PSYCHOPATHOLOGY IN HUNTINGTON'S DISEASE

Psychopathology in Huntington's Disease

PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. P.F. van der Heijden,
volgens besluit van het College voor Promoties,
te verdedigen op dinsdag 2 februari 2010
klokke 16.15 uur

door
Erik van Duijn

geboren te Katwijk
in 1971

Promotiecommissie

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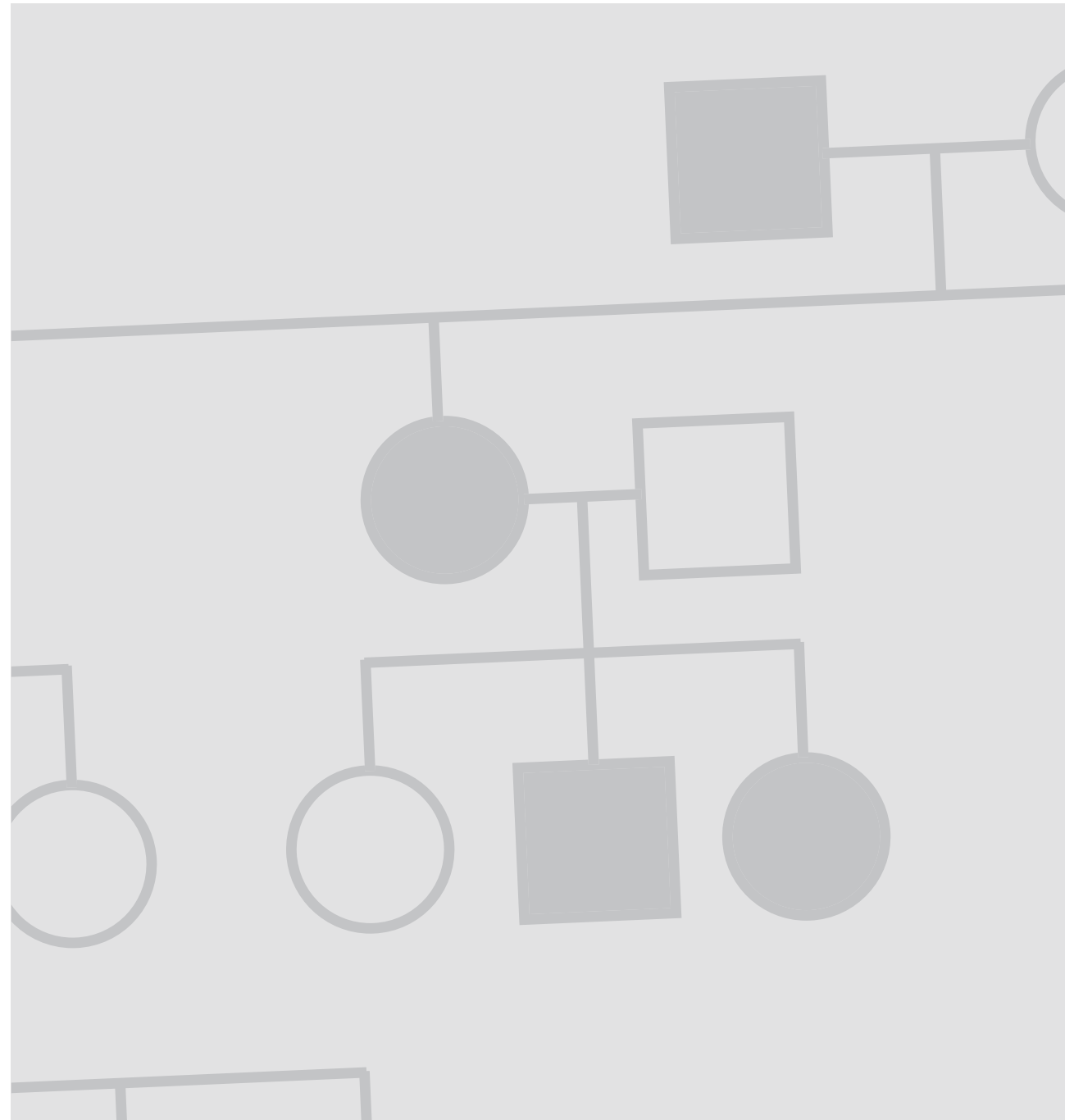
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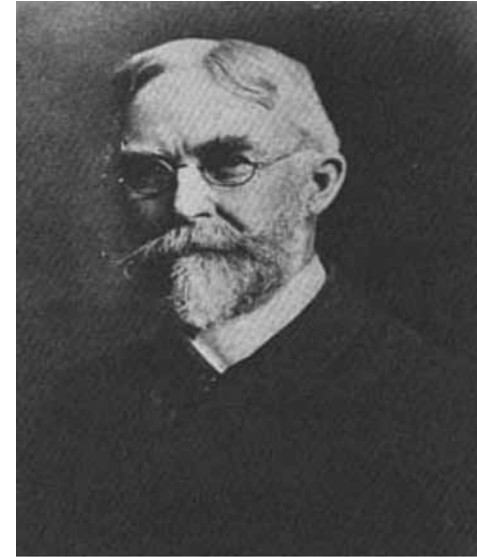
George Huntington (1850 – 1916)

