior, we also made use of the caregiver's information. The subject and his/ her informant are provided with four possible answers: 0 = not at all, 1 = slightly, 2 = some, and 3 = a lot.

The total score of the AS ranges from 0–42 points, with higher scores indicating more apathy. A total score of ≥14 points on the AS characterizes subjects as being apathetic.[17,18] The MMSE was used to assess global cognitive functioning.[19] Executive cognitive functioning was assessed using the Verbal Fluency Test (VFT), the Symbol Digit Modalities Test (SDMT), and the Stroop Tests. The VFT measures frontal executive dysfunction and semantic memory impairment.[20] The SDMT examines attention, working memory, and visuoverbal substitution speed.[21] The Stroop Tests

Figure 1. *Flow chart showing inclusion of the 96 study subjects.*



measure a person's sustained attention in three conditions: color naming, word reading, and naming the color of ink in an incongruous color name.[22]

Demographic variables (i.e., age, gender, education, marital status) were assessed using a standardized questionnaire. Global daily functioning was assessed using the Total Functioning Capacity (TFC) of the UHDRS.[12] The TFC score ranges from 0–13 points, with lower scores indicating poorer functional abilities.[23]

Statistical Analyses

Data are presented as n (%), means (±SD) or medians (and interquartile ranges, i.e., 25th to 75th percentiles), as appropriate. Chi-square tests for categorical data, *t*-tests for independent samples with normal distributions, or nonparametric Mann–Whitney *U*-tests were used to compare

premotor symptomatic mutation carriers and HD patients. Further analyses were performed only on data from the HD patients, who were divided into two subgroups using the median split of the hypokinesia level, i.e., those with no or mild hypokinesia and those with moderate to severe hypokinesia. For comparison of these two subgroups, univariate logistic regression analysis was performed to calculate odds ratios (OR) with 95% confidence intervals (95% CI) and *p*-values. As the TFC and MMSE scores were not normally distributed, their scores were also dichotomized using a median split for multiple logistic regression analysis. Because of multicollinearity, scores on the VFT, SDMT, and Stroop Tests were standardized, yielding Z scores that were subsequently averaged into an index for executive cognitive functioning (ExCig). ORs for moderate to severe hypokinesia were assessed using forward logistic regression analysis, with a significance level 0.10 for removal and of 0.05 for addition. Age and sex were forced into the model, together with low level of education, use of antipsychotics, presence of chorea and apathy, low MMSE score, and poor executive cognitive functioning as potential predictor variables. As depression can confound the association between apathy and hypokinesia, a sensitivity analysis was conducted to examine the association while excluding patients with a current depressive disorder. Moreover, we repeated our main analysis in the subjects with a confidence level of 4, as this confidence level was used in other studies reporting on motor symptomatic mutation carriers.[13]

Because we also hypothesized that worse global functioning is a consequence of hypokinesia (rather than a possible cause or correlate), TFC was analysed as the independent variable with hypokinesia as the dependent variable, using multinomial logistic regression analysis. The TFC score was categorized into tertiles. These analyses were tested in three models: an unadjusted model; a model adjusted for age, sex, and education; and a model additionally adjusted for the use of antipsychotics, presence of chorea, presence of apathy, performance on MMSE and ExCog. *p*-values were calculated using −2 log-likelihood tests. Scatter plots show the correlations between executive cognitive functioning and hypokinesia, and between hypokinesia and TFC. Linear regression lines are added and Pearson's correlation coefficients and *p*-values are given. All tests were performed in SPSS 17.0 and were done two-sided; a significance level of $p < 0.05$ was applied.

Results

The sociodemographic and clinical characteristics of the 96 HD patients are presented in Table 1. Compared with the 54 premotor symptomatic mutation carriers, the HD patients showed a significant difference on all clinical, neuropsychiatric, and cognitive measures (data not shown).

Using a median split, 45 (47%) HD patients had no or low hypokinesia (UHDRS-hypokinesia score <12 points), whereas 51 (53%) had moderate to severe hypokinesia (UHDRS-hypokinesia score ≥12 points) (Table 2). Compared with subjects with no or mild hypokinesia, univariate regression analysis showed that subjects with moderate to severe hypokinesia were older ($p = 0.04$), had a

lower level of education (p = 0.02), a higher chorea score (p = 0.02), a lower TFC score (p < 0.001), used more antipsychotic medication (p = 0.03), had a higher AS score (p = 0.03), and a lower MMSE score (p < 0.001) and ExCogn score (p < 0.001).

Forward multiple logistic regression analysis showed that diminished executive cognitive functioning was the only significant independent correlate of hypokinesia (OR 7.33; 95% CI: 2.82–19.0, p < 0.001), whereas apathy was not (Table 3). In a sensitivity analysis we repeated our

Table 1. *Sociodemographic and clinical characteristics of the study patients with Huntington's disease (n = 96)*

Sociodemographic characteristics	
Male gender	45 (47)
Age (yr)	51 ±11
Higher level of education[a]	50 (52)
Married or with partner	66 (69)
Clinical characteristics:	
Number of CAG repeats	45 ± 3
UHDRS motor scores	
Hypokinesia score (points)[b]	11 (6–18)
Chorea score (points)[c]	9 (3–16)
TFC score (points)[d]	7 (3–11)
Use of psychotropic medication	50 (52)
Antipsychotics	17 (18)
Antidepressants	35 (37)
Benzodiazepines	30 (31)
Neuropsychiatric characteristics:	
DSM-IV Depressive disorder[e]	4 (4)
Apathy Scale (points)[f]	12 (6–18)
Presence of apathy (AS ≥ 14 points)	41 (43)
High alcohol useg	8 (8)
Cognitive characteristics:	
MMSE score (points)h	26 (22–28)
VFTi	14 (7–22)
SDMTj	20 (9–35)
Stroop color-test[k]	35 (25–50)
Stroop word-test[k]	52 (35–74)
Stroop interference-test[k]	19 (10–30)
Executive cognitive functioning[l] (Excog)	−0.48 ± 0.82

Data are presented as n (%), mean (±SD) or median (interquartile range [IQR]) when appropriate.
[a] Higher level of education is ≥12 years of education.
[b] UHDRS hypokinesia score range from 0–32 points.
[c] UHDRS chorea score range from 0–28 points.
[d] Total Functioning Capacity score ranges from 0–13 points.
[e] Presence of depression or dysthymia according to CIDI.
[f] Apathy scale ranges from 0–42 points, with a score ≥14 indicating presence of apathy syndrome.
[g] alcohol use was considered high if >14 consumptions a week were consumed.
[h] Mini Mental State Examination tests global cognitive functioning.
[i] Verbal Fluency Test counts the number of words the patient can come up with.
[j] Symbol Digit Motor Test ranges from 0–110.
[k] Stroop tests range from 0–100.
[l] Executive cognitive function is defined by 5 index z scores derived from the SDMT, VFT and Stroop tests.

Table 2. *Sociodemographic and clinical correlates for hypokinesia in 96 patients with Huntington's disease*

	Mild hypokinesia* n = 45	Severe hypokinesia** n = 51	Univariate logistic regression OR (95% CI)	*p*-value
Sociodemographic characteristics:				
Male gender	22 (49)	23 (45)	0.86 (0.38–1.92)	0.71
Age in years	49 ± 10	54 ± 11	1.04 (1.00–1.08)	0.04
Higher level of education[a]	29 (64)	21 (41)	0.39 (0.17–0.88)	0.02
Married or with partner	35 (78)	31 (61)	0.44 (0.18–1.09)	0.44
Clinical characteristics:				
Number of CAG repeats > 44	18 (32)	27 (53)	1.69 (0.75–3.80)	0.21
Chorea score > 9 points[b]	32 (71)	46 (90)	3.74 (1.21–11.5)	0.02
TFC score < 7 points[c]	8 (18)	41 (80)	19.0 (6.77–53.1)	<0.001
Use of psychotropic medication	20 (44)	32 (63)	2.53 (1.11–5.76)	0.03
Antipsychotics	4 (9)	13 (26)	3.51 (1.05–11.7)	0.04
Antidepressant	16 (36)	19 (37)	1.08 (0.47–2.48)	0.86
Benzodiazepines	10 (22)	20 (39)	2.26 (0.92–5.55)	0.08
Psychiatric characteristics:				
DSM-IV Depressive disorder[d]	2 (4)	2 (5)	1.83 (0.32–10.5)	0.50
Apathy[e]	14 (31)	27 (53)	2.49 (1.08–5.75)	0.03
Cognitive characteristics:				
MMSE < 26 points[f]	14 (31)	33 (65)	8.05 (2.70–24.0)	<0.001
VFT < 14[g]	10 (22)	38 (75)	10.2 (3.98–26.3)	<0.001
SDMT < 20[h]	7 (16)	41 (80)	22.3 (7.70–64.4)	0.005
Stroop Color test < 35[i]	10 (22)	38 (75)	10.2 (3.98–26.3)	<0.001
Stroop Word test < 52[i]	10 (22)	38 (75)	10.2 (3.98–26.3)	<0.001
Stroop Interference test < 19[i]	15 (33)	35 (69)	4.38 (1.86–10.3)	0.005
ExCog < 0[j]	10 (22)	38 (75)	10.2 (3.98–26.3)	<0.001

Data are presented as n (%), mean (±SD) or median (interquartile range [IQR]) when appropriate.
*Mild hypokinesia was defined as a score of 0–11 points out of 32 and
**severe hypokinesia as a score of 12–32 points out of 32.
[a] Higher level of education is ≥12 years of education.
[b] UHDRS chorea score range from 0–28 points.
[c] Total Functioning Capacity score ranges from 0–13 points.
[d] Presence of depression or dysthymia according to CIDI.
[e] Apathy Scale with a score ≥14 indicating presence of apathy.
[f] Mini Mental State Examination, tests global cognitive functioning.
[g] Verbal Fluency Test counts the number of words the patient can come up with.
[h] Symbol Digit Motor Test ranges from 0–110.
[i] Stroop tests range from 0–100.
[j] Executive cognitive function is defined by 5 index z scores derived from the SDMT, VFT and Stroop tests.

analysis while excluding the four depressed subjects, which did not affect the strong relationship between hypokinesia and executive cognitive functioning (OR 8.23; 95% CI: 3.05–22.2). Also, the sensitivity analysis in the 84 subjects with a confidence level of 4 resulted in a similar adjusted odds ratio for the relationship between poor executive cognitive function and hypokinesia (OR 5.05; 95% CI: 1.89–13.5; $p = 0.001$).

Table 3. *Independent correlates of hypokinesia in 96 patients with Huntington's disease*

	No to mild hypokinesia n = 45	Moderate to severe hypokinesia n = 51	*p*-value
Male sex	1.00	0.99 (0.38–2.50)	0.98
Age	1.00	1.02 (0.98–1.07)	0.39
Poor executive cognitive function	1.00	7.33 (2.82–19.0)	<0.001

Odds ratios for moderate to severe hypokinesia were assessed using forward logistic regression analysis, with age and sex forced into the model, and low level of education, use of antipsychotics, presence of chorea and apathy, low MMSE score, and poor executive cognitive functioning as potential predictor variables. Poor executive cognitive function is defined by a score <0 for the mean of 5 index Z scores derived from the SDMT, VFT, and Stroop tests.

Table 4. *Data on tertiles of total functioning capacity (TFC) according to moderate to severe hypokinesia in 96 patients with Huntington's disease*

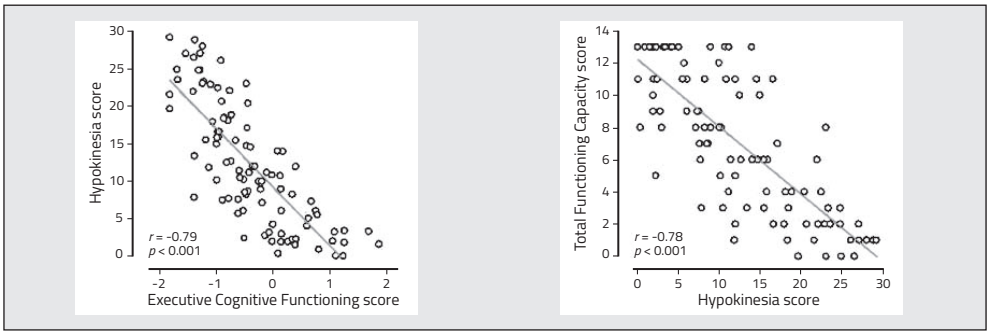
	Tertiles of TFC			
	1 n = 34	2 n = 31	3 n = 31	*p*-value
TFC, median (range)	13 (11–13)	8 (5–10)	2 (0–4)	
Cases of hypokinesia, n (%)	2 (5.9%)	19 (61.3%)	24 (77.4%)	
Unadjusted	1.00	25 (5–125)	55 (10–287)	<0.001
Adjusted[a]	1.00	24 (5–120)	50 (9–267)	<0.001
Fully adjusted[b]	1.00	32 (4–258)	37 (4–353)	<0.001

Data are given as odds ratios (95% confidence intervals) unless otherwise specified.
Odds ratios for tertiles of TFC according to hypokinesia were calculated by multinomial logistic regression analysis (with unadjusted and adjusted models), and *p*-values by 22 log likelihood tests.
[a] Adjusted for age, sex, and education.
[b] Additionally adjusted for use of antipsychotics, presence of chorea and apathy, MMSE score and executive cognitive function score.

Multinomial logistic regression analysis showed that a moderate to high hypokinesia score was strongly and inversely correlated with the TFC score. Furthermore, a moderate to high hypokinesia score was found in 77.4% of the group with the lowest tertile of the TFC score, compared with only 5.9% of the group with the highest tertile of the TFC score (Table 4). Adjustment for age, sex, education, use of psychotropic medication, chorea, apathy, global, and executive cognitive functioning, had no effect on these results (higher vs. lower tertile OR: 37; 95% CI: 4–353, $p < 0.001$).

Similarly, using linear univariate regression analyses, a strong correlation was found between the continuous scores of hypokinesia and ExCogn ($r = -0.79$; $p < 0.001$), and between the TFC score and hypokinesia ($r = -0.78$; $p < 0.001$) (Fig. 2).

Figure 2. *Scatter plot showing correlations between hypokinesia score and executive cognitive functioning score, and between TFC and hypokinesia. Univariate regression lines are shown. Pearson's correlation coefficients and p-values are given.*



Discussion

In this study, only executive cognitive dysfunction proved to be an independent correlate of hypokinesia. Compared to those with mild or no hypokinesia, HD patients with moderate to severe hypokinesia were more likely to be older, to have a lower level of education, to more often use antipsychotic medication, and to have more choreatic motor disturbances. In addition, they were more often afflicted by apathy and performed less well on global and executive cognitive tests. In accordance with our hypothesis, patients with moderate to severe hypokinesia indeed showed worse global functioning compared with the subjects with no or mild hypokinesia. This was independent of the presence of apathy, chorea, and diminished executive cognitive functioning.

However, in contrast to our expectations, apathy was not an independent correlate of hypokinesia whereas executive cognitive dysfunction was. In HD, apathy as well as cognitive dysfunction have been related to hypokinesia. In two studies comparing hyperkinetic movement disorders, including HD with hypokinetic movement disorders, a relationship was found between hypokinesia, hypoactive behavior (a construct that overlaps with apathy), and poor global cognitive dysfunction.[24,25] However, in these studies that considered HD as a hyperkinetic disorder, hypokinetic motor symptoms were not taken into account. Also, only global functioning, and not executive cognitive functioning, was measured. Therefore, these latter studies do not allow to draw conclusions about associations between particular motor disturbances in HD on one hand and neuropsychiatric symptoms and cognitive dysfunction on the other. Disease progression, corresponding to increased hypokinesia, apathy and executive cognitive dysfunction have earlier been linked in HD patients,[10] whereas in this study the strong correlation between executive cognitive dysfunction and hypokinesia may have "hidden" the effect of apathy on hypokinesia.

A possible explanation for the strong association between executive cognitive dysfunction and hypokinesia might be that, in HD, executive cognitive dysfunction may (as in hypokinesia) be related to basal ganglia pathology and disturbances in frontal-subcortical circuitry. Second, both phenomena may be attributed to underlying brain pathology developing in parallel; in that case hypokinesia and executive cognitive dysfunction merely co-occur. Third, HD patients with hypokinesia may perform less well on executive cognitive tests because some of these tests also require adequate motor performance.

In this study, hypokinesia was strongly correlated to a decreased TFC score. This is in line with another study reporting bradykinesia (or hypokinesia) to be the best predictor of HD disease stage according to the TFC score.[26] In our study, the effect of hypokinesia on global functioning was independent of the presence of chorea; this concurs with an earlier study reporting chorea to be associated with global functioning in early stage, but not late stage, HD.[27] Thus, hypokinesia may cause major impairments in global daily functioning, thereby contributing to increased distress among caregivers and perhaps earlier institutionalization of HD patients.

The strengths of this cross-sectional study are the relatively large number of HD patients, the detailed clinical information, and the use of specific and validated measurement tools in a standardized interview. However, some limitations need to be addressed. First, because this was a cross-sectional study, no inferences can be drawn about the temporal relationship between hypokinesia on one hand and cognitive dysfunction on the other. Second, neither the UHDRS subscales measuring different motor disturbances nor the cut-off scores for the presence of different motor disturbances have been accurately defined or validated. Therefore, we had to use the median split of the total scores of hypokinesia and chorea.

In conclusion, our findings indicate that, in patients with HD, hypokinesia co-occurs in particular with executive cognitive dysfunction but not with apathy, and has an adverse effect on global functioning in daily life. Prospective studies are needed to clarify the temporal relationship between hypokinesia and executive cognitive dysfunction, thereby making use of cognitive function tests that do not necessarily require adequate motor performance. This approach will avoid the influence of motor disturbances when assessing executive cognitive function in patients with HD.

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Chapter 3

Correlates of apathy in Huntington's disease

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Abstract

Objective: To study prevalence and clinical correlates of apathy in Huntington's disease.
Method: Apathy was defined as an Apathy Scale (AS) score ≥ 14 points in 152 Huntington's disease mutation carriers and 56 non-carriers. Correlates of apathy were analyzed cross-sectionally in mutation carriers using multivariable logistic regression analysis.
Results: Forty-nine (32%) Huntington's disease mutation carriers showed apathy compared to none of the non-carriers. After exclusion of 10 depressed subjects, apathy was independently associated with male sex, worse global functioning and higher use of neuroleptics and benzodiazepines.
Conclusion: Next to being male and worse global functioning, use of psychotropic medication was associated with apathy in Huntington's disease patients.

Introduction

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disorder resulting from an expanded trinucleotide cytosine-adenine-guanine (CAG) repeat (≥ 36 glutamines), coding for the mutant protein huntingtin on chromosome 4p16.3.[1] Symptomatic treatment is widely available although no cure is possible. Clinical features of HD consist of movement, neuropsychiatric, and cognitive disorders. Disease progression causes a decline of daily functioning and patients ultimately become totally dependent on the help of others.

