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

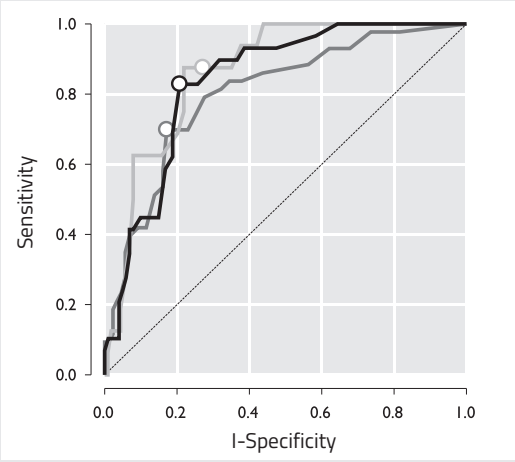
The Cronbach's alphas were 0.90 for the IS-self and 0.93 for the IS-informant. There was some evidence for convergent validity with the irritability item of the UHDRS-b indicated by a Spearman's correlation coefficient of 0.56 (p = 0.001, n = 32 with complete data for both scales). Using ROC

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.*

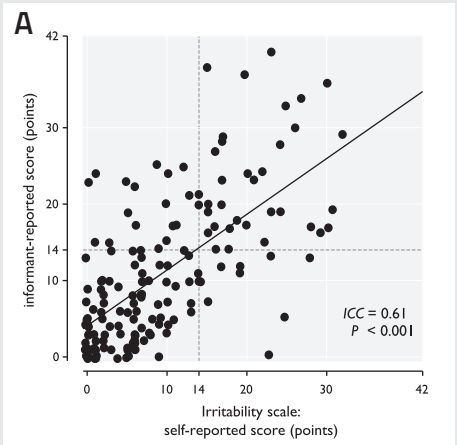


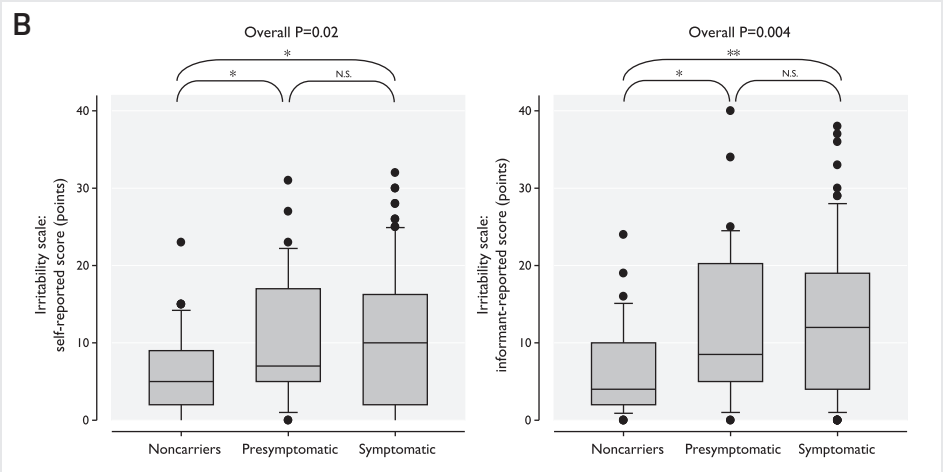
The dark grey line is with a cut-off score of 10 points (resulting in 33.1% with irritability). The black line is with cut-off score of 15 points (resulting in 22.3% with irritability). The light grey line is with a cut-off score of 20 points (resulting in 12.3% with irritability). The open dots indicate 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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