Contents

Chapter 1

Introduction

In his essay 'On Chorea', George Huntington (1850 - 1916) described three disease characteristics of what was since then called Huntington's chorea: the hereditary nature, the tendency to insanity and suicidal behavior, and the manifestation of the illness at adult age.[1] Clearly, he was already aware that next to the observable motor symptoms, patients also suffer from psychiatric disorders.

History

In the early twentieth century, the Dutch psychiatrist Gerbrandus Jelgersma (1859 - 1942) portrayed 'chorea hereditaria' as an organic brain disease with severe psychiatric symptoms that occurred in specific families. In his 'Leerboek der Psychiatrie', he discussed all kinds of psychiatric symptoms which he had seen in patients with this disease: melancholia, dysphoria, irritability, anxiety, delusional thoughts, indifference, ignorant behavior, and at the end dementia.[2] For a long period, patients with Huntington's disease were hospitalized mainly in psychiatric hospitals, because of their severe psychiatric symptoms.

In 1983, the localization of a DNA polymorphism linked with the transmission of Huntington's disease was reported.[3] Genetic linkage analysis to assess the risk of developing the disease with 95% accuracy became available in 1986. Finally, the causal genetic mutation of Huntington's disease was discovered in 1993.[4] Since this discovery, predictive testing with a theoretical 100% accuracy became available. Although predictive testing is widely available in the Netherlands, only 25% of all persons at risk choose to be tested.

Clinical features

Huntington's disease is characterized by a triad of psychiatric, motor, and cognitive symptoms.[5] These symptoms commonly co-occur, though in clinical practice patients are typically only diagnosed with Huntington's disease once motor symptoms appear.

Psychiatric symptoms

The occurrence of psychiatric symptoms can be the first sign of Huntington's disease.[6] A subtle, though progressive, personality change may herald the onset of the disease. Psychopathology in Huntington's disease includes psychiatric disorders such as depression, as well as neuropsychiatric behavioral problems such as apathy and impulsivity.[7,8]

Reported prevalences of different psychiatric disorders and behavioral problems vary widely, depending on the criteria used and disease stage examined. Also, major differences exist in applied measurements, study design being retrospective or prospective, sample sizes, use of informants, and the analyzed time period. Furthermore, assessment of psychopathology in Huntington's disease is complicated due to co-morbid somatic and cognitive disturbances, and diminished disease awareness.[9,10]