Apathy is a common neuropsychiatric feature of HD.[2-4] Reported prevalences of apathy in HD vary from 34% to 76%, depending on disease stages examined and assessment methods used,[5] and its prevalence and severity increase with disease progression.[6] Apathy has been described both as a symptom (i.e. of mood disorder, altered level of consciousness, or cognitive impairment), and as a syndrome.[7,8] An apathy syndrome is defined as a disorder of motivation; with loss of or diminished goal-directed behavior, cognitive activity, and/or emotion; as wells as functional impairments that are attributable to the apathy.[9,10] Clinically, apathy has been related to decline in activities of daily living (ADL) causing a great burden of disease and distress in caregivers,[11] also after adjusting for the presence of motor and cognitive deficits.[12,13]

In the present study, we aimed to assess the prevalence of apathy in HD mutation carriers and control non-carriers. Furthermore, we investigated sociodemographic, clinical and neuropsychiatric correlates of apathy comparing HD mutation carriers with apathy to those without apathy.

Method

Subjects

Between May 2004 and August 2006, HD mutation carriers were recruited from the out-patient departments of Neurology and Clinical Genetics of the Leiden University Medical Center (LUMC), and from a regional nursing home. Subjects with a CAG repeat length of 36 or more repeats were considered positive for HD mutation carriership.

The design of the study has been described in detail elsewhere.[14] In short, of 361 known subjects, 45 out-patients were untraceable, 17 subjects were excluded or were deceased, and 89 refused to participate because of various reasons. Fifty-six subjects appeared to be non-carriers. After the assessment, two more subjects were excluded because of a missing motor score. Thus, 152 HD mutation carriers and 56 non-carriers were included in the present analysis. All subjects gave written informed consent. The study was approved by the Medical Ethical Committee of the LUMC.

Instruments

Assessment of apathy

Apathy was assessed using the semi-structured Apathy Scale (AS) (Figure 1).[15] The AS is a modified version of the Apathy Evaluation Scale (AES),[7] and consists of 14 questions read by the interviewer, measuring different features of apathy in the two weeks prior to the interview. As patients with apathy often lack insight into their behavior, we also used caregivers' information. The subject and his/her informant are provided with four possible answers: 'not at all', 'slightly', 'some', and 'a lot'. The total score of the AS ranges from 0 – 42 points, with higher scores indicating greater apathy. The AS has shown good interrater reliability, good test-retest reliability, as well as high internal consistency in patients with Parkinson's disease.[15] We used an AS total score ≥ 14 points to characterize subjects as apathetic, and those scoring below this cut-off score as non-apathetic.[15,16]

Figure 1. *Apathy Scale, patient version*

	Not at all	slightly	some	a lot
1. Are you interested in learning new things?	3	2	1	0
2. Does anything interest you?	3	2	1	0
3. Does someone have to tell you what to do each day?	0	1	2	3
4. Are you concerned about your condition?	3	2	1	0
5. Are you indifferent to things?	0	1	2	3
6. Do you put much effort into things?	3	2	1	0
7. Are you always looking for something to do?	3	2	1	0
8. Do you have plans and goals for the future?	3	2	1	0
9. Do you have motivation?	3	2	1	0
10. Do you have energy for daily activities?	3	2	1	0
11. Are you unconcerned with many things?	0	1	2	3
12. Do you need a push to get started on things?	0	1	2	3
13. Are you neither happy nor sad, just in between, no matter what happens?	0	1	2	3
14. Would you consider yourself to be apathetic?	0	1	2	3

Sociodemographic and clinical characteristics

Information on sociodemographic and clinical characteristics of mutation carriers and controls was collected in a standardized manner. Global functioning was assessed with the Total Functioning Capacity (TFC) scale of the Unified Huntington's Disease Rating Scale (UHDRS).[17] The TFC scale consists of five questions assessing employment, capacity to handle financial affairs, to manage domestic chores, to perform activities of daily living, and the care level provided (range 0 – 13 points, lower scores indicate poorer functional abilities).[18]

Assessment of motor function

Neurological examination was done by a neurologist with experience in HD, blind for the genetic status of the subject and according to the motor section of the Unified Huntington's Disease Rating Scale (UHDRS-m).[17] The UHDRS-m consists of 15 items that are rated on a scale from 0 (normal) to 4 (severe) points. The total UHDRS-m score is the sum of all individual motor ratings (total score range 0 – 124 points; higher scores indicating worse motor performance).

The Confidence Level (CL) of the UHDRS-m was used to define subjects as pre-motor symptomatic (CL score = 0 or 1 points) or motor symptomatic (CL score = 2 – 4 points).

Assessment of depression

Composite International Diagnostic Interview

Because symptoms of apathy may overlap with depression, we assessed the presence of depression (major depressive disorder and dysthymia) according to the criteria of the Diagnostic Statistical Manual (DSM) of mental disorders, Version IV.[19] Psychiatric assessment was done by a psychiatrist (EvD) or a trained research assistant under his supervision. Raters for psychiatric and cognitive function were informed about the genetic status of the subjects, because non-disclosure could considerably influence subjects' answering to questions about symptoms that are directly related to mutation carriership.

The Dutch translation of the computerized version of Composite International Diagnostic Interview (CIDI, Version 2.1) was used to classify depression according to DSM-IV criteria.[20] The CIDI was not administered in subjects with score < 18 points on the Mini-Mental State Examination (MMSE), since the CIDI cannot be reliably administered to patients with such a severe cognitive dysfunction. In these subjects the presence of a depression was assessed clinically, based on the psychiatric examination, medical reports, and information of caregivers.

Neuropsychological assessment

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

The MMSE consists of 11 items that has been found to be reliable and valid in assessing global cognitive function. Scoring range of the MMSE is 0 – 30 points with lower scores indicating worse global cognitive performance.[21]

The SDMT examines attention, working memory, and visuoverbal substitution speed.[22] Subjects have 90 seconds to write down the number that matches each of the geometric figures, which are printed on several lines.

The VFT is sensitive to frontal executive dysfunction and subtle degrees of semantic memory impairment.[23] Subjects are instructed to generate as many words as possible in one minute. A total VFT score of less than 30 words is considered abnormal.

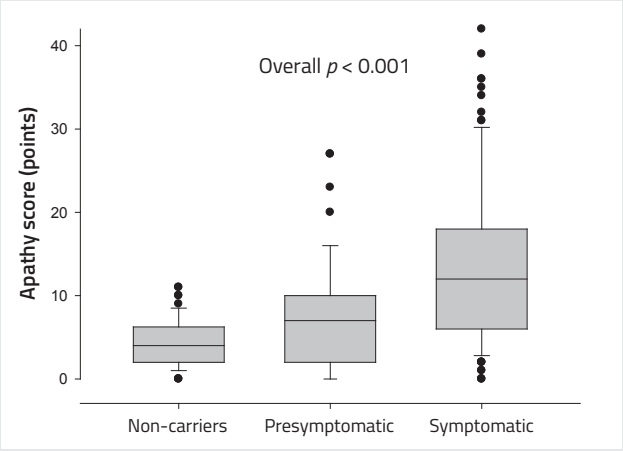
The Stroop Color-Word test was used to measure a person's sustained attention in three conditions: color naming, word reading, and naming the color of the ink of an incongruous color name (interference).[24] For each condition the subject had 45 seconds and the total of all right answers was scored, with maximum 100 points per condition.

Statistical analyses

Data are presented as n (%), mean (± SD) or median (interquartile range [IQR], i.e. 25th to 75th percentiles) when appropriate. Chi-square tests for categorical data. *t*-tests for independent samples with normal distributions, or non-parametric Mann-Whitney *U*-tests were conducted to compare mutation carriers and non-carriers. Mutation carriers with and without apathy were compared to determine correlates of apathy using univariate logistic regression analyses. Odds ratio's (OR) and their corresponding 95% confidence interval (CI) were computed. TFC, UHDRS-m, MMSE, SDMT, VFT and Stroop Color-Word test scores were divided into two groups using a median split. A *p*-value < 0.05 was considered statistically significant.

Because of a strong collinearity between the SDMT, VFT, and Stroop Color-Word test, a new variable for executive cognitive function (ExCogn) was computed by averaging the 4 index z-scores (i.e. subtracting the mean from an individual raw score and then dividing the difference by the standard deviation).

Figure 2. *Box plot showing Apathy Scale scores of non-carriers, pre-motor symptomatic and motor symptomatic mutation carriers.*



The line within the box represents the median; the boundaries of the box represent the inter-quartile range, while the error bars represent the 10th and 90th percentile values.
The three groups were significantly different with the non-parametric Kruskal-Wallis test (overall $p < 0.001$), while all three groups differed from the other groups in Mann-Whitney tests in 3 post-hoc comparisons between two groups (all $p < 0.05$).

Table 1. *Sociodemographic, clinical, and neuropsychiatric characteristics of Huntington's disease in mutation carriers and non-carriers*

	Mutation carriers n = 152	Non-carriers n = 56	*p*-value*
Sociodemographic and clinical characteristics			
Male gender (n, %)	68 (45%)	25 (45%)	1.00
Age (years ± SD)	47.2 ± 11.9	39.7 ± 11.2	< 0.001
Higher level of education[a] (n, %)	92 (61%)	42 (75%)	0.05
Married or with partner (n, %)	98 (65%)	46 (82%)	0.18
CAG repeats (number ± SD)	44.1 ± 3.1	21.0 ± 4.8	< 0.001
Neuropsychiatric characteristics			
AS[b] (points, IQR)	10 (5 – 16)	4 (2 – 6)	< 0.001
AS ≥ 14 (n, %)	49 (32%)	0	-
DSM-IV[c] depression (n, %)	8 (5%)	0	-

Data are presented as n (%), mean (± SD) or median (interquartile range [IQR]) when appropriate.
**P*-values by chi-square tests for categorical data, by *t*-test for independent samples with normal distributions, or non-parametric Mann-Whitney U tests.
[a] Higher level of education: ≥ 12 years of education.
[b] AS = Apathy Scale.
[c] DSM-IV = Diagnostic Statistical Manual of mental disorders, Version IV.

Multiple logistic regression analysis, identified by a forward stepwise selection procedure, was used to determine the independent correlates of apathy. For this analysis, the following variables with *p*-value < 0.05 in the univariate regression analysis were used: sex, age, TFC score, UHDRS-m score, use of antidepressants, use of neuroleptics, use of benzodiazepines, presence of depression, MMSE score, and ExCogn score. The overall use of psychotropic medication was not entered, because of the inclusion of the three medication subcategories. Statistical analysis was carried out by means of the Statistical Package for the Social Sciences (SPSS) for Windows, release 16.0.

Results

Sociodemographic and clinical characteristics of HD mutation carriers versus non-carriers

The sociodemographic, clinical, and neuropsychiatric characteristics of 152 HD mutation carriers and 56 non-carriers are shown in Table 1. Mutation carriers were older and had significantly more symptoms of apathy than non-carriers (Table 1). Mutation carriers also had more often a formal DSM-IV diagnosis of depression compared to non-carriers. Assessment of the CIDI was not possible in 12 mutation carriers because of severe cognitive impairment (MMSE < 18 points). Using information of caregivers, medical reports and clinical impression during the assessment, 2 of these 12 mutation carriers were diagnosed as depressed.

Mutation carriers with motor symptoms showed significantly more symptoms of apathy than pre-motor symptomatic mutation carriers and non-carriers, and pre-motor symptomatic mutation carriers showed significantly more symptoms of apathy than non-carriers (all $p < 0.001$) (Figure 2).

HD mutation carriers with and without apathy

Forty-nine mutation carriers (32%) were considered apathetic (median AS score = 20 points; IQR = 16 – 27), whereas 103 mutation carriers (68%) were not (median AS score = 7 points; IQR = 3 – 10) (Table 2).

Univariate regression analysis showed that, in comparison with non-apathetic mutation carriers, apathetic subjects were more often male and older, had a lower TFC score, a higher UHDRS-m total score, used more psychotropic medication, were diagnosed more often as depressed, and showed worse global and executive cognitive function.

Table 2. *Sociodemographic, clinical, and neuropsychiatric characteristics as predictors of apathy in Huntington's disease mutation carriers*

	No apathy n = 103	Apathy* n = 49	Univariate logistic regression OR (95% CI)	*p*-value**
Sociodemographic characteristics				
Male (n, %)	40 (39%)	28 (57%)	2.10 (1.05–4.19)	0.04
Age (years ± SD)	45.5 ± 11.3	50.8 ± 12.3	1.04 (1.01–1.07)	0.01
Higher level of education (n, %)	66 (64%)	26 (53%)	0.62 (0.31–1.24)	0.18
Married or with partner (n, %)	35 (34%)	19 (39%)	1.23 (0.61–2.49)	0.56
Clinical characteristics				
CAG repeats (number ± SD)	44.0 ± 3.1	44.2 ± 3.2	1.02 (0.92–1.14)	0.71
TFC [a] [< 11 points] (n, %)	39 (38%)	37 (76%)	5.06 (2.36–10.9)	< 0.001
UHDRS-m[b] [> 15 points] (n, %)	43 (42%)	36 (74%)	4.02 (1.91–8.48)	< 0.001
Use of psychotropic medication (n, %)	27 (26%)	35 (71%)	7.04 (3.29–15.0)	< 0.001
- Antidepressants (n, %)	19 (18%)	24 (49%)	4.24 (2.01–8.98)	< 0.001
- Neuroleptics (n, %)	5 (5%)	13 (27%)	7.08 (2.36–21.3)	< 0.001
- Benzodiazepines (n, %)	14 (14%)	22 (45%)	5.18 (2.34–11.5)	< 0.001
Neuropsychiatric characteristics				
AS [c] (points, IQR)	7 (3–10)	20 (16–27)	–	< 0.001
DSM-IV [d] depression (n, %)	1 (1%)	7 (14%)	21.9 (2.59–184)	< 0.001
MMSE [e] [< 27 points] (n, %)	49 (48%)	34 (69%)	2.60 (1.26–5.34)	0.01
SDMT [f] [< 34 points] (n, %)	41 (40%)	35 (71%)	3.78 (1.81–7.88)	< 0.001
VFT [g] [< 19 points] (n, %)	42 (41%)	34 (69%)	3.29 (1.60–6.79)	0.001
Stroop-Color [< 50 points] (n, %)	41 (40%)	33 (67%)	3.12 (1.53–6.38)	0.002
Stroop-Word [< 72 points] (n, %)	40 (39%)	36 (74%)	4.36 (2.07–9.21)	< 0.001
Stroop-Interference [< 29 points] (n, %)	41 (40%)	34 (69%)	3.43 (1.66–7.07)	0.001
ExCogn [h] [< 0.05] (n, %)	42 (41%)	34 (69%)	3.29 (1.60–6.79)	0.001

Data are n (%) or mean (± SD) when appropriate.
Odds ratio's (OR) and the corresponding 95% confidence interval (CI) are provided.
* Apathy was defined as an Apathy Scale score ≥ 14 points.
** *P*-values by univariate logistic regression analysis, or non-parametric Mann-Whitney U tests.
[a] TFC = Total Functional Capacity; [b] UHDRS-m = Unified Huntington's Disease Rating Scale, motor section; [c] AS = Apathy Scale; [d] DSM-IV = Diagnostic Statistical Manual of mental disorders, Version IV; [e] MMSE = Mini-Mental State Examination; [f] SDMT = Symbol Digit Modality Test; [g] VFT = Verbal Fluency Test; [h] ExCogn = executive cognitive function defined by 5 index z-scores derived from SDMT, VFT, and Stroop tests).
TFC, UHDRS-m, MMSE, SDMT, VFT, Stroop tests, and ExCogn scores are divided into two groups using a median split.

Table 3a. *Independent predictors of apathy in 49 Huntington's disease mutation carriers.*

	No apathy Reference n = 103	Apathy OR (95% CI) n = 49	*p*-value*
Male sex	1.00	2.46 (1.05–5.78)	0.04
Use of antidepressants	1.00	2.72 (1.13–6.55)	0.03
Use of neuroleptics	1.00	4.40 (1.20–16.1)	0.03
Depression	1.00	23.84 (2.40–237)	0.007

Table 3b. *Independent predictors of apathy in 40 Huntington's disease mutation carriers, after exclusion of 10 subjects with a depression.*

	No apathy Reference n = 102	Apathy OR (95% CI) n = 40	*p*-value*
Male sex	1.00	2.73 (1.15–6.50)	0.02
TFC score (Total Functional Capacity)	1.00	2.88 (1.18–7.07)	0.02
Use of neuroleptics	1.00	3.64 (1.01–13.1)	0.048
Use of benzodiazepines	1.00	2.91 (1.07–7.86)	0.04

Odds ratio's (OR) and the corresponding 95% confidence intervals (CI) are provided.
**P*-values by multivariate forward logistic regression.
TFC = Total Functional Capacity.

Independent correlates of apathy in HD mutation carriers

Using logistic regression analysis male sex, higher use of both antidepressants and neuroleptics, and the presence of depression were statistically significant independent correlates of apathy in a multivariable analysis (Table 3a).

In addition, a sensitivity analysis was conducted to evaluate the robustness of our model and to eliminate the possibility of confounding influences of depression on the correlates of apathy. As described above, eight subjects had a formal diagnosis of depression according to the CIDI (7 subjects in the apathetic group and 1 subject in the non-apathetic group), and 2 without the CIDI assessment were clinically depressed (both in the apathetic group). After exclusion of these 10 subjects with depression, higher use of antidepressants was no longer independently associated with the presence of apathy. However, male sex and higher use of neuroleptics were still independent predictors of apathy, together with lower TFC score, and higher use of benzodiazepines (Table 3b).

Discussion

The results of our study confirm that apathy frequently occurs in HD with a prevalence of 32% in mutation carriers compared to 0% in non-carriers. Mutation carriers with apathy were more

likely to be male, of older age, and were using more psychotropic medication. When comparing mutation carriers with apathy to those without apathy, significantly more depression, worse total functioning with more severe motor and cognitive symptoms, and increased use of psychotropic medication was shown. After exclusion of mutation carriers with depression, the independent associations with the presence of apathy in HD mutation carriers were male sex, worse global functioning, higher use of neuroleptics, and higher use of benzodiazepines.

Apathy and depression

The relationship between apathy and depression varies across diagnostic groups and depends on assessment tools used.[25] Apathy can be a clinical sign of depression, but can also occur independently. In HD, apathy has been shown to be associated with the presence of depressed mood,[3] but inconsistently.[26,27,11] Contrary to our findings, one other study using the CIDI found no association between a formal diagnosis of depression and apathy in patients with traumatic brain injury.[28] In another study applying a factor analysis of the Montgomery and Åsberg Depression Rating Scale (MADRS)[29] in patients with acquired brain damage, 'negative symptoms' of depression were highly associated with apathy, whereas 'depressed mood' or 'somatic symptoms' were not.[30]

Apathy and the use of psychotropic medication

The presence of apathy was associated with higher use of different types of psychotropic medication. The association with the use of antidepressants – not surprisingly – disappeared after the exclusion of subjects with depression. Higher use of neuroleptics remained independently predictive, together with higher use of benzodiazepines.

Since this study has a cross-sectional design, we cannot conclude whether the use of psychotropic medication is a cause or consequence of apathy. In clinical practice, antidepressants may be prescribed as a treatment for apathy, but in our study their use seems to be related to presence of depression. Development of apathy as a side-effect of the use of neuroleptics and benzodiazepines is very well possible, due to their blunting and sedative effects, which may result in lethargy and fatigue.

Furthermore, distinguishing apathy from depression is of clinical importance because of potential differences in the use of pharmacological and non-pharmacological interventions. Pharmacotherapy for depression may improve the clinical profile, but can also have a counteractive effect on apathy.[31] For example, serotonin reuptake inhibitors may increase apathy and withdrawal from engagement with the environment.[32]

To date, no specific treatments for apathy are known. Preliminary studies suggest that apathy may respond to pharmacotherapy with stimulants, dopamine agonists, acetylcholinesterase inhibitors, or NMDA-receptor antagonists.[33,34]

Apathy and cognitive function

Using univariate analysis we found an association between presence of apathy and worse cognitive function. This result is in line with a previous study among patients with early HD, that found severe deficits in attention, executive function, and episodic memory to be related to apathy.[35] In other neurodegenerative disorders, an association between apathy and cognitive dysfunction has also been described. For example, apathy correlated with initiation-perseveration in subjects with progressive supranuclear palsy,[36] and a correlation between apathy and worse performance on several cognitive tests among which executive cognitive function in Parkinson's disease has been reported.[27] Also, in Alzheimer's disease, patients with apathy performed worse on the SDMT and the Stroop-Interference test, than those without apathy.[37]

In patients with dementia and apathy, a faster cognitive and functional decline has been found compared to patients without apathy.[34] In an earlier study,[6] we found significantly more apathy in advanced stage HD. Therefore, apathy may be a sign of disease progression in HD, including progressive motor and cognitive impairments, and worse global functioning, but longitudinal studies are needed to investigate precise relationships.

The strengths of this study are a relatively large study population with HD, the use of a comparison group, and the use of specific and validated measurement tools in a standardized interview. However, there are some limitations that warrant discussion. First, this study involved the analysis of cross-sectional data which precludes conclusions about the direction of causality. Second, as discussed before, assessment of the AS was done during a clinical interview with the mutation carrier and an informant, whereas the CIDI was assessed in absence of the informant. This may have reduced the validity of the CIDI assessment, as HD patients may have a lack of insight into their own behavior and feelings. Another limitation was that some of the explanatory variables were rather strongly intercorrelated and that the automated variable selection method in the logistic regression may therefore have produced models of somewhat limited stability. Further, all subjects volunteered to participate in this study, which may have led to an underestimation of the prevalence of apathy in HD patients due to selection bias, as subjects who did not respond to the invitation to participate in the study may have been more apathetic.

We conclude that apathy is highly prevalent in HD and is strongly associated with the presence of depression, worse global functioning, and the use of psychotropic medication (especially neuroleptics and benzodiazepines). Therefore, we advise to evaluate the use of all psychotropic medications to exclude an iatrogenic cause of apathy.

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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

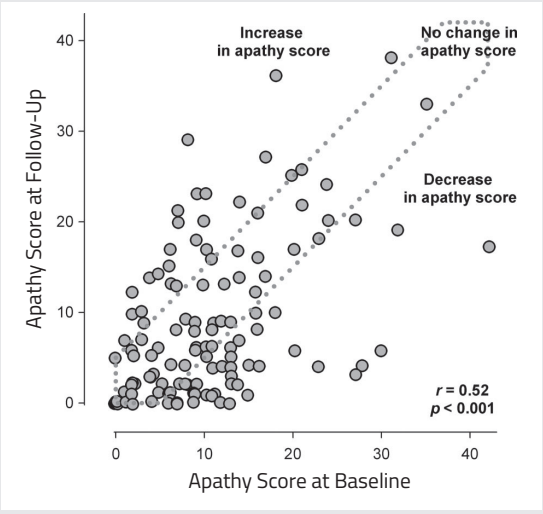
Data were analyzed using multivariate logistic regression analysis. Data are presented as ORs (95% confidence intervals). Sex and age were forced into the model. As potential variables in the model, Total Functional Capacity score, use of antipsychotics, and Symbol Digit Motor Test (SDMT) score were 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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Chapter 5

Irritability in Huntington's disease

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Abstract

Irritability is a frequent neuropsychiatric symptom in patients with Huntington's disease (HD). The Irritability Scale (IS) and the irritability factor of the Problem Behaviours Assessment (PBA) was used to assess irritability among 130 HD mutation carriers and 43 verified non-carriers. The IS was tested using receiver operating characteristic analysis against different cut-offs of the PBA irritability factor. A robust IS cut-off score of ≥14 points was found indicating that 45 (35%) of the 130 mutation carriers were irritable vs. 4 (9%) of the 43 non-carriers (p = 0.001). The level of agreement between self-report and informant-report IS was of moderate strength (intraclass correlation=0.61). Using univariate and multivariate regression analyses, significant independent correlates of irritability were: being married/living together (p = 0.02), CAG repeat length (p = 0.01), and use of benzodiazepines (p = 0.008). Using the same model with the informant's irritability score, use of benzodiazepines was the only significant independent correlate of irritability (p = 0.005). Irritability is a prominent symptom of HD and can be reliably assessed with the IS using a cut-off score ≥14 points. Although it is unclear whether benzodiazepine use causes irritability, or irritability leads to the prescription of benzodiazepines, clinical evaluation with respect to the use of benzodiazepines in HD warrants attention.

Introduction

Huntington's disease (HD) is a progressive autosomal dominant neurodegenerative disorder resulting from an expanded trinucleotide cytosine-adenine-guanine (CAG) repeat in the huntingtin (*HTT*) gene on chromosome 4.[1] Clinical features of HD include motor disturbances, cognitive deterioration and a variety of psychiatric symptoms.[2] Psychiatric symptoms such as depressed mood, perseverative behaviour and irritability are frequently reported, and often precede the manifestation of motor abnormalities of HD.[3,4,5]

Despite its frequent occurrence, negative clinical consequences for mutation carriers and its heavy burden for caregivers, irritability has scarcely been studied in HD. The term 'irritability' has been used as a description of behaviour ranging from bad temper to violent outbursts, but is also defined as a mood state characterised by a reduction in control over temper possibly (but not necessarily) resulting in verbal or behavioural outbursts.[6,7]

Few reliable data on the prevalence of irritability in HD are available due to small sample sizes, use of different methodologies, and lack of control groups. Reported prevalence rates for irritability range from 38-73%.[5] This variation in prevalence can be explained by the use of different assessment methods with varying definitions and different study populations. No follow-up studies have covered a long period of time. Irritability may occur in all stages of HD, even before motor symptoms are present, and may cause severe distress to mutation carriers and their families, determining the need for admittance to a nursing home.

The instruments used to assess the presence and severity of irritability in HD include the Neuropsychiatric Inventory (NPI),[3,8] the behavioural section of the Unified Huntington's Disease Rating Scale (UHDRS-b),[9] the Irritability Scale (IS),[10,11] and the Problem Behaviours Assessment (PBA).[12,13] However, no gold standard (cut-off) to assess the presence of irritability is available.

The present study uses the IS and the PBA to assess irritability in HD. The aim was to investigate the psychometric properties of the IS against the irritability factor of the PBA, in order to establish reliable cut-off scores for irritability. Prevalence rates of both self-reported and informant-reported irritability in HD and their correlates were assessed.

Methods

Participants

Between May 2004 and August 2006, HD mutation carriers and first-degree non-carriers were recruited from the outpatient department of Neurology and Clinical Genetics of the Leiden University Medical Centre (LUMC) and from a regional nursing home. Subjects with a CAG repeat length of 36 or more repeats were considered to be HD mutation carriers. Details of the study design are described elsewhere.[13] A second measurement was conducted two years after the baseline visit.

Since the use of the IS was introduced while the first wave was already underway, subjects for this study comprised (non-overlapping) 130 mutation carriers and 43 non-carriers from both the first and second waves. Additional information was available from 120 informants of the 130 mutation carriers, and from 38 informants of the 43 non-carriers. Of the 120 mutation carriers' informants, 70 were spouses or partners, 4 were neighbours or friends, 10 were first-degree family members, 15 were specialized caregivers, and the status of 21 informants was unknown. The study was approved by the Medical Ethical Committee of the LUMC, and all participants gave informed consent.

Figure 1. *Irritability Scale (self-report version) with the level of agreement between self-reported and informant-reported level of irritability.*

Irritability Scale

Self-report version

	Not at all	slightly	some	a lot	ICC*
1. Are you easily irritated?	0	1	2	3	**0.49**
2. Do you pout if things don't go your way?	0	1	2	3	**0.37**
3. Do you have good control of your temper with the family (or persons living with you)?	3	2	1	0	**0.31**
4. Do little things cause you to fly off the handle?	0	1	2	3	**0.44**
5. Do you adjust well to a change in plans?	3	2	1	0	**0.43**
6. When you lose your temper, do you have a hard time calming down again?	0	1	2	3	**0.38**
7. Do you insist on having your own way?	0	1	2	3	**0.28**
8. Are you easily agitated by minor problems?	0	1	2	3	**0.38**
9. Can you discuss problems together and agree to a reasonable solution?	3	2	1	0	**0.47**
10. Do disagreements often lead to arguments?	0	1	2	3	**0.40**
11. Can you appreciate a different point of view from yours?	3	2	1	0	**0.30**
12. Do you yell a lot?	0	1	2	3	**0.59**
13. Are you able to control your temper with persons outside the family?	3	2	1	0	**0.25**
14. Do you consider yourself to be irritable?	0	1	2	3	**0.45**

*Level of agreement for each score between IS-self and IS-inf as determined by ICC with a 1-way random effects model with single-measure reliability.
ICC = Intraclass Correlation Coefficients;
IS-self = Irritability Scale self-report;
IS-inf = Irritability Scale informant-report.

Instruments

Assessment of irritability

The IS was used to assess irritability (Figure 1); this scale has previously been used to assess irritability in HD.[10,11] The IS poses 14 questions about the presence of various phenomena of irritability in the two weeks prior to the interview. Each question has four answer categories scored on a 4-point Likert scale: 'not at all', 'slightly', 'some', and 'a lot'. The total sum score of the IS ranges from 0-42 points, with higher scores indicating more severe irritability. The participant was asked to rate the self-report version of the IS (IS-self), and the informant was asked to rate the irritable behaviour of the participant with the identical informant-report version of the IS (IS-informant). Until now, no studies have assessed the psychometric properties of the IS.

The PBA is a reliable instrument to assess neuropsychiatric symptoms in HD.[12,13] The severity and frequency of each of the 36 items of the PBA are rated on a scale from 0-4 points, with higher scores indicating more psychopathology. The interrater reliability of the PBA was 0.82 (95%CI=0.65-1.00) for severity scores and 0.73 (95%CI=0.47-1.00) for frequency scores.[13] A factor analysis of the PBA revealed three symptom clusters (factors): irritability, depression, and apathy. The irritability factor of the PBA consists of five items: 'irritability', 'aggression', 'verbal outbursts', 'inflexibility', and 'self-centredness/demanding behaviour'. The irritability factor score is obtained by the sum of the multiplied frequency and severity scores of the five items (range 0-80 points). We chose to validate the IS against the PBA irritability factor, as we consider the PBA to be the best measurement tool available to assess irritability in HD.

Since the UHDRS-b is widely used in HD studies, we also scored the severity and frequency of the 11 neuropsychiatric items of this scale.[14] Severity and frequency are rated on a scale from 0-4 points, with higher scores indicating more psychopathology.

Sociodemographic and clinical characteristics

Information on sociodemographic and clinical characteristics of mutation carriers and controls was collected in a standardized manner. Global daily functioning was assessed with the Total Functional Capacity (TFC) scale of the UHDRS.[15] The TFC consists of five questions assessing employment, capacity to handle financial affairs, capacity to manage domestic chores, capacity to perform activities of daily living, and the care level provided, with higher scores indicating better functional capabilities.

The neurological examination was performed by a neurologist with experience in HD, blinded for the genetic status of the subject. Motor functioning was assessed according to the motor section of the UHDRS (UHDRS-m).[14] Mutation carriers with UHDRS Confidence Level score 0 or 1 were considered pre-motor symptomatic, and mutation carriers with Confidence Level score >1 were considered motor symptomatic.

Estimated duration of disease was calculated by the estimated age of onset according to the equation of Vassos et al.: ln [age of onset (years)] = 6.18 – 0.054 * [CAG repeats (number)],[16] minus the current age.

Assessment of cognitive functioning

The Mini-Mental Status Examination (MMSE),[17] Symbol Digit Modalities Test (SDMT),[18] Verbal Fluency Test (VFT),[19] and Stroop tests[20] were administered to assess both global and frontal executive cognitive functioning.

Assessment of psychiatric disorders

The Dutch translation of the computerised version of the Composite International Diagnostic Interview (CIDI, version 2.1)[21] was used to assess the presence of a depressive disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).[22] The CIDI was not administered in subjects with an MMSE score <18 points, since the CIDI cannot be reliably administered to patients with severe cognitive dysfunction.

Statistical analyses

Data are presented as n (%), mean (± standard deviation; SD), or median (inter-quartile range; IQR) when appropriate. Chi-square tests for categorical data, *t*-tests for independent samples with normal distribution, or nonparametric Mann-Whitney U tests were conducted to compare mutation carriers and non-carriers. Convergent validity was assessed by the Spearman's correlation coefficient. Kruskal-Wallis tests were conducted to compare IS-self and IS-informant scores among the three groups of non-carriers, pre-motor symptomatic carriers, and motor symptomatic mutation carriers.

Because no known cut-off score exists for the presence of irritability as assessed with the IS, Receiver Operator Characteristic (ROC) analyses were performed against different cut-offs (i.e. 10, 15, and 20 points) of the irritability factor of the PBA that yielded optimal sensitivity and specificity. The area under the ROC curve (AUC) was used as an indicator of the discriminatory power of the IS to distinguish between irritable and non-irritable subjects according to the irritability factor of the PBA.

Using univariate logistic regression analyses, mutation carriers with an IS score ≥14 points were compared to those with an IS score <14 points to determine correlates of irritability. Odds ratios (OR) and their corresponding 95% confidence interval (CI) were computed. Because of a non-normal distribution of TFC, UHDRS-m and MMSE scores, these data were dichotomized using a median split. To yield the independent correlates of irritability (IS-self), multiple logistic regression analysis with a forward selection procedure was used, selecting the following univariate correlates with $p < 0.10$: being married/living together with a partner, CAG repeat length, TFC, use of benzodiazepines, and Stroop interference test. This model was adjusted for age and sex (i.e., forced into the model). In addition, the same variables were entered using the IS-informant score as the dependent variable. In sensitivity analyses, models were repeated using different cut-off scores of the IS.

Table 1. *Sociodemographic and clinical characteristics of HD mutation carriers and non-carriers.*

	Mutation carriers (n = 130)	Non-carriers (n = 43)	*p*-value
Sociodemographic and clinical characteristics			
Male (n, %)	58 (45)	20 (47)	0.83
Age, years (mean ± S.D.)	49 ± 11	41 ± 11	< 0.001
Higher level of education[a] (n, %)	78 (60)	31 (72)	0.17
Married/living together (n, %)	81 (62)	35 (81)	0.02
Excessive use of alcohol (n, %)	13 (10)	1 (2)	0.14
CAG repeat length (mean ± S.D.)	44 ± 3	22 ± 4	< 0.001
UHDRS-m (median, IQR)	18 (4–48)	1 (0–4)	< 0.001
Neuropsychiatric characteristics			
IS-self (median, IQR)	9 (3–17)	5 (2–9)	0.01
IS-self with cut-off ≥ 14 (n, %)	45 (35)	4 (9)	0.001
IS-informant (median, IQR)	11 (5–19)	4 (2–10)	0.01
IS-informant with cut-off ≥ 14 (n, %)	51 (39)	5 (12)	0.001
PBA irritability (IQR)	7 (1–16)	1 (0–5)	< 0.001
Any psychiatric disorder[b] (n, %)	13 (10)	1 (2)	0.10
Major depressive disorder[b] (n, %)	8 (6)	0 (0)	0.09

Data are presented as n (%), mean (± standard deviation (S.D.)), or median (inter-quartile range (IQR)) when appropriate. UHDRS-m, Unified Huntington's Disease Rating Scale motor section; IS-self = Irritability Scale self-report; IS-informant = Irritability Scale informant-report; PBA = problem behaviours assessment.

[a] Higher education ≥ 12 years of education.

[b] The presence of psychiatric disorders in the last two weeks are diagnosed with the Composite International Diagnostic Interview.

Agreement between IS-self and IS-informant scores was assessed using one-way random, single measure intraclass correlation coefficients (ICCs). The same analysis was performed to assess the level of agreement on each of the 14 items of the IS. All tests were two-tailed with $p < 0.05$ denoting statistical significance. The SPSS version 16.0 (SPSS Inc., Chicago, USA) was used for the analyses.

Results

Sociodemographic, clinical, and neuropsychiatric characteristics

Table 1 presents the sociodemographic, clinical and neuropsychiatric characteristics of the 130 (39 pre-motor symptomatic and 91 motor symptomatic) HD mutation carriers and the 43 non-carriers. Mutation carriers were older and less often married/living together with a partner than non-carriers. Mutation carriers had significantly higher irritability scores (both IS-self and IS-informant) than non-carriers, and 45 (35%) of the 130 mutation carriers were irritable according to an IS-self score ≥14 points, compared to 4 (9%) of the 43 non-carriers. Although the CIDI assessment was not possible in 11 mutation carriers due to severe cognitive impairment (MMSE<18 points), there

were 13 (10%) mutation carriers of whom 8 had a major depressive disorder vs. one (2%) non-carrier with a psychiatric disorder.