Motor symptoms

Early motor signs of Huntington's disease include the gradual onset of clumsiness and balance difficulties, that might be unrecognized by the patient. Movement disorders are usually slowly progressive. The most prominent movement disorder in Huntington's disease is chorea,

characterized by unwanted, jerky movements of head, trunk, and limbs. The gait is poorly coordinated and mimics a dance, and was therefore called chorea (Greek: to dance). As the disease progresses, chorea may become more pronounced, but other movement disorders also occur, such as dystonia, rigidity, bradykinesia, hypokinesia, and postural instability. Swallowing and speech dysfunction develop during the course of the illness and ultimately lead to dysphagia and an inability to communicate. In the most advanced stage of the disease, almost all patients are totally dependent on full time skilled nursing.

Cognitive symptoms
Cognitive disorders are also prevalent in Huntington's disease, and can occur before motor symptoms are present.[11] Severity and progression of cognitive disorders vary considerably, but many patients develop severe subcortical dementia in advanced disease stage.[12] Cognitive assessment typically shows deficits predominantly in frontal executive functions, including abstract thinking, problem solving, attention, mental set shifting, sequencing, and mental generation of information.[13] A loss of cognitive speed and flexibility may not be acknowledged as a disease symptom, and may subsequently cause problems in social relations.

Inheritance
Huntington's disease is a neurodegenerative disorder with an autosomal dominant pattern of inheritance, resulting in an a-priori 50% risk of developing the disease for every child when one of the parents is affected.[14] The causal genetic mutation of Huntington's disease is localized on the short arm of chromosome 4 (4p16.3). This genetic modification is an expanded cytosine-adenine-guanine (CAG) trinucleotide repeat coding for the protein huntingtin. A CAG expansion of 36 repeats or more is associated with Huntington's disease, though a repeat between 36 to 39 repeats has a reduced penetrance and may not in all cases result in the clinical phenotype. Higher repeat length is associated with a younger age of onset, but the repeat length seems to determine the age of onset only partially (about 60%).[15] Previous studies have shown that parental age of onset is an additional predictor of the age of onset, and presumably reflects genetic and/or environmental influences.[16]

Epidemiology
The prevalence of Huntington's disease varies widely, depending on the geographic region; in Europe and Northern-America the prevalence is approximately 7 - 9 per 100,000 inhabitants.[17] The total number of symptomatic patients in The Netherlands is about 1,200 - 1,500.[18] Another 6,000 to 9,000 persons have a 50% risk of developing Huntington's disease.

The mean age of onset is difficult to estimate accurately, because onset symptoms differ widely. The age of onset of motor symptoms is usually between 30 and 50 years (range 2 - 80 years), but many patients experience psychiatric symptoms before the presence of motor symptoms. The mean duration of illness is approximately 16 years.[19]

Neuropathology
So far, the neuropathology of Huntington's disease is not understood. A regional selectivity of atrophy and neuronal loss in the caudate nucleus and putamen of the striatum is common, but other regions may also be affected. Some neurons contain intranuclear inclusions that are characteristic for Huntington's disease, though their role in the pathogenesis of the disease is not known.[20]

Disease stage
The period before the onset of symptoms is called the presymptomatic or premanifest period. The appearance of one of the characteristic motor, psychiatric or cognitive symptoms is the start of the disease, and – if one has not been tested – reveals the carriership of the disease.

The progression of the disease can be defined by the duration of illness, the presence and severity of symptoms, or the level of functional impairment. So far, no objective criterion for disease stage (e.g., atrophy of the striatum) is available. In this study, a conservative approach is applied to differentiate presymptomatic and symptomatic mutation carriers. A neurologist expressed his level of confidence that the presence of motor symptoms in a study subject is a sign of clinically manifest Huntington's disease. This confidence level is an item of the widely used motor section of the Unified Huntington's Disease Rating Scale (UHDRS), and ranges from 0 to 4.[5] All mutation carriers with confidence level score 0 (normal) or score 1 (nonspecific motor abnormalities; < 50% confidence) were classified as presymptomatic. The remaining mutation carriers with score 2 (motor abnormalities that may be signs of Huntington's disease; 50% - 89% confidence), score 3 (likely signs of Huntington's disease; 90% - 98% confidence), or score 4 (unequivocal signs of Huntington's disease; ≥ 99% confidence) were considered symptomatic.