Psychometric properties of the Irritability Scale

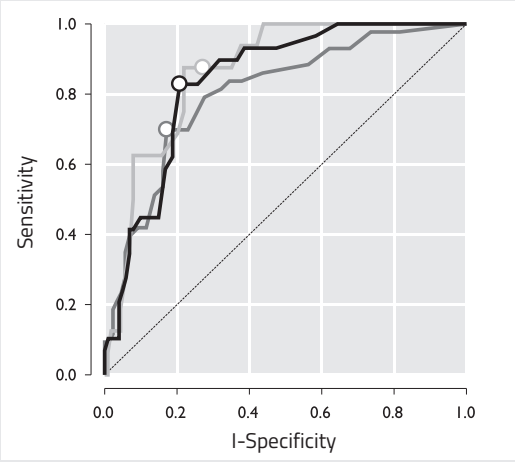
The Cronbach's alphas were 0.90 for the IS-self and 0.93 for the IS-informant. There was some evidence for convergent validity with the irritability item of the UHDRS-b indicated by a Spearman's correlation coefficient of 0.56 (p = 0.001, n = 32 with complete data for both scales). Using ROC

Table 2. *ROC analysis for IS-self scores among 152 HD mutation carriers against three different cut-off scores for PBA irritability factor.*

	PBA irritability cut-off score		
	> 10 points	> 15 points	> 20 points
Prevalence of irritability	33%	22%	12%
Optimal IS-self cut-off	13–14	13–14	13–14
Sensitivity	0.58	0.69	0.88
Specificity	0.84	0.81	0.78
AUC	0.80	0.84	0.87

ROC = receiver operator characteristic; IS-self = irritability scale self-report; PBA = problem behaviours assessment; AUC = area under the curve.

Figure 2. *ROC curves for the irritability scores among 152 HD mutation carriers according to the PBA scores.*

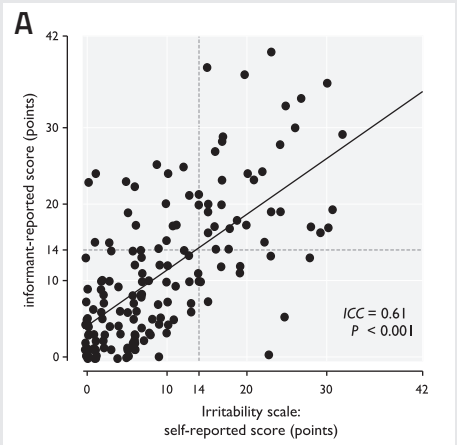


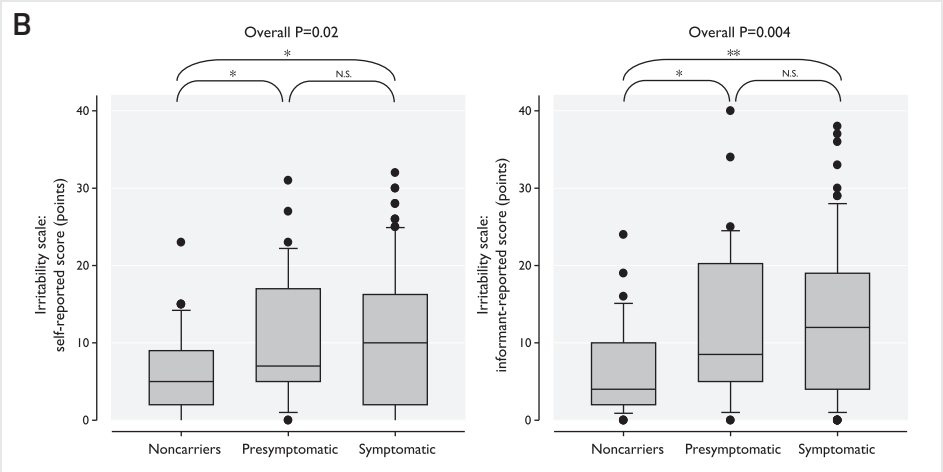
The dark grey line is with a cut-off score of 10 points (resulting in 33.1% with irritability). The black line is with cut-off score of 15 points (resulting in 22.3% with irritability). The light grey line is with a cut-off score of 20 points (resulting in 12.3% with irritability). The open dots indicate the sensitivity and 1 – specificity for a cut-off score of ≥14 points for the irritability scale.
ROC = Receiver Operator Characteristic;
PBA = Problem Behaviours Assessment.

Figure 3. *A. Scatter plot representing the intercorrelation between IS-self and IS-inf scores; B. IS-self and IS-inf scores (median, IQR) in non-carriers, pre-motor symptomatic carriers and motor symptomatic mutation carriers.*

A. An univariate regression line is shown, with the intraclass-correlation coefficient (ICC). Dotted lines indicate the cut-off score of ≥14 points being indicative of the presence of irritability.

B. The line within the box represents the median and the boundaries of the box represent the interquartile range, while the error bars represent the 10th and 90th percentile values (P_{10} and P_{90}). * $p < 0.05$; ** $p < 0.005$, n.s. = non significant.





analysis, a score of ≥14 points on the IS-self was identified as a robust indicator for irritability according to all three cut-off points (i.e. 10, 15, and 20 points) of the irritability factor of the PBA; the three cut-off points corresponded to prevalence rates for irritability of 33%, 22% and 12% (Table 2; Figure 2). The IS cut-off score of ≥14 points yielded an acceptable sensitivity and high specificity for all three cut-off points.

Level of agreement between the IS-self and IS-informant scores

The overall ICC for IS-self and IS-informant scores was 0.61 (95%CI=0.50–0.72, $p < 0.001$) (Figure 3A). The ICC for IS-self and IS-informant was higher (ICC=0.75) when spouses/partners

were their informants than when others (e.g. family members, friends, or nurses) were informants (ICC=0.48). On item level, ICCs were highest for question 12: "Do you yell a lot?" (ICC=0.59, $p < 0.001$) and question 1: "Are you easily irritated?" (ICC=0.49, $p < 0.001$), and lowest for question 7: "Do you insist on having your own way?" (ICC=0.28, $p < 0.001$) and question 13: "Are you able to control your temper with persons outside the family?" (ICC=0.25, $p < 0.001$) (Figure 1).

Table 3. *Sociodemographic, clinical and neuropsychiatric characteristics as correlates of irritability in HD mutation carriers.*

	No irritability n = 85	Irritability[a] n = 45	Univariate logistic regression OR (95%CI)	*p*-value
Sociodemographic characteristics				
Male (n, %)	38 (45)	20 (44)	0.99 (0.48–2.05)	0.98
Age, years (mean ± S.D.)	49 ± 11	48 ± 12	1.00 (0.97–1.03)	0.80
Higher level of education[b] (n, %)	53 (62)	26 (58)	0.83 (0.40–1.73)	0.61
Married/living together (n, %)	48 (57)	33 (73)	2.12 (0.96–4.66)	0.06
Clinical characteristics				
Excessive use of alcohol (n, %)	6 (7)	6 (13)	2.03 (0.61–6.69)	0.25
CAG repeat length (mean ± S.D.)	44 ± 3	45 ± 3	1.16 (1.02–1.30)	0.02
Estimated duration of disease[c] (mean ± S.D.)	-2.6 ± 11.5	5.2 ± 11.0	1.02 (0.99–1.06)	0.21
TFC < 8.5 points (n, %)	37 (44)	28 (62)	2.12 (1.02–4.48)	0.04
UHDRS-m >18 points (n, %)	38 (45)	26 (58)	1.69 (0.82–3.51)	0.16
Use of psychotropics (n, %)	39 (46)	29 (64)	2.14 (1.02–3.51)	0.16
Antidepressants (n, %)	27 (32)	18 (40)	1.43 (0.68–3.04)	0.35
Antipsychotics (n, %)	22 (26)	10 (22)	0.82 (0.35–1.92)	0.65
Benzodiazepines (n, %)	17 (20)	18 (40)	2.67 (1.20–5.92)	0.02
Neuropsychiatric characteristics				
IS-self (median, IQR)	5 (1–8.5)	20 (16.5–25.0)	–	–
IS-informant (median, IQR)	7 (3–12)	19 (12.5–27.5)	–	–
Major depressive disorder[d] (n, %)	3 (7)	5 (6)	1.15 (0.26–5.08)	0.85
MMSE < 28 points (n, %)	46 (54)	30 (67)	1.82 (0.85–3.90)	0.13
SDMT	0.08 (1.05)	–0.12 (0.90)	0.80 (0.55–1.15)	0.23
VFT	0.01 (0.94)	–0.02 (1.12)	0.98 (0.68–1.40)	0.89
Stroop word	0.14 (1.04)	–0.26 (0.86)	0.66 (0.45–0.97)	0.11
Stroop colour	0.10 (1.05)	–0.19 (0.88)	0.75 (0.51–1.08)	0.12
Stroop interference	0.11 (1.06)	–0.21 (0.86)	0.73 (0.50–1.05)	0.09

Data are presented as n (%), mean (± standard deviation (S.D.)), or median (inter-quartile range (IQR)) when appropriate. Odds ratios (ORs) with 95% confidence intervals (CI) and *p*-values by univariate logistic regression.

TFC, total functioning capacity; UHDRS-m, Unified Huntington's Disease Rating Scale motor section; IS-self, Irritability Scale self-report; IS-informant, Irritability Scale informant-report; MMSE, mini-mental state examination; SDMT = symbol digit modality test; VFT = verbal fluency test.SDMT, VFT, and Stroop tests scores are in standardized z-scores.

SDMT, VFT, and Stroop tests scores are in standardized z-scores.

[a] Irritability was considered present if IS-self ≥ 14 points.

[b] Higher education ≥ 12 years of education.

[c] Estimated duration of disease (years) was calculated by the estimated age of onset minus the currentage. Estimated duration of disease can be negative.

[d] The presence of major depressive disorder in the last twoweeks are diagnosed with the Composite International Diagnostic Interview.

Using a cut-off point of ≥14 points for both IS-self and IS-informant, 33 (28%) mutation carriers were considered irritable according to both IS scales, whereas 60 (50%) mutation carriers were found not irritable according to both IS scales. For the remaining 27 (23%) mutation carriers, there was disagreement between participants and informants, with the majority of participants (n = 18; 67%) not rating themselves as irritable whereas their informants did.

Presence and severity of irritability in non-carriers and HD mutation carriers

There were important group differences for the IS-self and IS-informant scores among the 43 non-carriers, 39 pre-motor symptomatic, and 91 motor symptomatic carriers. Both for the IS-self (p = 0.02) and for the IS-informant (p = 0.004) there was a trend for increasing irritability scores from non-carriers, pre-motor symptomatic, to motor symptomatic carriers (Figure 3B). In post-hoc comparisons, non-carriers had lower levels of irritability than both groups of mutation carriers.

Correlates of irritability in HD mutation carriers

Table 3 shows that mutation carriers with an IS-self ≥14 points had a higher mean CAG repeat length (OR = 1.16 per CAG triplet, 95%CI = 1.02–1.30, p = 0.02), a lower TFC score (OR = 2.12, 95% CI = 1.02–4.48, p = 0.04), and more often used benzodiazepines (OR = 2.67, 95%CI = 1.20–5.92, p = 0.02) compared to those with an IS-self score < 14 points.

In the multivariate logistic regression model, being married/living together (OR = 2.85, 95% CI = 1.19–6.83, p = 0.02), CAG repeat length (OR = 1.20 per CAG triplet, 95%CI = 1.04–1.39, p = 0.01), and the use of benzodiazepines (OR = 3.28, 95% CI = 1.36–7.89, p = 0.008) were independent correlates of self-reported irritability (Table 4). Using the same model with the dichotomized IS-informant score as the dependent variable, the use of benzodiazepines was the only significant independent correlate of irritability (OR = 3.54, 95%CI = 1.45–8.64, p = 0.005).

In sensitivity analyses, being married/living together and the use of benzodiazepines remained independent correlates of self-reported irritability when cut-off scores of IS-self ≥12 points and ≥16 points were used. However, CAG repeat length was no longer an independent correlate.

Table 4. *Independent correlates of self-reported and informant-reported irritability in HD mutation carriers.*

	Self-reported (n = 130)		Informant-reported (n = 120)	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	1.01 (0.98–1.06)	0.48	1.00 (0.96–1.04)	0.87
Male	0.98 (0.43–2.21)	0.96	1.73 (0.77–3.87)	0.18
Married/living together	2.85 (1.19–6.83)	**0.02**	1.75 (0.75–4.06)	0.19
CAG repeat length	1.20 (1.04–1.39)	**0.01**	1.14 (0.99–1.32)	0.06
Use of benzodiazepines	3.28 (1.36–7.89)	**0.008**	3.54 (1.45–8.64)	**0.005**

Odds ratios (ORs) with 95% confidence intervals (CI) and p-values by multivariate logistic regression.

Discussion

Using the optimal cut-off score of IS ≥14 points, the prevalence of irritability in HD mutation carriers was 35%. There was a moderate level of agreement between mutation carriers and their informants in reporting irritability, with a tendency for mutation carriers to underestimate their level of irritability. Being married/living together, a higher CAG repeat length, and the use of benzodiazepines were independent correlates of self-reported irritability, whereas the use of benzodiazepines was the only independent correlate of both self-reported and informant-reported irritability.

Since there is no gold standard or formal criteria for the assessment of irritability, any cut-off point remains somewhat arbitrary. Therefore, we investigated the psychometric properties of the IS against the irritability factor of the PBA, an instrument especially developed for the assessment of behavioural problems in HD. ROC analysis showed that a cut-off score of ≥14 points was robust over three PBA cut-off scores. This cut-off score had face validity, since we considered it likely that irritable subjects would score at least 1 point on each of the 14 questions of the IS. In an earlier study using the IS (n=53), the median IS-self score of 15 points was used as a cut-off, defining irritability by IS >15 points; however, that study did not perform a ROC analysis.[10]

Whereas other (smaller) studies found prevalence rates of 38-73% for irritability in HD,[5] we found a relatively low prevalence. This may partly be explained by the different assessment tools we used: all other studies used non-specific measures for neuropsychiatric symptoms. Besides differences in methodology, also sociodemographic and clinical factors (e.g. use of medication) may have contributed to the variation in the prevalence of irritability. Unfortunately, the only two studies that used the IS do not report prevalence rates of irritability, but do report a mean IS-self score of 14 points,[10] and 12 points,[11] respectively. Furthermore, although high levels of hostility may be present before motor symptoms occur,[23] the prevalence of irritability may vary between disease stages. So far, no significant differences between different disease stages have been found.

Of the two earlier studies using the IS, both assessed self-reported and informant-reported irritability. In the first study, agreement between (motor symptomatic) mutation carriers and informants for the presence of irritability (median IS-self >15 points, median IS-informant >16 points) was moderate to poor;[10] disagreement was greater among mutation carriers with more intact cognition. The second study assessed irritability in 15 pre-motor symptomatic mutation carriers and found no significant differences between self-reported and informant-reported irritability.[11] In the present study, we found moderate agreement between self-reported and informant-reported irritability. Mutation carriers tended to underestimate their level of irritability compared to their informants, since in 18 of the 27 cases with discordant scores, mutation carriers

rated themselves as non-irritable (IS <14 points), whereas their informants scored above the cut-off. This may indicate denial or a lack of awareness by mutation carriers of their level of irritability. Since we did not ask informants of non-carriers to rate the level of irritability, we cannot conclude whether or not this is related to the disease itself. On the other hand, caregiver burden may be a source of disagreement between self-reported and informant-reported irritability, contributing to a possible overestimation of irritability by informants. However, there was a higher level of agreement between IS-self and IS-informant scores when spouses/partners rated the IS than when the other informants did so, suggesting a more correct estimation by the most intimate informants.
Of all the sociodemographic and clinical characteristics, being married/living together, CAG repeat length, and use of benzodiazepines were independent correlates of self-reported irritability. While most partners and other caregivers are extremely helpful and important for mutation carriers, a higher level of irritability may become more pronounced in intimate relationships that may comprise more potential triggers of increased irritability.

The CAG repeat length of mutation carriers was also independently correlated with self-reported irritability but not with informant-reported irritability, whereas sensitivity analysis also showed that CAG repeat length was not an independent correlate. This is in line with studies that found no relationship between CAG repeat length of the *HTT* gene and any kind of psychopathology.[16,24,25,26]
In the present study use of benzodiazepines was independently correlated with both self-reported and informant-reported irritability. Although benzodiazepines may have been prescribed more often to irritable mutation carriers, this cross-sectional study does not allow to draw any conclusions about causality. Even if the occurrence of irritability in HD is (in part) iatrogenic and induced by the use of benzodiazepines, no longitudinal studies have examined the use of benzodiazepines and their effects on irritability in HD or other neurodegenerative diseases. Nevertheless, it is established that some patients may show paradoxical 'aggressive' behaviour, or behavioural disinhibition, with benzodiazepines.[27,28,29]

The strength of this study is the use of three different assessment methods for irritability, with standardized interviews, in a relatively large HD study population. However, some limitations also need to be addressed. First, in the absence of criteria or a gold standard for the assessment of irritability, we used the PBA for validation of the IS. Second, only subjects who volunteered to participate were included; this may have led to underestimation of the prevalence of irritability in HD, since irritable subjects were more likely to refuse to participate. Third, our study involved the analysis of cross-sectional data which precludes drawing conclusions about the direction of causality.

In conclusion, we recommend the use of the IS to assess irritability in HD in a standardized manner, since this scale proved to be a valid and easy to use instrument. Being married/living together and the use of benzodiazepines were independently associated with the presence of irritability,

although only the use of benzodiazepines was also correlated with informant-reported irritability and confirmed in the sensitivity analyses. Longitudinal studies are needed to further explore these relationships. Given the strong association between irritability and the use of benzodiazepines, close monitoring of the effect of benzodiazepines is important, since clear evidence for an effective treatment of irritability in HD is still lacking.[30]

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Chapter 6

Course of irritability, depression, and apathy in Huntington's disease during a 2-year follow-up period in relation to motor symptoms

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Abstract

Objective: This longitudinal study investigated the course of irritability, depression, and apathy in Huntington's disease (HD) during a 2-year follow-up period.

Method: In 121 HD mutation carriers the change in presence of irritability, depression, and apathy was measured with the Problem Behaviours Assessment (PBA) during a 2-year follow-up period. Multivariate linear regression analysis was performed to assess their relationships with the change of the motor score of the Unified Huntington's Disease Rating Scale (UHDRS-m) in pre-motor symptomatic (n = 46) and motor symptomatic mutation carriers (n = 75).

Results: During two years of follow-up the median depression score of all participants decreased (p = 0.002), whereas irritability and apathy scores did not change significantly. In the total group of mutation carriers, borderline significant associations were found between an increase in motor symptoms on the one hand, and an increase in irritability and a decrease in depression on the other hand during follow-up (both p = 0.05). Only in the initial pre-motor symptomatic mutation carriers, an increase in motor symptoms was significantly related to an increase in irritability (p = 0.02). Apathy scores did not change.

Conclusion: Pre-motor symptomatic mutation carriers who showed an increase in motor symptoms show an increase in irritability during a 2-year follow-up period, which may be an early and sensitive marker for disease progression before a clinical diagnosis of HD is made.

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by motor, psychiatric, and cognitive symptoms.[1] HD results from an expanded trinucleotide CAG sequence in the huntingtin (*HTT*) gene on chromosome 4.[2] The average age at onset of motor symptoms is between 30 and 50 years. HD shows a progressive course and comprises a disease duration of 15 to 20 years. In the Netherlands, about 1,200 to 1,500 patients are clinically affected of HD, and 6,000 to 9,000 persons are at risk for HD. Although symptomatic treatment has improved significantly as a result of, amongst others, increased awareness of non-motor symptoms,[3] no cure is available.

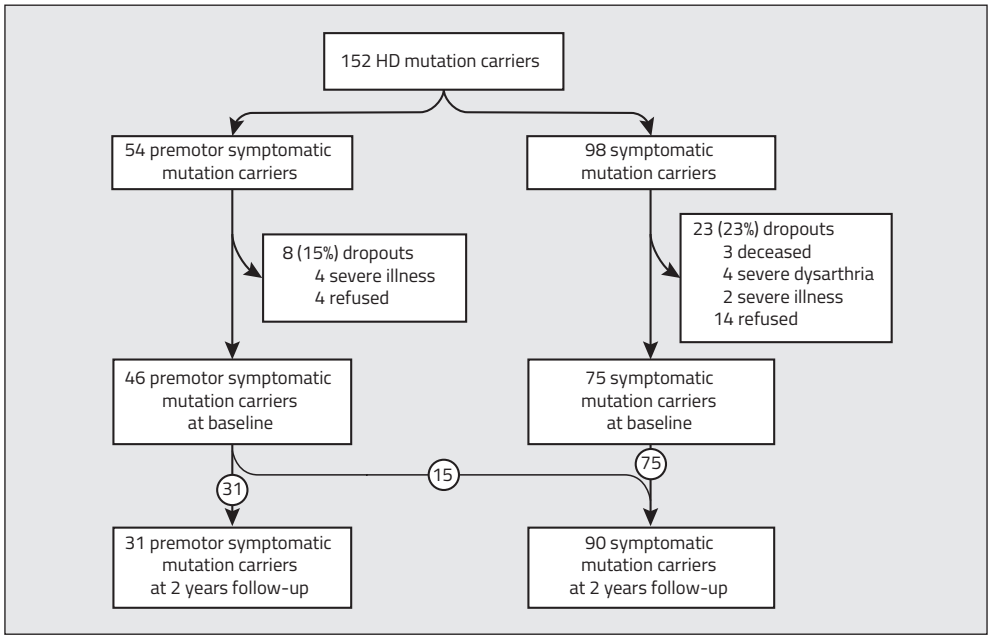
Prevalence rates of psychiatric symptoms and disorders vary widely,[4] but probably all mutation carriers experience some form of psychopathology during lifetime, varying from tensed feelings to psychosis. These psychiatric symptoms usually precede motor symptoms by many years.[5] Reported prevalence rates of psychopathology in HD strongly depend on the measurement tools used, the definition of psychopathology, and the disease stage studied. For example, studies using formal criteria of the Diagnostic Statistical Manual (DSM)[6] for mental disorders have reported much lower prevalence rates for psychopathology than studies using a single item like 'depressed mood' from the Unified Huntington's Disease Rating Scale (UHDRS),[7] since the DSM uses strict criteria for a psychiatric diagnosis. However, use of DSM criteria for the assessment of psychopathology in HD is less suitable, since the disease is often accompanied by physical symptoms with a clear neurophysiological substrate such as sleep disturbance, weight loss, fatigue, and cognitive symptoms that overlap and therefore interfere with psychiatric diagnostic criteria. Furthermore, patients with HD show distinct psychopathological features that are not included in the DSM, e.g., irritability, apathy, and perseverations.[8] These neuropsychiatric features may cause major functional and psychosocial impairments and should be acknowledged as part of the psychiatric phenotype of HD. Therefore, the use of questionnaires and dimensional rating scales that measure frequency and severity of a broad spectrum of psychiatric symptoms is more appropriate in HD patients.[9,10] Because the Problem Behaviours Assessment (PBA) also allows for the use of caregiver information,[10] this instrument has proven to be very suitable for the assessment of psychiatric symptoms in HD in all stages of the disease including the advanced disease stage.

In this study we aimed to assess the course of the three symptom clusters (factors) irritability, depression, and apathy that were found by factor analysis in a previous cross-sectional studies using the PBA-scale.[8,11] We investigated the course of these factors during a 2-year follow-up period in relation to motor symptoms.

Methods

Between May 2004 and August 2006, 343 genetically tested participants at initial 50% risk of HD were contacted via the Departments of Neurology and Clinical Genetics of the Leiden University Medical Centre and a long-term care facility in the Netherlands. The design of the study has been described in detail elsewhere.[12] Of 241 verified HD mutation carriers (CAG repeat length ≥ 36), 152 were willing and able to participate in this study. Two years after the first measurement, a total of 121 (79.6%) mutation carriers participated in this follow-up assessment. Thirty-one (20.4%) subjects dropped-out for various reasons (Figure 1). The medical ethical committee of the Leiden University Medical Centre approved the study. All participants gave informed consent.

Figure 1. *Flowchart for the 121 participating HD mutation carriers and 31 drop-outs.*



Sociodemographic and clinical characteristics

Information on sociodemographic and clinical characteristics was obtained during a standardized interview by trained interviewers. Raters for psychiatric and cognitive function were informed about the genetic status of the participants, because nondisclosure could considerably influence participants' answering questions about symptoms (e.g., worrying) that are directly related to mutation carriership. The estimated age of disease onset was calculated according to the following

equation: log (age) = α + β (number of CAG repeats), where α = 6.15 and β = −0.053.[13] The Total Functional Capacity (TFC) scale was administered to assess global daily functioning.[14] Global cognitive functioning was measured with the Mini-Mental State Examination (MMSE).[15]
All participants were assessed using the motor section of the UHDRS (UHDRS-m).[7] The neurologist was blinded to the genetic status of the participants and the results of all other assessments. The total UHDRS-m score (range 0 – 124 points) was used for the assessment of the severity of motor symptoms. Furthermore, the neurologist assigned a score indicating to what degree he was confident that the presence of an extrapyramidal movement disorder in a subject might be due to HD. Mutation carriers with confidence level score 0 (normal) or 1 (nonspecific motor abnormalities; < 50% confidence) were considered pre-motor symptomatic (n = 46). The remaining mutation carriers (n = 58) with score 2 (motor abnormalities that may be signs of HD; 50 – 89% confidence), 3 (likely signs of HD; 90 – 98% confidence), or 4 (unequivocal signs of HD; ≥ 99% confidence) were considered symptomatic (n = 75).

Assessment of psychopathology

The Dutch translation of the original version of the semi-structured PBA scale was used to assess the severity and frequency of psychiatric symptoms in HD.[11] The severity and frequency of each of the 36 items are scored on a scale from 0 to 4 points, with higher scores indicating more psychopathology. The severity and frequency scores are multiplied to assess the total score for each item. Where possible, participants were interviewed in the presence of a knowledgeable informant. When no informant was present, we conducted a telephone interview with an informant. Scores were determined by the interviewer based on the combination of information gathered, and clinical observations. Previously, we performed a factor analysis on the 36 items of the PBA, and distinguished three underlying factors: irritability (five items: irritability, aggression, verbal outbursts, inflexibility, and self-centered, demanding behavior; range 0 – 80 points), depression (five items: depressed mood, depressive cognitions, anxiety, tension, and suicidal ideation; range 0 – 80 points), and apathy (consisting of four items: lack of perseverance, poor quality of work, lack of initiative, and poor self-care; range 0 – 64 points).[11] The interrater reliability of the PBA was 0.82 (95% CI = 0.65 – 1.00) for severity scores and 0.73 (95% CI = 0.47 – 1.00) for frequency scores. Since this is a follow-up assessment, we used the same three factors as in the baseline assessment.

Statistical analysis

Data are presented as n (%), mean (± SD) or median (interquartile range (IQR), i.e., 25th to 75th percentiles) when appropriate. Chi-square tests for categorical data, *t*-tests for independent samples with normal distributions, or nonparametric Mann-Whitney tests were conducted to assess group differences in case of non-normal distributions. One sample *t*-tests were used to assess whether absolute changes over two years time were statistically significant. Multivariate

linear regression analysis was used for analysis of the associations between change over two years in the PBA factors irritability, depression, and apathy on the one hand and change in UHDRS-m score on the other hand, with adjustment for sex and age (Model 1), for sex and age, baseline use and changes in use of psychotropics, and baseline UHDRS-m score (Model 2), and additionally for scores of the other two PBA factors (Model 3). A *p*-value < 0.05 was considered significant. All analyses were performed in Statistical Package for Social Sciences (SPSS) for Windows release 17.0.

Table 1. *Sociodemographic, clinical, and PBA factor scores of all participants*

	All participants (n = 121)	Pre-motor symptomatic (n = 46)	Symptomatic (n = 75)	*p*-value*
Sociodemographic characteristics				
Male (n, %)	56 (46)	20 (44)	36 (48)	0.63
Age (mean ± SD)	47.5 ± 11.7	41.3 ± 9.9	51.3 ± 11.2	< 0.001
Higher education (n, %) [a]	72 (60)	33 (72)	39 (52)	0.03
Institutionalized (n, %)	9 (7)	1 (2)	8 (11)	0.15
Married or living together (n, %)	89 (74)	36 (78)	53 (71)	0.36
Clinical characteristics				
CAG repeats (mean ± SD)	44.0 ± 3.1	42.7 ± 2.4	44.8 ± 3.2	< 0.001
Age of disease onset (median, IQR) [b]	47 (40 – 50)	47 (43 – 56)	45 (38 – 50)	0.001
TFC (median, IQR) [c]	11 (7 – 13)	13 (12 – 13)	8 (4 – 11)	< 0.001
MMSE (median, IQR) [d]	27 (25 – 29)	29 (28 – 30)	26 (23 – 28)	< 0.001
UHDRS-m (median, IQR) [e]	13 (2 – 45)	1 (0 – 3)	34 (15 – 51)	< 0.001
High alcohol use (n, %) [f]	15 (12)	9 (20)	6 (8)	0.06
Use of psychotropics (n, %)	46 (38)	10 (22)	36 (48)	0.004
- Antidepressants (n, %)	34 (28)	7 (15)	27 (36)	0.01
- Antipsychotics (n, %)	12 (10)	1 (2)	11 (15)	0.03
- Benzodiazepines (n, %)	26 (22)	4 (9)	22 (29)	0.007
PBA factors				
Irritability (median, IQR) [g]	6 (1-16)	5.5 (1-15)	7 (1-16)	0.54
Depression (median, IQR) [h]	9 (4-23)	11 (2-23)	9 (4-23)	0.75
Apathy (median, IQR) [i]	4 (0-18)	0 (0-7)	8 (0-24)	< 0.001

**p*-value for comparison of pre-motor symptomatic and symptomatic mutation carriers by chi-squared test, *t*-test for independent samples, or Mann-Whitney test, when appropriate; PBA = Problem Behaviours Assessment; SD = Standard Deviation; IQR = Inter Quartile Range;

[a] Education was considered high if > 12 years;

[b] Estimated age of disease onset was calculated by the formula of Vassos[11];

[c] TFC = Total Functional Capacity, with scores ranging from 0 to 13 points;

[d] MMSE = Mini-Mental State Examination, with scores ranging 0 to 30 points;

[e] UHDRS-m = Unified Huntington's Disease Rating Scale motor score, with scores ranging from 0 to 124 points;

[f] Alcohol use was considered high if more than 14 glasses per week were consumed;

[g] PBA irritability factor, consisting of five items, with scores ranging from 0 to 80 points;

[h] PBA depression factor, consisting of five items, with scores ranging from 0 to 80 points;

[i] PBA apathy factor, consisting of four items, with scores ranging from 0 to 64 points.

Table 2. *Changes in UHDRS-m scores and PBA factor scores (irritability, depression, and apathy) during two years of follow-up in 121 participants.*

	All participants (n = 121)	Pre-motor symptomatic (n = 46)	Symptomatic (n = 75)
UHDRS-m[a]			
Baseline score (median, IQR)	13 (2 – 45)	1 (0 – 3)	34 (15 – 51)
2-year score (median, IQR)	19 (5 – 48)	4 (1 – 10)	43 (20 – 59)
Change (mean, SE)	6.2 (SE: 1.0)	3.9 (SE: 0.9)	7.6 (SE: 1.5)
p-value	**< 0.001**	**< 0.001**	**< 0.001**
Irritability[b]			
Baseline score (median, IQR)	6 (1 – 16)	5.5 (1 – 15)	7 (1 – 16)
2-year score (median, IQR)	4 (0 – 15)	3 (0 – 15)	4 (0 – 15)
Change (mean, SE)	−0.9 (SE: 1.1)	0.0 (SE: 1.2)	−1.5 (SE: 1.5)
p-value	0.38	0.97	0.34
Depression[c]			
Baseline score (median, IQR)	9 (4 – 23)	11 (2 – 23)	9 (4 – 23)
2-year score (median, IQR)	4 (0 – 13)	4.5 (0 – 13)	4 (0 – 13)
Change (mean, SE)	−4.3 (SE: 1.4)	−4.2 (SE: 2.5)	−4.4 (SE: 1.6)
p-value	**0.002**	0.11	**0.008**
Apathy[d]			
Baseline score (median, IQR)	4 (0 – 18)	0 (0 – 7)	8 (0 – 24)
2-year score (median, IQR)	4 (0 – 19)	0 (0 – 5)	8 (0 – 24)
Change (mean, SE)	−0.3 (SE: 1.1)	−1.4 (SE: 1.2)	0.3 (SE: 1.6)
p-value	0.76	0.27	0.84

**p*-value for comparison of scores at baseline and after 2 years;
UHDRS-m = Unified Huntington's Disease Rating Scale motor section; PBA = Problem Behaviours Assessment; IQR = Inter Quartile Range; SE = Standard Error;
[a] UHDRS-m = Unified Huntington's Disease Rating Scale motor section, with scores ranging from 0 to 124 points;
[b] Irritability factor according to the PBA, consisting of five items, with scores ranging from 0 to 80 points;
[c] Depression factor according to the PBA, consisting of five items, with scores ranging from 0 to 80 points;
[d] Apathy factor according to the PBA, consisting of four items, with scores ranging from 0 to 64 points.

Results

Baseline characteristics

Baseline sociodemographic and clinical characteristics for all 121 HD mutation carriers are shown in Table 1. Symptomatic mutation carriers were significantly more apathetic at baseline than pre-motor symptomatic mutation carriers (8 versus 0 points, $p < 0.001$), whereas no differences were found for irritability and depression PBA factor scores at baseline.

The 121 participants showed significantly better scores in TFC (11 versus 5 points, $p = 0.002$), UHDRS-m (13 versus 41 points, $p = 0.01$), and MMSE (27 versus 26 points, $p = 0.05$), than the 31 drop-outs at baseline, indicating that the clinically more impaired patients dropped out. No significant differences were found in other sociodemographic and clinical characteristics, use of

Table 3. *Associations of changes in PBA factor scores (irritability, depression, and apathy) and UHDRS-m scores during two years of follow-up for 121 participants*

	All participants (n = 121)		Pre-motor symptomatic (n = 46)		Symptomatic (n = 75)	
	Beta	*p*-value	Beta	*p*-value	Beta	*p*-value
Irritability						
Crude	0.141	0.12	0.229	0.13	0.142	0.23
Model 1[a]	0.139	0.13	0.248	0.11	0.133	0.25
Model 2[b]	0.124	0.18	0.185	0.22	0.123	0.30
Model 3[c]	0.184	**0.05**	0.462	**0.02**	0.154	0.21
Depression						
Crude	–0.119	0.19	–0.236	0.12	–0.097	0.41
Model 1[a]	–0.124	0.18	–0.233	0.13	–0.093	0.43
Model 2[b]	–0.151	0.12	–0.160	0.35	–0.095	0.45
Model 3[c]	–0.185	**0.05**	–0.285	0.12	–0.129	0.32
Apathy						
Crude	–0.024	0.79	–0.111	0.46	–0.024	0.84
Model 1[a]	–0.025	0.79	–0.133	0.41	–0.053	0.66
Model 2[b]	–0.068	0.47	–0.108	0.52	–0.111	0.38
Model 3[c]	–0.061	0.51	–0.301	0.13	–0.101	0.43

PBA = Problem Behaviours Assessment; UHDRS-m = Unified Huntington's Disease Rating Scale motor section. Multivariate linear regression analysis was used for analysis of the associations between a change in PBA factor score and the change in UHDRS-m score over two years.

[a] Model 1: adjusted for sex and age;

[b] Model 2: adjusted for sex, age, baseline use of and changes in use of psychotropics, and baseline UHDRS-m;

[c] Model 3: adjusted for sex, age, baseline use of and changes in use of psychotropics, baseline UHDRS-m, and change in the two other PBA factor scores.

psychotropics or PBA scores between participants and drop-outs at baseline (data not shown).