Focus of this thesis: Psychopathology in Huntington's disease
During the course of Huntington's disease, most patients will develop psychiatric disorders or behavioral problems that have an important negative impact on their quality of life and add greatly to their suffering and the burden of caregivers. Therefore, it is important to gain insight in the prevalence and characteristics of psychopathology. However, diagnosis of psychopathology in Huntington's disease is complicated by the presence of co-morbid disorders, overlapping symptoms, and a diminished insight. Apathy, for example, may be a symptom of depression, but can also occur independently as a syndrome in its own right, and is more often a complain of caregivers rather than of patients themselves.

An important previous study describing psychopathology in Huntington's disease showed that behavioral problems can be divided in three symptom clusters: depression, apathy and irritability.[8] This study also showed that psychopathology in Huntington's disease may have disease specific features, that fluctuate during the progression of the disease.

No association has been found between psychopathology in Huntington's disease and the expanded CAG repeat length.[21] Furthermore, it is unknown to what extend alternative genetic, biologic or environmental factors contribute to the presence of psychopathology. For example, exposure to potential stressful life circumstances, e.g., growing up in stressful family circumstances and being at risk for Huntington's disease, can result in an increase of stress hormones by hyperactivity of the hypothalamic-pituitary adrenal axis. This increased level of stress hormones may be one of the biological factors that contribute to the manifestation of the first subtle symptoms of Huntington's disease, including psychiatric symptoms.[22]

Aims of the study

Primary aim

The primary aim of this thesis was to assess the prevalence of both formal psychiatric disorders and behavioral problems. We assumed that members of families with Huntington's disease, regardless of their genetic status, would all show an increased prevalence of psychiatric disorders and behavioral problems compared to the general population.

We started with a review of the literature, that was used to guide the design of the study, to identify psychiatric disorders and behavioral problems in Huntington's disease, and to obtain a set of reference data (Chapter 2). Since differences in study population and measurement tools used, resulted in widely variable prevalences, we assessed psychopathology both conservatively with diagnostic criteria according to the Diagnostic and Statistical Manual of mental disorders, Version IV (DSM-IV) (Chapter 3), and with the recently developed Problem Behaviors Assessment scale (Chapter 4).

Secondary aims

We hypothesized that measurement tools using caregiver information are more appropriate to detect psychopathology in advanced stage of Huntington's disease. Therefore, we assessed the concurrent validity of two rating scales using caregiver information, that were specifically designed for the assessment of psychopathology in Huntington's disease, in comparison with a categorical assessment of psychiatric disorders as defined by criteria of the DSM-IV (Chapter 5). Since apathy showed to be a frequent neuropsychiatric symptom in Huntington's disease, we aimed to assess the prevalence as well as the sociodemographic, clinical and neuropsychiatric correlates of apathy in Huntington's disease (Chapter 6). Furthermore, we aimed to investigate the function of the hypothalamic-pituitary-adrenal axis as one of the potential biological markers in relation to symptoms of Huntington's disease in an explorative way (Chapter 7).