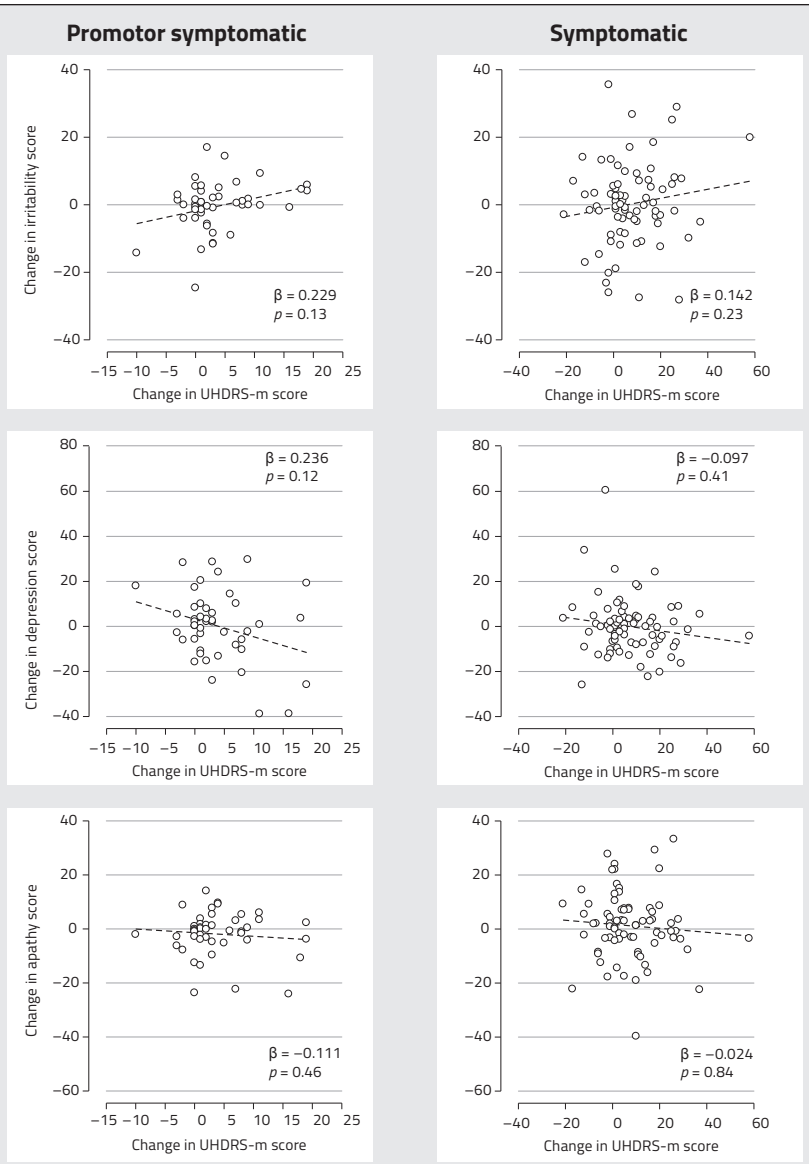
Change in clinical and cognitive characteristics over two years of follow-up

During the 2-year follow-up period the mean UHDRS-m score increased 6.2 points (SE = 1.0; Table 2), the mean TFC score increased with 1.6 points (SE = 0.2; $p < 0.001$), and the mean MMSE score decreased by 0.5 points (SE = 0.1; $p = 0.07$). Many participants (n = 49, 40.5%) had a change in the use of psychotropic drugs: 39 participants had started a new psychotropic medication and 10 participants had stopped their psychotropic medication. Antipsychotics (n = 26) were the most frequently started medication, followed by benzodiazepines (n = 14) and antidepressants (n = 14).

Course of irritability, depression, and apathy over two years of follow-up

Of the three PBA factors, a lower score after two years of follow-up was found for the PBA depression factor that decreased by 4.3 points (SE = 1.4; $p = 0.002$), whereas the irritability and apathy scores did not change significantly (Table 2).

Figure 2. *Association between change in UHDRS-m score and PBA factor scores (irritability, depression, and apathy) over 2 years in 46 pre-motor symptomatic and 75 symptomatic HD mutation carriers, adjusted for sex and age (Model 1).*



UHDRS-m = Unified Huntington's Disease Rating Scale motor section; PBA = Problem Behaviours Assessment. Participants were pre-motor symptomatic (Confidence Level = 0 – 1) or symptomatic (Confidence Level = 2 – 4) at baseline.
Absolute changes are calculated and univariate regression lines and statistics are shown.

For all mutation carriers together, no significant associations were found between the absolute (crude) changes in PBA factor scores and change in UHDRS-m score over two years (Table 3). These crude associations between delta scores are presented in Figure 2. But after full adjustment (Model 3), borderline significant associations were found between an increased UHDRS-m score on the one hand and an increased irritability score and decreased depression score on the other hand (both $p = 0.05$). In participants that were pre-motor symptomatic (Confidence Level = 0 – 1) at baseline, the strongest relationship during the 2-year follow-up period was between an increased UHDRS-m score and increased irritability score ($p = 0.02$).
Of the, at baseline, 46 pre-motor symptomatic mutation carriers, 15 subjects became symptomatic over two years follow-up. These 15 subjects showed non-significant increases in irritability and apathy scores (+2.4; SE 2.6; $p = 0.36$; and +1.2; SE 2.7; $p = 0.64$, respectively) and a non-significant decreases in depression scores (–7.5; SE 5.4; $p = 0.17$) compared to the 31 subjects who remained pre-motor symptomatic. These findings remained similar in the fully adjusted models.

Discussion

In the total group of HD mutation carriers, the absolute depression score decreased over 2 years. No significant changes were found in irritability and apathy over time. In the fully adjusted model, a relationship was found between an increase in UHDRS-m score and an increase in irritability and a decrease in depression, that approached significance. In the subgroup of pre-motor symptomatic mutation carriers (Confidence Level = 0 – 1), however, an increase in motor symptoms was positively associated with change in irritability.

So far, few studies have assessed the progression of psychopathology in HD using a dimensional scale. The PBA was especially designed for the use in HD and this is the first follow-up assessment with the original long version. Currently, TRACK-HD, a multinational longitudinal observational study uses an extensive battery of novel assessment scales, including an abbreviated version of the PBA (PBA-short) to assess different aspects of HD in pre-motor symptomatic, motor symptomatic and controls.[16] Two other studies using the behavioural section of the UHDRS have reported distinct factors for irritability, depression, and executive function, and an additional factor for psychosis.[17,18]

Irritability
In the total group of mutation carriers, a progression in motor symptoms was related to an increase in irritability, although mainly in (at baseline) pre-motor symptomatic mutation carriers. This suggests that mutation carriers who are closer to the overt onset of motor symptoms become more irritable. This is in line with earlier longitudinal studies, that showed an increase of irritability in pre-motor symptomatic mutation carriers,[19,20] although another cross-sectional study did not

find a relationship between proximity to onset and prevalence of irritability symptoms.[21]
The REGISTRY study described that 19% of the participants who had a behavioural assessment showed disruptive or aggressive behaviour at disease onset,[22] but high levels of hostility may already be present before motor symptoms occur.[23] In a cohort of motor symptomatic HD patients, 64% showed some aggressive behaviour at their first visit to an HD clinic.[17] In contrast, cross-sectional analysis of TRACK-HD data showed irritability scores to be higher in advanced disease stages,[16] but no significant difference (all $p \geq 0.22$) was found in change after 12 months between pre-motor symptomatic, motor symptomatic mutation carriers, and controls.[24] Although TRACK-HD measured over a shorter period of time, the lack of difference between subgroups may be a result of the categorical disease staging. Our analysis was based on changes in UHDRS-m scores (as a continuous variable) that may have yielded more statistical power than using the distinct categorical disease stages in TRACK-HD.

Depression
Many cross-sectional studies have reported that depressed mood and sadness are early symptoms of HD and peak during the early motor symptomatic phase,[25,26] whereas significantly lower rates of depression are present in advanced stages of the disease.[25] Pre-motor symptomatic mutation carriers who are close to onset of motor symptoms may already show an increase in depressive symptoms many years before a clinical diagnosis.[21,27,28] Although marginally significant ($p = 0.05$), we found that a increase of motor symptoms was related to a decrease of depressive symptoms. From a psychological point of view, subjects in later stages of the disease may demonstrate adaptation to illness and acceptance of their diagnosis and future. Alternatively, progression of this neurodegenerative disease may have adversely affected the central nervous system and communicative capacity to express their negative affective states. However, lower depression scores in a advanced stage of the disease can also be a result of attrition bias, although no differences in psychopathology were present at baseline between participants and drop-outs.

Apathy
At baseline, motor symptomatic mutation carriers showed significantly more apathy than pre-motor symptomatic carriers, but apathy scores did not change during the 2-year follow-up period and were not related to an increase of the UHDRS-m score. This contrasts somewhat with previous studies, that showed that apathy is more prevalent in advanced disease stages.[8,11,16] These latter studies however had cross-sectional designs. Our 2-year follow-up period may be too short to detect expected changes over time. Another explanation may be the drop-out of more advanced disease mutation carriers who would have shown stronger increases in apathy over time.

Some limitations of our study need to be discussed. First, assessment of psychiatric symptoms in advanced stages of the disease may be hampered by communication difficulties, poor insight, other

cognitive disturbances, and physical co-morbidity that influence the assessment of a psychiatric diagnosis. Secondly, the use of medication might have influenced study outcomes, although we adjusted for the use of psychotropic medication. However, we cannot exclude that the use or discontinuation of medications for motor symptoms, such as tetrabenazine, have influenced our results. Third, although this study has a relatively large population for a study on psychopathology in HD, the numbers for analysis are relatively small, resulting in a possible lack of power, especially when groups of pre-motor symptomatic and symptomatic participants were analyzed separately. Fourth, drop-outs were especially found in patients with more advanced disease stages, resulting in attrition bias. Therefore, absolute changes in time are difficult to interpret, that may also be influenced by regression to the mean effects.

Our clinically relevant findings show that an increase of motor symptoms is related to an increase of irritability in pre-motor symptomatic mutation carriers. Early identification of (pre)clinical changes in HD is of great importance for the design and implementation of future clinical trials to slow the progression of the disease. Furthermore, insights in the occurrence and course of psychiatric symptoms are important to target specific psychiatric symptoms that may result in significant improvements in quality of life.

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Chapter 7

Psychiatric disorders in Huntington's disease; a 2-year follow-up study.

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Abstract

Objective: This study investigates the presence and course of formal psychiatric disorders according to the Diagnostic and Statistical Manual of mental disorders, 4th edition (DSM-IV) in 142 Huntington's disease (HD) mutation carriers in a two-year follow-up design.

Method: Of the 142 mutation carriers, 106 (75%) participated in the second measurement of an ongoing cohort study on psychopathology in HD. Presence of psychiatric disorders was assessed using the Composite International Diagnostic Interview.

Results: Of the 91 patients without a formal psychiatric disorder at baseline, 14 (15%) had a psychiatric disorder after two years, mostly a major depressive disorder (MDD) (64%). The baseline characteristics of lower education, having no children, a lower level of global daily functioning, a lifetime psychiatric diagnosis, and the use of psychotropic medication were predictive of incident psychiatric disorders after 2 years. Of the 15 patients with a psychiatric diagnosis at baseline, 8 (53%) no longer had a psychiatric disorder at follow-up. All 7 patients (47%) with a persistent psychiatric disorder were female and their most prevalent diagnosis was generalized anxiety disorder.

Conclusion: This cohort study confirms that psychiatric disorders, in particular MDD, frequently occur in patients with HD. Professionals working with HD patients should therefore be aware of the high risk of psychopathology in HD, because early diagnosis and treatment of psychiatric disorders may improve the quality of life of patients and their caregivers.

Introduction

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disorder caused by an expanded trinucleotide CAG repeat of the *HTT* gene on chromosome 4p16.3.[1] Clinical features of HD comprise motor abnormalities such as chorea and hypokinesia, cognitive dysfunction, as well as behavioral problems and psychiatric disorders. Behavioral and psychiatric symptoms often precede the manifestation of motor abnormalities of HD.[2,3] In most cases, the age of onset of HD is between 35 and 45 years, whereas the mean duration of disease is 16 years.[4,5] There is no cure for HD and only symptomatic treatment is available.

Depressed mood, anxiety, apathy and irritability are frequently reported neuropsychiatric symptoms in HD, with prevalence rates between 33% and 76%.[4] This broad range can be explained by the use of different assessment methods with varying definitions and cutoffs of neuropsychiatric phenomena in different stages of HD. Of these neuropsychiatric symptoms, only apathy seems to be positively related to the progression of HD.[6]

In a cross-sectional study, we found that both pre-motor symptomatic and symptomatic HD mutation carriers had more formal psychiatric disorders according to the *Diagnostic and Statistical Manual of mental disorders*, 4th edition (DSM-IV), especially major depressive disorder (MDD) and obsessive-compulsive disorder (OCD), compared to the general population.[4] Until now, there are no follow-up studies on the course of psychiatric disorders in HD.

For many patients and their relatives, psychiatric disorders are severely disabling manifestations of HD.[7] Diagnosing and acknowledging the presence of psychopathology in HD is of major importance and may help patients and their families to better cope with the severe symptoms of this progressive disease. Moreover, adequate symptomatic treatment can improve the quality of life of HD patients and their caretakers.

This follow-up study investigates the presence and course of formal psychiatric disorders according to the DSM-IV, as well as their predictors in verified HD mutation carriers.

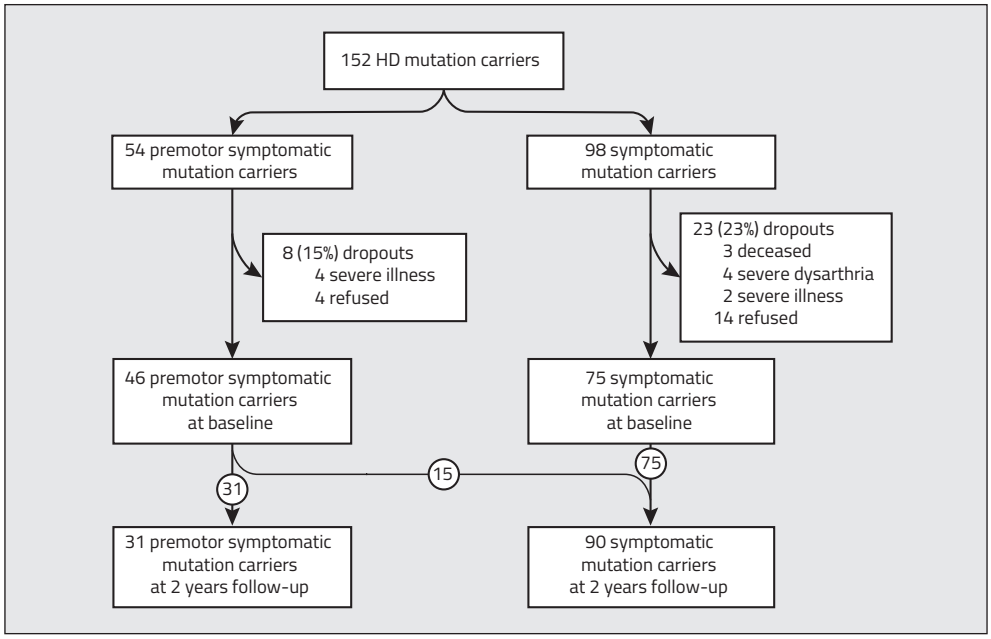
Method

Subjects

Subjects were recruited between May 2004 and August 2006 from the outpatient departments of Neurology and Clinical Genetics of the Leiden University Medical Center, and from a regional nursing home (Overduin in Katwijk) with a specialized ward for HD patients. A detailed description of the study design has been published earlier.[3] In short, this study included 142 verified 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. Three subjects were deceased, whereas 22 (15%) were excluded because of severe cognitive

dysfunctioning (n = 7), end-stage disease (n = 8), and severe dysarthria (n = 7). At follow-up, 11 subjects (10%) refused to participate for various other reasons. This resulted in 106 eligible subjects for the present study (Figure 1). The study was approved by the Medical Ethical Committee of the Leiden University Medical Center. All subjects gave written informed consent.

Figure 1. *Flowchart of the study population*



Instruments

Socio-demographic and clinical characteristics

Information on socio-demographic and clinical characteristics was collected using a standardized interview. The estimated age of onset was calculated according to the formula of Vassos et al.: ln [age of onset (years)] = 6.18 - 0.054 * [CAG repeats (number)].[8] Global daily functioning was assessed using the Total Functioning Capacity (TFC) scale, which is part of the Unified Huntington's Disease Rating Scale (UHDRS).[9] The TFC scale consists of five items and the total score ranges from 0 to 13 points, with lower scores indicating worse performance on daily functioning. Presence of motor symptoms was assessed by a neurologist with extensive experience of HD using the motor section of the UHDRS (UHDRS-m). The UHDRS-m ranges from 0 to 124 points, with higher scores indicating more severe motor impairment. On the basis of the clinical examination, the neurologist assigned a score indicating to what degree he was confident that the presence of the movement disorder in a subject was due to HD. This confidence level score ranges from 0 to 4 points. Mutation

carriers with a confidence level score of 0 (normal) or 1 point (nonspecific motor abnormalities [< 50% confidence]) were classified as pre-motor symptomatic. Mutation carriers with a score of 2 to 4 points (2 = motor abnormalities that may be signs of HD [50% – 89% confidence], 3 = likely signs of HD [90% – 98% confidence], 4 = unequivocal signs of HD [≥ 99% confidence]) were considered motor symptomatic. Use of psychotropic medication was registered.

Assessment of psychiatric disorders

Both at baseline and at follow-up, a computerized version of the Composite International Diagnostic Interview (CIDI) was used to assess the presence of MDD, dysthymia, mania, OCD, panic disorder, generalized anxiety disorder (GAD), social phobia, agoraphobia, and psychosis, according to the DSM-IV criteria.[10] The interrater reliability of the CIDI is excellent, and the test-retest reliability and validity are good,[11] except for patients with significant cognitive impairments. Therefore, the CIDI was not administered to subjects with a Mini-Mental State Examination (MMSE) score < 18 points. At baseline, a psychiatric disorder was considered present when the subject fulfilled the DSM-IV criteria on the day of the interview or in the prior month. When subjects reported a psychiatric disorder which ended before the month preceding the interview at baseline, this was considered a lifetime psychiatric diagnosis. After two years the same interview was repeated to assess the presence of a psychiatric disorder in the period between baseline and follow-up.

Neuropsychological assessment

The MMSE, Symbol Digit Modalities Test (SDMT), Verbal Fluency Test (VFT), and Stroop tests were administered to assess cognitive functioning. The MMSE was used to assess global cognitive functioning.[12] The SDMT examines attention, working memory, and visuo-verbal substitution speed.[13] The VFT is sensitive to frontal executive dysfunction and subtle degrees of semantic memory impairment.[14] The Stroop tests were 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).[15]

Statistical analysis

Data are presented as numbers with percentages, means with standard deviations (SD), or medians with interquartile ranges (IQR) when appropriate. Unpaired *t*-test or non-parametric Mann-Whitney *U*-test, chi-square test, or Fisher's exact test were used when appropriate.

Baseline characteristics of subjects who were lost to follow-up were compared with participants who completed the study.

We categorized the subjects into four groups. The first group consisted of subjects without any psychiatric disorder at either measurement (no psychiatric disorder); the second group was free of psychiatric disorders at baseline, but had one or more psychiatric disorder(s) at follow-up (incident psychiatric disorder); the third group had one or more psychiatric disorder(s) both at baseline and

Table 1. *Baseline socio-demographic and clinical characteristics of 106 mutation carriers based on the presence/absence of psychiatric disorder(s) at two-year follow-up.*

	All Mutation carriers (n=106)	NP (n=77)	IP (n=14)	*p*-value	PP (n=7)	RP (n=8)	*p*-value
Socio-demographic characteristics							
Male gender (n, %)	48 (45)	38 (48)	6 (46)	0.60	0 (0)	5 (83)	0.20
Age (years ± SD)	46 ± 12	46 ± 12	45 ± 11	0.67	45 ± 10	47 ± 19	0.28
Higher education (n, %) [a]	69 (65)	55 (70)	6 (46)	0.001	5 (56)	3 (50)	0.80
Any children (n, %)	78 (74)	60 (76)	8 (62)	< 0.001	7 (78)	4 (67)	0.82
Married or living together (n, %)	80 (76)	58 (73)	10 (77)	0.10	7 (78)	5 (83)	0.17
Clinical characteristics							
CAG repeats (n ± SD)	44 ± 3	43 ± 3	45 ± 2	0.80	43 ± 3	43 ± 2	0.14
Estimated age of onset (years ± SD) [b]	46 ± 7	46 ± 8	44 ± 6	0.36	47 ± 4	48 ± 2	0.44
TFC (points, IQR) [c]	11 (8-13)	12 (9-13)	11 (7-13)	0.03	7 (5-12)	8 (7-10)	0.78
UHDRS-m (points, IQR) [d]	10 (1-32)	11 (1-34)	10 (3-41)	0.13	17 (1-40)	5 (2-21)	0.69
Lifetime psychiatric diagnosis (n, %)	44 (42)	21 (27)	9 (64)	0.01	7 (100)	7 (88)	0.99
Use of psychotropic medication (n, %)	41 (39)	23 (29)	8 (62)	0.002	5 (56)	5 (83)	0.20
MMSE (points, IQR) [e]	28 (26-29)	28 (26-29)	27 (26-29)	0.27	26 (24-28)	28 (25-30)	0.69
ExCog [f]	0.00	0.06	-0.27	0.93	0.14	-0.26	0.97

NP = no psychiatric disorder both at baseline and follow-up; IP = incident psychiatric disorder; PP = persistent psychiatric disorder; RP = remitted psychiatric disorder.
Data are presented as numbers (%), means (± SD) or medians (IQR) when appropriate. *P*-values are calculated by chi-square test, non-parametric Mann Whitney-U test and unpaired *t*-test.

[a] Higher education = > 12 years of education;
[b] Estimated age of onset is computed according to the Vassos formula;[7]
[c] TFC = Total Functioning Capacity: range 0-13 points, with lower score indicating worse performance;
[d] UHDRS-m = Unified Huntington's Disease Rating Scale motor section: range 0-124 points, with higher score indicating more neurological symptoms;
[e] MMSE = Mini-Mental State Examination: range 0-30 points;
[f] ExCog = executive cognitive function is defined by 5 index *z*-scores derived from SDMT, VFT, and 3 Stroop tests in SD from the mean, with lower score indicating worse performance.

at follow-up, independent of the type of psychiatric disorder (persistent psychiatric disorder); and the fourth group had one or more psychiatric disorders at baseline, but none at follow-up (remitted psychiatric disorder).

Because of the low numbers of incident, persistent, and remitted psychiatric disorders, we mainly used simple descriptive statistics for the presence and course of psychiatric disorders, since formal statistical comparison of these groups was hampered by a low statistical power and a high risk of type I errors.

A composite variable for executive cognitive functioning (ExCog) was computed because of strong collinearity (r > 0.80) between the SDMT, VFT, and three Stroop tests. This variable was computed by averaging the standardized *z*-scores of these 5 tests total scores (i.e. subtracting the mean from an individual raw score and then dividing the difference by the SD).

To analyze possible differences in socio-demographic and clinical characteristics, we compared the baseline characteristics of the group with incident psychiatric diagnoses with the group without psychiatric diagnoses at follow-up. All tests were two-tailed with $p < 0.05$ denoting statistically significance. SPSS 17.0 for Windows (SPSS Inc., Chicago, Ill) was used for the statistical analyses.

Results

Table 1 presents the baseline characteristics of all participating mutation carriers combined, as well as the four follow-up groups separately. Of the 91 subjects without a psychiatric diagnosis at baseline, 14 (15%) had one or more incident psychiatric disorder(s) over the two-year follow-up period. Of these, 3 subjects had more than one psychiatric disorder. All 7 subjects with a persistent psychiatric disorder were female, and GAD was the most prevalent disorder in this group. Of the 15 subjects with one or more psychiatric disorder(s) at baseline, 8 had a remission of the psychiatric disorder(s) at follow-up.

The baseline characteristics low education ($p = 0.001$), having no children ($p < 0.001$), lower TFC score ($p = 0.03$), a lifetime psychiatric diagnosis, and the use of psychotropic medication ($p = 0.002$) were predictive of incidence of psychiatric disorders, as compared to the group without psychiatric disorders at both baseline and follow-up. No significant differences were found between the persistent and remitted groups.
The 36 (25%) subjects who were lost to follow up (Figure 1) had a similar baseline prevalence rate of psychopathology as compared to the participants (22% and 26%, respectively). These drop-outs showed a higher median UHDRS-m score (37 points versus 10 points; $p < 0.001$), a lower median MMSE score (26 points versus 28 points; $p = 0.008$), and a lower median TFC score (7 points versus 11 points; $p = 0.001$), compared to the participating subjects, indicating that they were in a more advanced disease stage at baseline (data not shown).

Incident psychiatric disorders
Of the 14 subjects with an incident psychiatric disorder in the follow-up period, 9 (64%) had a MDD. Two subjects with MDD had one (panic disorder) or two (GAD and social phobia) comorbid psychiatric disorder(s). Furthermore, one subject had psychosis, one panic disorder and comorbid mania, one social phobia, one OCD, and one subject had agoraphobia (Table 2). Ten subjects with an incident psychiatric disorder used psychotropic medication at follow-up, whereas four subjects with MDD did not use psychotropic medication. Eight subjects were already using psychotropic medication at baseline, despite the fact that they did not fulfill the criteria for a formal DSM-IV diagnosis at that time. Nine subjects showed a decline of 3 points or more on the TFC scale in the two-year follow-up, indicating a deterioration of their functioning over time. Nine subjects were pre-motor symptomatic at baseline, of whom two became motor symptomatic during the follow-up period.

Persistent psychiatric disorders
Seven HD mutation carriers, all female, had one or more persistent psychiatric disorder(s) at follow-up, although in five subjects the diagnosis was changed into another psychiatric disorder during the

Table 2. *Socio-demographic and clinical characteristics of 14 mutation carriers (I-XIV) with incident psychiatric disorder(s) at two-year follow-up.*

Incident psychiatric disorder	I MDD	II MDD	III MDD	IV MDD	V MDD	VI MDD	VII MDD, PD	VIII MDD, GAD, SPH	IX MDD	X PSY	XI PD, M	XII SPH	XIII OCD	XIV APH
Socio-demographic characteristics														
Gender	m	f	m	f	m	f	f	f	m	f	M	f	m	m
Age (years)	32	33	35	38	40	40	46	53	63	48	44	50	66	69
Higher education[a]	-	+	+	-	+	+	-	-	-	-	+	-	-	+
Children	0	2	0	0	1	2	0	1	2	3	3	4	0	0
Married or living together	-	+	+	+	+	-	+	+	+	+	+	-	-	+
Clinical characteristics														
CAG repeats	47	45	45	45	44	47	43	46	44	46	40	51	41	42
Estimated age of onset (years)[b]	38	43	43	43	45	38	47	40	45	36	56	31	53	50
TFC at baseline (points)[c]	13	12	13	11	9	13	7	7	6	2	12	4	3	13
TFC at follow-up (points)	8	13	7	8	3	13	6	3	3	5	5	0	2	9
UHDRS-m at baseline (points)[d]	10	2	0	10	24	4	9	36	46	54	0	47	67	4
UHDRS-m at follow-up (points)	9	2	3	7	32	17	7	56	47	81	8	34	65	10
Motor symptomatic at baseline[e]	+	-	-	+	+	+	-	+	+	+	-	+	+	-
Lifetime psychiatric diagnosis	-	MDD	MDD, GAD	OCD	MDD	-	MDD, GAD, PD	MDD, DYS, PD	MDD, PSY	-	PD	DYS	-	-
Use of psychotropic medication at baseline[f]	-	-	SSRI	B	SSRI	-	-	SSRI, B	Tiap, SSRI	SSRI	SSRI	SSRI, AAP	-	-
Use of psychotropics at follow-up	-	-	SSRI	AAP, B	SSRI	-	-	SSRI, AAP, B	Tiap, SSRI	SSRI, AAP, B	SSRI, AAP, B	SSRI, AAP, B	AAP	B
MMSE at baseline (points)[g]	25	29	29	25	27	26	28	29	27	18	27	27	27	28
MMSE at follow-up (points)	28	30	29	28	26	28	30	28	29	21	29	22	20	29
ExCog decline[h]	+	-	-	-	+	+	-	-	-	-	+	-	-	-

MDD = major depressive disorder; PD = panic disorder; GAD = generalized anxiety disorder; SPH = social phobia; PSY = psychosis; M = mania; OCD = obsessive-compulsive disorder; APH = agoraphobia.

[a] Higher education ≥ 12 years of education.

[b] Estimated age of onset is computed according to the Vassos formula.[7]

[c] TFC = Total Functioning Capacity: range 0-13 points, with lower score indicating worse performance.

[d] UHDRS-m = Unified Huntington's Disease Rating Scale motor section: range 0-124 points, with higher score indicating more neurological symptoms.

[e] '-' = pre-motor symptomatic (Confidence Level score: 0 - 1); '+' = motor symptomatic (Confidence Level score: 2 - 4).

[f] SSRI = selective serotonin re-uptake inhibitors; AAP = atypical antipsychotics; B = benzodiazepines, Tiap = tiapridal.

[g] MMSE = Mini-Mental State Examination: range 0-30 points.

[h] ExCog = executive cognitive function: '+' = decline, '-' = incline. ExCog is defined by 5 index *z*-scores derived from SDMT, VFT, and 3 Stroop tests in SD from the mean, lower score indicating worse performance.

Table 3. *Socio-demographic and clinical characteristics of 7 mutation carriers (I-VII) with persistent psychiatric disorder(s) at two-year follow-up.*

	I	II	III	IV	V	VI	VII
Socio-demographic characteristics							
Gender	f	f	F	f	f	f	f
Age (years)	54	51	44	31	29	55	53
Higher education[a]	+	-	+	+	+	-	-
Children	0	1	2	1	0	2	2
Married or living together	+	+	+	+	-	+	+
Clinical characteristics							
Psychiatric disorder at baseline	MDD, PD	MDD, DYS, SPH	OCD	GAD, SPH	MDD, GAD, SPH	GAD, PD	MDD
Psychiatric diagnosis at follow-up	APH	MDD, GAD, PD	MDD, OCD	MDD, DYS, GAD, SPH	GAD, SPH	GAD, PD	MDD
CAG repeats	42	43	43	45	45	44	41
Estimated age of onset (years)[b]	50	47	47	42	42	45	53
TFC at baseline (points)[c]	9	7	5	13	10	6	4
TFC at follow-up (points)	8	4	2	11	12	6	4
UHDRS-m at baseline (points)[d]	17	31	4	0	2	60	30
UHDRS-m at follow-up (points)	42	19	23	5	3	59	48
Motor symptomatic at baseline[e]	+	+	-	-	-	+	+
Lifetime psychiatric diagnosis	DYS, GAD, PD	MDD, DYS, SPH	MDD, GAD, OCD	MDD, GAD, SPH	MDD, GAD, SPH	GAD, PD	MDD, PD
Psychotropic medication at baseline[f]	SSRI	TCA, AAP, B	-	-	SSRI, B	-	SSRI, B
Psychotropics at follow-up	SSRI	TCA, AAP, B	SSRI, Tiap, B	SSRI	SSRI	B	SSRI, AAP, B
MMSE at baseline (points)[g]	30	22	25	25	30	26	26
MMSE at follow-up (points)	28	24	28	27	30	28	24
ExCog decline[h]	-	-	+	+	+	+	+

MDD = major depressive disorder; PD = panic disorder; GAD = generalized anxiety disorder; PSY = psychosis; SPH = social phobia; OCD = obsessive-compulsive disorder; APH = agoraphobia; M = mania.

[a] Higher education ≥ 12 years of education.

[b] Estimated age of onset is computed according to the Vassos formula.[7]

[c] TFC = Total Functioning Capacity: range 0-13 points, with lower score indicating worse performance.

[d] UHDRS-m = Unified Huntington's Disease Rating Scale motor section: range 0-124 points, with higher score indicating more neurological symptoms.

[e] '-' = pre-motor symptomatic (Confidence Level score: 0 - 1); '+' = motor symptomatic (Confidence Level score: 2-4).

[f] SSRI = selective serotonin re-uptake inhibitors; AAP = atypical antipsychotics; B = benzodiazepines, Tiap = tiapridal.

[g] MMSE = Mini-Mental State Examination: range 0-30 points.

[h] ExCog = executive cognitive function: '+' = decline, '-' = incline. ExCog is defined by 5 index *z*-scores derived from SDMT, VFT, and 3 Stroop tests in SD from the mean, lower score indicating worse performance.

Table 4. *Socio-demographic and clinical characteristics of 8 mutation carriers (I-VIII) with remitted psychiatric disorder(s) at two-year follow-up.*

Psychiatric disorder at baseline	I OCD	II MDD, OCD	III GAD, SPH, APH	IV SPH	V PD, OCD	VI SPH	VII MDD	VIII MDD
Socio-demographic characteristics								
Gender	f	m	m	m	F	M	F	m
Age (years)	43	72	31	57	41	37	24	60
Higher education[a]	-	-	-	+	+	+	+	-
Children	1	0	0	2	2	1	1	2
Married or living together	-	+	-	+	+	+	+	+
Clinical characteristics								
CAG repeats	41	43	43	43	43	43	44	42
Estimated age of onset (years)[b]	53	47	47	47	47	47	45	50
TFC at baseline (points)[c]	13	4	8	8	3	11	8	10
TFC at follow-up (points)	11	1	12	5	2	12	12	10
UHDRS-m at baseline (points)[d]	0	65	2	6	49	4	0	5
UHDRS-m at follow-up (points)	4	59	18	8	60	9	-	16
Motor symptomatic at baseline[e]	-	+	-	+	+	+	-	-
Lifetime psychiatric diagnosis	MDD, OCD	OCD	DYS, GAD, SPH, APH	GAD, SPH	MDD, PD, OCD	SPH	-	MDD
Psychotropic medication at baseline[f]	-	SSRI, AAP, B	-	SSRI	SSRI, B	SSRI, B	B	B
Psychotropic medication at follow-up	-	SSRI	SSRI	SSRI, Tiap	SSRI, AAP, B	SSRI, B	B	SSRI, AAP, B
MMSE at baseline (points)[g]	26	23	30	28	22	28	30	26
MMSE at follow-up (points)	26	25	29	27	20	30	30	25
ExCog decline[h]	-	+	+	+	+	-	-	-

MDD = major depressive disorder; PD = panic disorder; GAD = generalized anxiety disorder; PSY = psychosis; SPH = social phobia; OCD = obsessive-compulsive disorder; APH = agoraphobia; M = mania.

[a] Higher education ≥ 12 years of education.

[b] Estimated age of onset is computed according to the Vassos formula.[7]

[c] TFC = Total Functioning Capacity: range 0-13 points, with lower score indicating worse performance.

[d] UHDRS-m = Unified Huntington's Disease Rating Scale motor section: range 0-124 points, with higher score indicating more neurological symptoms.

[e] '-' = pre-motor symptomatic (Confidence Level score: 0 - 1); '+' = motor symptomatic (Confidence Level score: 2-4).

[f] SSRI = selective serotonin re-uptake inhibitors; AAP = atypical antipsychotics; B = benzodiazepines, Tiap = tiapridal.

[g] MMSE = Mini-Mental State Examination: range 0-30 points.

[h] ExCog = executive cognitive function: '+' = decline, '-' = incline. ExCog is defined by 5 index z-scores derived from SDMT, VFT, and 3 Stroop tests in SD from the mean, lower score indicating worse performance.

follow-up period (Table 3). MDD (n=3 at baseline, and n=3 at follow-up) and GAD (n=3 at baseline, and n=4 at follow-up) were the most frequently occurring psychiatric disorders in this group. Three subjects with a persistent psychiatric disorder did not use psychotropic medication at baseline, but all 7 received psychotropic medication at follow-up.

Remitted psychiatric disorders
Eight HD mutation carriers had one or more psychiatric disorder(s) at baseline, but no longer after two years (Table 4). The most frequent remitted psychiatric disorders in this group were MDD (n=3), OCD (n=3), and social phobia (n=3). Six subjects used psychotropic medication at baseline, and only one did not receive psychotropic medication at follow-up. This medication-free subject had a remitted OCD.

Discussion

In this prospective cohort study among HD mutation carriers, 15% of the subjects without a psychiatric disorder at baseline had a formal psychiatric disorder after two years, mostly a MDD (64%). Baseline predictors for these subjects with incident psychopathology were lower education, less often having children, poorer daily global functioning, a lifetime psychiatric diagnosis, and the use of psychotropic medication. Of the 15 subjects with a psychiatric diagnosis at baseline, 8 (53%) no longer had a psychiatric disorder at follow-up. All 7 subjects (47%) with a persistent psychiatric disorder were female and GAD was their most prevalent diagnosis; some of these affected women were diagnosed with different psychiatric disorders after two years of follow-up. Most subjects with a psychiatric diagnosis at follow-up received psychopharmacological treatment, although not always adequately.

Because of the small number of subjects with psychopathology and a subsequent lack of power for further analysis, our results need to be interpreted with caution. Nevertheless, we have confirmed the high incidence of MDD in HD. Although longitudinal studies are lacking, this result is consistent with reported high prevalences of MDD of up to 30%.[4,16] This result contrasts with incidence rates found in other neurodegenerative disease, i.e. Parkinson's disease, in which an incidence rate of MDD of 2% per year is reported,[17,18] and with incidence rates found among the general population, as the two-year incidence rates of psychopathology among the general population are around 4%.[19] No follow-up studies on the incidence of formal psychiatric disorders in HD have been published, but some studies assessed the incidence and course of psychiatric symptoms and behavioral problems during the progression of HD.[20-22] Large multi-center studies are currently in progress to assess the course of HD in more detail, including psychiatric symptoms and behavioral problems.[23-25]

In the present study, some subjects with a persistent psychiatric disorder switched to another psychiatric disorder after two years. These transitions between specific psychiatric diagnoses and the occurrence of comorbid psychiatric disorders indicate diagnostic instability. There are several explanations for this instability in HD. First, diagnostic instability may be due to profound fluctuations in disease manifestations over time, or merely to a consequence of rigid diagnostic criteria. Consequently, the features and course of psychopathology in HD are probably not fully captured with the formal DSM-IV criteria, as has been reported for other neurodegenerative diseases.[26,27] Moreover, the presence of physical symptoms of HD (such as chorea, weight loss, and sleeping problems) may interfere with the psychiatric diagnosis. Second, assessing psychopathology in patients with moderate to severe HD is often challenging due to a possible lack of insight or poor disease awareness, combined with comorbid cognitive impairments. Caregivers or other informants are often needed to provide information during the assessment of psychopathology in advanced symptomatic HD patients, which may lead to information that is inconsistent with that elicited by patients and to overestimated prevalences of psychiatric disorders.