In the general discussion the results of this thesis are put into a wider perspective together with recommendations for future research (Chapter 8).
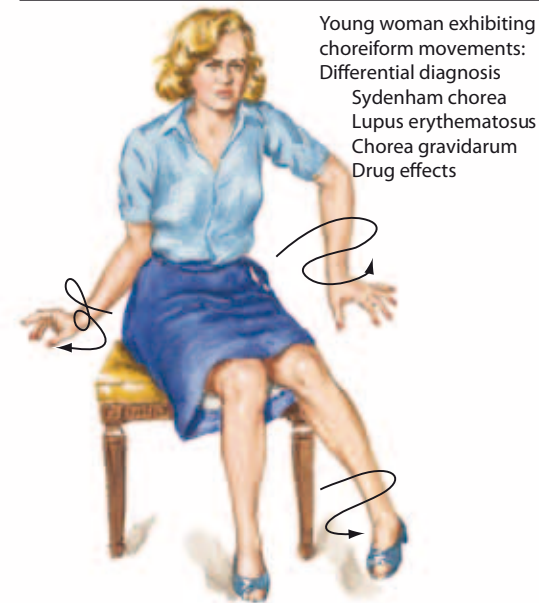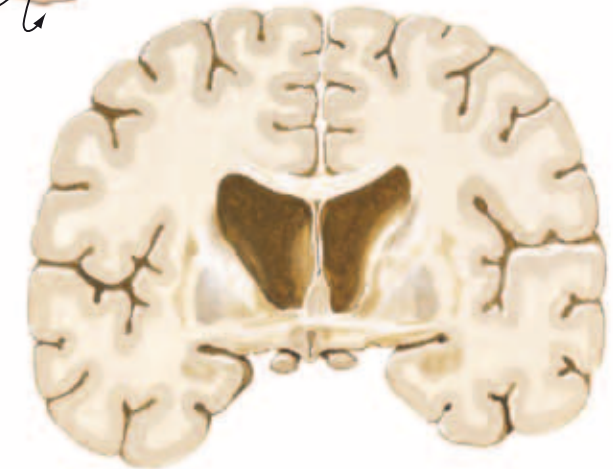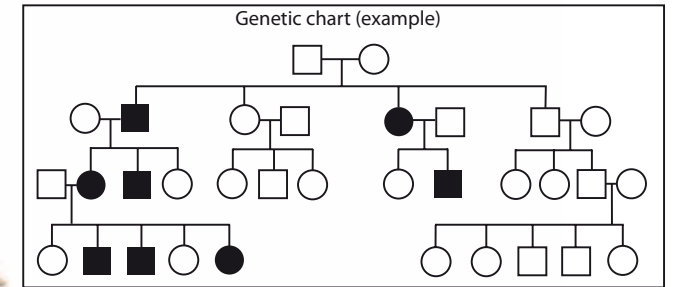
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Chorea

Huntington disease
Middle-aged person: mental deterioration, grimacing, choreiform movements

Genetic chart (example)

Degeneration and atrophy of caudate nucleus and cerebral cortex, with resulting enlargement of ventricles

Young woman exhibiting choreiform movements:
Differential diagnosis
Sydenham chorea
Lupus erythematosus
Chorea gravidarum
Drug effects
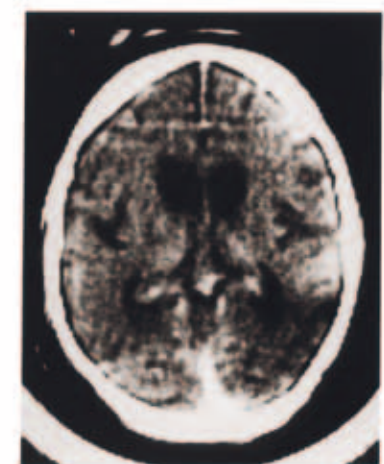
CT scan of brain: atrophy of caudate nucleus and enlargement of ventricles

Chapter 2

Psychopathology in verified Huntington's disease mutation carriers
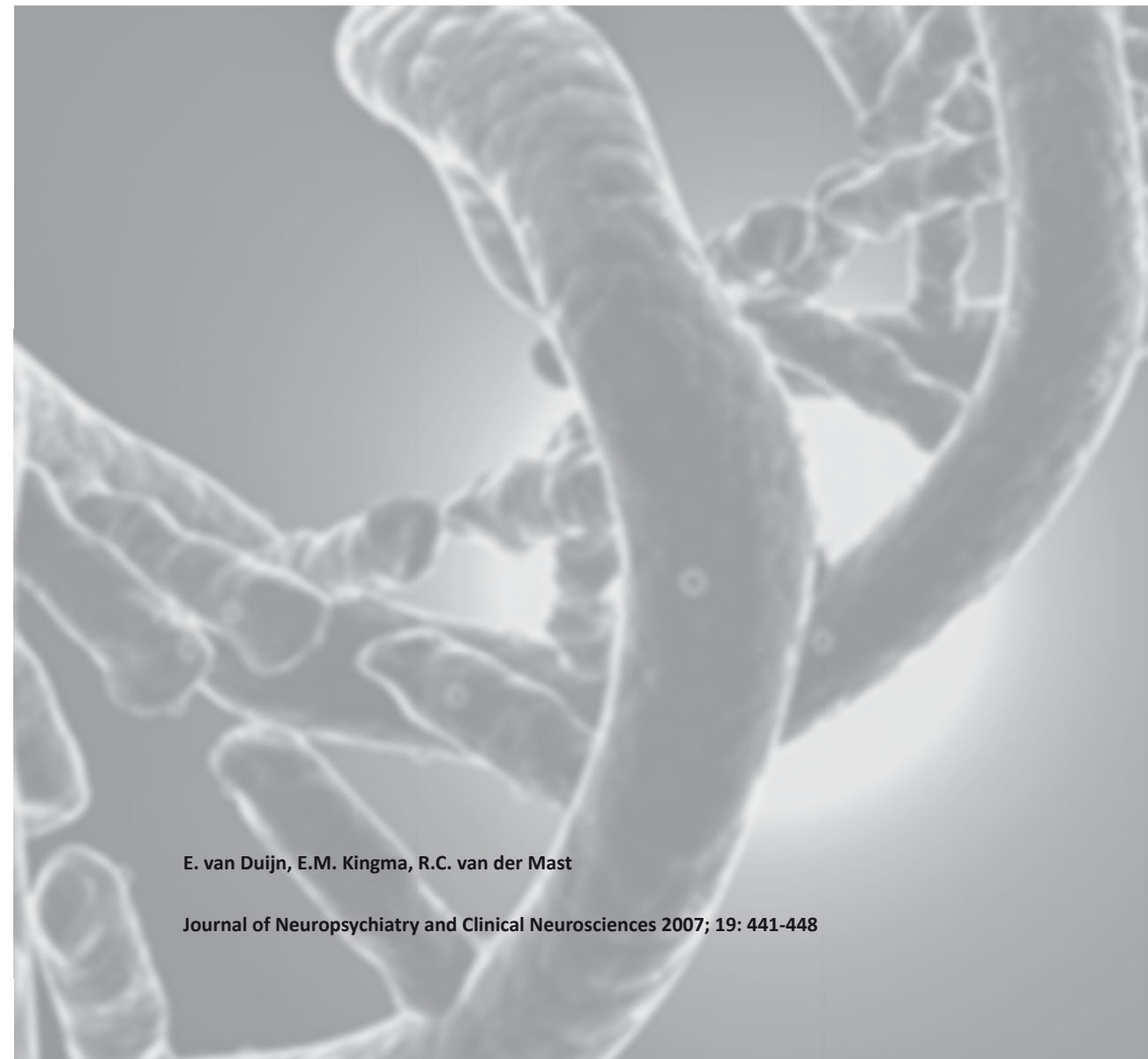
E. van Duijn, E.M. Kingma, R.C. van der Mast

Abstract

Huntington's disease is characterized by motor, cognitive, and neuropsychiatric symptoms. This study reviews original research on psychopathology in Huntington's disease that uses standardized instruments in verified mutation carriers. Frequently reported neuropsychiatric symptoms are depressed mood, anxiety, irritability, and apathy, with prevalences of 33% to 76%. Obsessive-compulsive symptoms and psychosis occur less often with prevalences of 10% to 52% and 3% to 11%, respectively. Available research provides little insight into the true prevalences of psychopathology in Huntington's disease due to small sample sizes, use of different methodologies, and lack of comparison groups. Future research requires larger cohorts stratified to disease stage, consistent methodologies, and adequate comparison groups.