Although it was not the focus of this study, only 57% of the subjects with an incident psychiatric disorder at follow-up appeared to receive adequate psychopharmacological treatment according to the Dutch treatment protocols. However, it remains unclear whether this was related to a lack of recognition of psychopathology in HD. Nevertheless, adequate treatment is important to induce remission of the psychiatric disorder, to improve the quality of life, and to reduce the risk of suicide. All subjects with a persistent psychiatric disorder used some kind of psychotropic medication that is indicated for the distinct disorders. Selective serotonin reuptake inhibitors (SSRI) were the most often used antidepressants, whereas almost no tricyclic antidepressants were used; this is in line with recommendation made in an earlier review.(28) However, we do not know whether subjects received non-pharmacological interventions (e.g., psychotherapy) instead of – or parallel to – medication, although the efficacy of psychotherapy has scarcely been studied in HD. Psychotropic medication was also used by 29% of the subjects free of a psychiatric diagnosis at baseline. This group may have had a psychiatric diagnosis prior to baseline, being adequately treated.

The group with incident psychopathology had a slightly, but significantly, lower baseline TFC score compared to the group without psychiatric diagnoses at both measurements. Since the persistent and remitted groups also had lower baseline TFC scores, this indicates that having a psychiatric disorder is inversely associated with global daily functioning. This is in line with a recent study reporting that motor, cognitive, and mood symptoms are highly associated with poorer general function.[29]

We found no association between baseline measures of motor functioning or global cognitive functioning and transitions in the presence of psychiatric disorders. This confirms the results of earlier studies, in which no associations were found between psychopathology (such as depressive or anxiety symptoms), and cognitive or motor deterioration, or CAG length.[30,31]

The strength of this study is its prospective design and the use of validated and fully structured instruments to assess formal psychiatric disorders in HD mutation carriers. Limitations of the study are the relatively low number of subjects and the high number of drop-outs. Although the prevalence rates of psychiatric disorders at baseline were similar in the participating group versus drop-outs, different forms of bias cannot be ruled out.

We conclude that professionals working with HD patients should be aware of the high risk of psychopathology in HD. Adequate and early diagnosis and treatment of psychiatric disorders may improve the quality of life of patients and their caregivers, and lower suicide risk. Larger longitudinal studies are needed to confirm our findings, and to assess the independent predictors for incident psychiatric disorders in HD.

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Chapter 8

Summary and concluding remarks Nederlandse samenvatting

Summary and concluding remarks

This thesis describes a study on neuropsychiatric symptoms in Huntington's Disease (HD). This cohort study was performed in HD mutation carriers (both pre-motor symptomatic and motor symptomatic), and a control group of non-carriers that had an a-priori 50% risk for HD. The study started in may 2004 and a second measurement was performed 2 years later. The aim of this study was to study the presence and course of both formal psychiatric disorders and neuropsychiatric symptoms, and to find correlates and predictors associated with the psychiatric phenomena.

Irritability is a common neuropsychiatric symptom in patients with HD. The term 'irritability' has been used as a description of behaviour varying from bad temper to violent outbursts. We used the Irritability Scale to assess the prevalence of irritability in HD; the results are presented in Chapter 2. Since it was not known what cut-off should be used in HD for the assessment of irritability in HD, we began with a psychometric study of the Irritability Scale. The Irritability Scale was tested using receiver operating characteristic analysis against different cut-offs of the irritability factor of the Problem Behaviours Assessment (PBA) scale. A robust cut-off score of ≥ 14 points was found, indicating that 35% of the mutation carriers were irritable, while only 9% of the non-carriers were irritable (p = 0.001). There was a moderate level of agreement between self-report and informant-report scores (intraclass correlation (ICC) = 0.61). Using univariate and multivariate regression analyses, independent correlates of self-reported irritability were being married/living together, CAG repeat length, and the use of benzodiazepines. Using the same model with the informant's irritability score, use of benzodiazepines was the only significant independent correlate of irritability.

The results of our cross-sectional study on apathy are described in Chapter 3. Apathy is characterized as a syndrome with a lack of motivational behaviour, with loss of goal directed behaviour, cognitive activities, and emotions. Using the Apathy Scale and a previously described cut-off score of ≥14 points, we found that 32% of all mutation carriers were apathetic, whereas none of the controls were. Mutation carriers with apathy were more often depressed, and used more often antidepressants or neuroleptics. Since apathy may be a symptom of depression, we also analyzed mutation carriers with apathy after exclusion of 10 depressed patients. Multivariable logistic regression analysis showed that these non-depressed mutation carriers with apathy were more often male, used more often neuroleptics or benzodiazepines, and were in a more advanced stage of the disease.

Hypokinesia is an important motor disturbance in HD but its clinical, neuropsychiatric, and cognitive correlates are largely unknown. The results of our study on associations between hypokinesia and mental rigidity and apathy are described in Chapter 4 Our hypothesis was that motor rigidity (hypokinesia) and mental rigidity or apathy are related in HD. Analysis of our data showed an

association between hypokinesia and the presence of apathy and cognitive deterioration, both global and executive cognitive functioning. Hypokinesia was also associated with the use of antipsychotics and disease stage. Hypokinesia score was inversely associated with the TFC score (a measure for global daily functioning), also after adjusting for chorea, use of antipsychotics, apathy, and global and executive cognitive functioning. Using forward logistic regression analysis, poor executive cognitive functioning was the only independent correlate of hypokinesia. In conclusion, the presence of moderate to severe hypokinesia in HD patients co-occurs with executive cognitive dysfunction and adversely affects global functioning.

The results of our longitudinal study on apathy and its predictors are given in Chapter 5. At 2-year follow-up, 14% of the subjects without apathy at baseline had developed apathy according to the Apathy Scale. The only predictor for the development of apathy at follow-up was a lower score on the Mini-Mental State Examination at baseline, suggesting that poorer cognitive functioning precedes apathy in HD. Unexpectedly, 41% of the subjects with apathy at baseline did no longer fulfill the criteria of apathy at follow-up. Unfortunately, we could not assess predictors of remittance of apathy in this group because of the small sample size. Twenty subjects had persistent apathy, with a low baseline score on the Symbol Digits Modalities Test as the only predictor. These results showed that apathy in HD is closely linked to global and executive cognitive performance.

We describe the course of the common neuropsychiatric symptoms depression, irritability, and apathy in HD using the PBA during a 2-year follow-up period in Chapter 6. Multivariate linear regression analysis was performed to assess their relationships with the change of the motor score of the Unified Huntington's Disease Rating Scale (UHDRS-m) in premotor symptomatic and motor symptomatic mutation carriers. These factors were related to the progression of motoric symptoms over a 2-year period.
The median depression score of all participants decreased, whereas irritability and apathy scores did not change significantly. An increase in irritability was related to an increase in motor score in at baseline premotor symptomatic mutation carriers only. Irritability may therefore be an early marker for disease progression.

The presence and course of formal psychiatric disorders is described in Chapter 7. Formal psychiatric disorders according to the Diagnostic and Statistical Manual of mental disorders, 4th edition (DSM-IV) were assessed using the Composite International Diagnostic Interview. Of all mutation carriers without a formal psychiatric disorder at baseline, 15% had an incident psychiatric disorder after two years, mostly a major depressive disorder (64%). Baseline characteristics that were predictive of incident psychiatric disorders after 2 years were lower education, having no children, a lower level of global daily functioning, a previous psychiatric disorder, and the use of psychotropic medication. Of the 15 patients with a formal psychiatric diagnosis at baseline, eight patients no longer had a

psychiatric disorder at follow-up. All seven patients with a persistent psychiatric disorder were female and their most prevalent diagnosis was generalized anxiety disorder.

This cohort study confirms that neuropsychiatric symptoms frequently occur in patients with HD. We expected a diminished insight in patients with a neuropsychiatric symptoms like irritability, but most patients were aware of their irritability, which was shown with a moderate level of agreement between self-report and informant-report scores.
A strong relationship was found between the presence of psychopathology, cognitive functioning and global daily functioning. Since early diagnosis and treatment of psychiatric disorders may improve the quality of life of both patients and their caregivers, professionals working with HD patients should be aware of the high prevalence of psychopathology in HD. Irritability may be an early sign of the disease, but only apathy was closely related to the progression of HD indicating a relationship with the progressive neurodegenerative nature of the disease. However, we also found associations with the use of psychotropic medications. Therefore, we recommend a frequent evaluation of the use of psychotropic medication, in particular in advanced stage patients who often use many types of medications.
Unfortunately, there are only a few small studies on treatments of neuropsychiatric symptoms of HD. Since there is no cure for this disease yet, we recommend to develop randomized controlled trials for symptomatic treatments to improve the quality of life of patients.

Samenvatting en conclusies

Dit proefschrift beschrijft onderzoek naar neuropsychiatrische fenomenen bij de ziekte van Huntington. Het onderzoek is verricht bij zowel presymptomatische als symptomatische mutatiedragers van de ziekte van Huntington en een controlegroep van niet-mutatiedragers die een a-priori 50% risico hadden op de ziekte van Huntington. De studie is gestart in mei 2004 en 2 jaar na de baseline meting is een tweede meting verricht. Het doel van de studie was om de aanwezigheid en het beloop van neuropsychiatrische symptomen te onderzoeken. Ook werden correlaten en voorspellers van de neuropsychiatrische fenomenen onderzocht.

Prikkelbaarheid is een veelvoorkomend neuropsychiatrisch symptoom bij patiënten met de ziekte van Huntington. De term 'prikkelbaarheid' werd gebruikt om gedrag te beschrijven dat kan variëren van een slecht humeur tot impulsdoorbraken. In ons onderzoek is de Prikkelbaarheidsschaal gebruikt om de prevalentie van prikkelbaarheid bij de ziekte van Huntington te onderzoeken. De resultaten hiervan zijn weergegeven in hoofdstuk 2. Omdat er geen afkappunt bekend was voor de aanwezigheid van prikkelbaarheid volgens de Prikkelbaarheidsschaal bij de ziekte van Huntington, werd eerst een psychometrische studie verricht van de Prikkelbaarheidsschaal. De Prikkelbaarheidsschaal werd middels een 'receiver operating characteristic' analyse afgezet tegen verschillende afkappunten voor prikkelbaarheid volgens de Problem Behaviours Assessment (PBA) schaal.
Een afkappunt van ≥ 14 punten werd vastgesteld, waarbij bleek dat 35% van de mutatiedragers prikkelbaar was, tegen 9% van de niet-mutatiedragers (p = 0.001).
Er werd een redelijke overeenkomst vastgesteld tussen de zelfrapportagevragenlijst en de bij de informant afgenomen vragenlijst (intraclass correlatie (ICC) = 0.61). Middels univariate en multivariate regressieanalyse werden het samenwonen/getrouwd zijn, de CAG-repeatlengte en het gebruik van benzodiazepines als onafhankelijke variabelen voor prikkelbaarheid gevonden. Bij toepassing van hetzelfde model op de vragenlijst van de informanten, werd het gebruik van benzodiazepines als enige onafhankelijke variabele gevonden.

De resultaten van het cross-sectionele onderzoek naar apathie bij de ziekte van Huntington worden beschreven in hoofdstuk 3. Apathie is een neuropsychiatrisch syndroom dat gekenmerkt wordt door een gebrek aan motivatie, verminderd doelgericht gedrag en afvlakking van emoties. Met de Apathieschaal (afkappunt van ≥14 punten) werd gevonden dat 32% van de mutatiedragers apathisch was, terwijl van de controlegroep niemand apathisch was.
Mutatiedragers met apathie waren vaker depressief en gebruikten vaker antidepressiva of neuroleptica. Omdat apathie een symptoom van depressie kon zijn, werd de analyse herhaald in de mutatiedragers zonder depressie. Multivariate logistische regressieanalyse liet zien dat deze niet-

depressieve mutatiedragers met apathie vaker van het mannelijke geslacht waren, dat ze vaker neuroleptica of benzodiazepines gebruikten en dat de ziekte bij hen verder gevorderd was.

Hypokinesie is een belangrijk motorisch symptoom van de ziekte van Huntington. Het is onduidelijk welke neuropsychiatrische en cognitieve correlaten samengaan met hypokinesie. Onze hypothese was dat motorische rigiditeit (hypokinesie) en mentale rigiditeit (apathie) samen voor zouden komen bij de ziekte van Huntington. De resultaten van dit onderzoek worden beschreven in hoofdstuk 4. Analyse van onze data liet een associatie zien tussen hypokinesie en de aanwezigheid van apathie en cognitieve achteruitgang (zowel globaal als executief). Hypokinesie was ook geassocieerd met het gebruik van antipsychotica, het ziektestadium en een verminderd algemeen functioneren. Na logistische regressieanalyse was alleen een slechter executief cognitief functioneren onafhankelijk gecorreleerd met hypokinesie.

De resultaten van onze longitudinale studie betreffende voorspellers van apathie bij de ziekte van Huntington zijn beschreven in hoofdstuk 5. Bij het vervolgonderzoek na 2 jaar bleek dat 14% van de onderzochte deelnemers die geen apathie hadden bij de beginmeting, apathie had ontwikkeld. De enige voorspeller voor het ontwikkelen van apathie was een lagere score op de Mini-Mental State Examination bij de beginmeting, wat suggereert dat slechter cognitief functioneren voorafgaat aan apathie bij de ziekte van Huntington.
Een onverwachte bevinding was dat 41% van de deelnemers die bij de beginmeting apathie had, bij de vervolgmeting niet meer apathisch was. Helaas konden we geen voorspellers vinden voor het in remissie gaan van de apathie omdat het aantal patiënten te klein was. Twintig deelnemers hadden nog steeds apathie bij de vervolgmeting, en bij hen was een lagere score bij de beginmeting op de executieve Symbol Digits Modalities Test de enige voorspeller. Deze resultaten laten zien dat apathie bij de ziekte van Huntington sterk samenhangt met zowel globaal als executief cognitief functioneren.

In hoofdstuk 6 wordt het beloop van frequent voorkomende neuropsychiatrische symptomen als depressie, prikkelbaarheid en apathie bij de ziekte van Huntington beschreven. Deze symptomen werden vastgesteld met de PBA en het beloop daarvan werd over een periode van 2 jaar onderzocht. Multivariate lineaire regressieanalyse werd verricht om de veranderingen in motorscore volgens de Unified Huntington's Disease Rating Scale (UHDRS-m) in premotorsymptomatische en motorsymptomatische mutatiedragers te onderzoeken in relatie tot deze neuropsychiatrische symptomen.
Gedurende de twee jaar nam de depressiescore af, terwijl de prikkelbaarheids- en apathiescores niet significant veranderden. Alleen bij de oorspronkelijk premotorsymptomatische mutatiedragers was een toename van prikkelbaarheid gerelateerd aan een toename in de motorscore. Prikkelbaarheid zou daarom een vroege manifestatie voor ziekteprogressie kunnen zijn.

De aanwezigheid en het beloop van formele psychiatrische stoornissen is beschreven in hoofdstuk 7. De aanwezigheid en het beloop van psychiatrische stoornissen werd vastgesteld met behulp van het Composite International Diagnostic Interview waarbij de criteria van de Diagnostic and Statistical Manual of Mental disorders, 4de editie (DSM-IV) worden gebruikt.
Vijftien procent van alle mutatiedragers zonder een formele psychiatrische diagnose bij de beginmeting, had een psychiatrische stoornis bij de vervolgmeting. Meestal was dit een (ernstige) depressieve stoornis (64%).
Bij de patiënten zonder een psychiatrische stoornis bij de beginmeting waren een lager opleidingsniveau, kinderloosheid, een lager niveau van algemeen functioneren, een eerdere psychiatrische stoornis en het gebruik van psychotrope medicatie bij de beginmeting voorspellend voor het ontwikkelen van een psychiatrische stoornis na 2 jaar.
Van de 15 patiënten met een formele psychiatrische diagnose bij de beginmeting hadden er acht geen psychiatrische diagnose meer bij de vervolgmeting. De zeven patiënten met een persisterende psychiatrische diagnose waren van het vrouwelijke geslacht en de meest gestelde diagnose was een gegeneraliseerde angststoornis.

Het in dit proefschrift beschreven onderzoek bevestigt dat neuropsychiatrische fenomenen frequent voorkomen bij patiënten met de ziekte van Huntington. Aangezien vroege diagnostiek en behandeling van psychopathologie de kwaliteit van leven van zowel patiënten als hun verzorgers/familie kan verbeteren, moeten professionals die Huntingtonpatiënten behandelen gericht diagnostiek doen naar psychopathologie. Uit het beschreven onderzoek is gebleken dat prikkelbaarheid mogelijk een vroege manifestatie is van het ziekteproces en dat apathie een relatie heeft met progressie van de ziekte van Huntington. Omdat het gebruik van psychotrope medicatie mogelijk geassocieerd is met apathie, is frequente evaluatie van het gebruik van psychotrope medicatie belangrijk, vooral in een meer gevorderd stadium van het ziekteproces, omdat er dan vaak sprake is van polyfarmacie.
Verder onderzoek naar mogelijke effectieve symptomatische behandelingen van psychiatrische fenomenen van de ziekte van Huntington is noodzakelijk om hen als behandelaars beter bij te kunnen staan.

Chapter 9

Curriculum Vitae
Publicatielijst
Dankwoord

Curriculum Vitae

Nanda Reedeker is 20 maart 1977 te Dordrecht geboren. Na het behalen van het gymnasium diploma in 1995 aan de Guido de Brès te Rotterdam Lombardijen, studeerde zij geneeskunde aan de Erasmus Universiteit te Rotterdam. Tijdens het afstuderen heeft zij enige tijd onderzoek gedaan naar de rol van stress factoren in het veroorzaken van exacerbaties bij Multiple Sclerose. In 2003 ontving zij de artsenbul.

Aansluitend werkte zij gedurende anderhalf jaar als arts-assistente bij Bavo Europoort te Rotterdam Zuid. Daarna werkte zij vanaf 2005 gedurende een jaar als arts-assistente bij de afdeling neurologie van het Amphia Ziekenhuis te Breda. Voor zij in opleiding ging tot psychiater heeft zij nog gedurende een half jaar bij Bavo Europoort te Spijkenisse gewerkt. In 2006 startte zij met haar opleiding tot psychiater in het Leids Universitair Medisch Centrum met prof.dr. F.G. Zitman als opleider.

Tijdens de opleiding tot psychiater onderbrak zij voor twee jaar haar opleiding om fulltime promotieonderzoek te doen naar neuropsychiatrische symptomen bij de Ziekte van Huntington. In 2013 werd zij geregistreerd als psychiater, waarna zij ging werken bij Bavo Europoort binnen een FACT Team en de polikliniek/ dagbehandeling Niet Aangeboren Hersenletsel (NAH). Hier is zij nog steeds werkzaam.

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Dankwoord

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