Introduction

Huntington's disease, a progressive autosomal-dominant neurodegenerative disorder, is traditionally characterized by choreiform motor disturbances. In addition to motor symptoms and cognitive deterioration, neuropsychiatric symptoms comprise part of the Huntington's disease phenotype.[1-3] The genetic defect underlying Huntington's disease is an unstable and expanded CAG repeat in exon 1 of gene IT15 on the short arm of chromosome 4, which is expressed as a mutant polyglutamic tract in the protein huntingtin (Htt).[4-7] The mechanisms by which the mutant Htt protein induces a cascade of cellular changes, leading to cell dysfunction and degeneration, have not yet been fully elucidated. Modulation of genetic functioning through the IT15 gene, neuronal death in relation to intranuclear inclusions of aggregated mutant Htt, and progressive cerebral degeneration starting in the caudate nucleus and the putamen may all be part of the pathophysiology of Huntington's disease.[8-11]

Estimated rates for lifetime prevalence of psychiatric disorders among Huntington's disease patients vary widely between 33% and 76%.[3,10] The investigated neuropsychiatric symptoms include depressed mood, anxiety, irritability, apathy, obsessions and compulsions, and psychosis. This variation in prevalences can be explained by the use of different assessment methods with varying definitions of neuropsychiatric phenomena. No follow-up studies covering a longer period have been performed.

For many patients and their relatives, these neuropsychiatric symptoms constitute the most distressing aspect of Huntington's disease and often constitute reason for hospitalization.[12] Whereas severity of motor and cognitive dysfunction is only moderately related to the severity of functional decline, behavioral symptoms and psychiatric disorders seem to have a more severe negative effect on daily functioning.[13] Previous findings have suggested, although inconclusively, that psychopathology as well as cognitive dysfunction may precede the onset of motor symptoms in many patients.[14-16]

To get more insight into the occurrence and prevalence of behavioral problems and psychiatric disorders in Huntington's disease, we review the literature on psychopathology in verified Huntington's disease mutation carriers, with particular reference to its relationship with disease onset and progression, as well as possible underlying neuropathological pathways. We conclude with several recommendations for future research.

Data sources

We searched two literature databases, Embase and PubMed, for prevalence of psychopathology in Huntington's disease. We used a variety of search terms, all synonyms for Huntington's disease and various (neuro)psychiatric phenomena. Where possible, these were mapped onto the following standard database terms (subject headings/MeSH terms): 'Huntington's disease', 'Huntington's chorea', 'mood disorder(s)', 'affect', 'anxiety disorder(s)', 'obsessive behavior', 'compulsive behavior', 'schizophrenia and disorders with psychotic features', 'psychosis', 'thought disorder', 'dissociative disorder(s)', 'neurotic disorder(s)', 'neurosis', 'impulse control disorder(s)', 'impulsive behavior', 'irritable mood', 'apathy', 'behavioral symptoms', 'behavior disorder(s)', and 'personality disorder(s)'. Animal studies and studies on pathophysiology were

excluded and the language was limited to English. The references of the resulting articles were hand searched for further relevant literature. This search resulted in 134 articles, including 59 articles describing original research, 29 review articles, 25 articles on psychopharmacological treatment, 19 case reports/series, and two editorials.

In order to estimate the cumulative prevalences and 95% confidence intervals (CI) of psycho-pathological phenomena, the 59 articles on original research were further selected for meeting the following conclusive set of criteria:

1) The study was original and measured the prevalence of psychopathology in a motor symptomatic Huntington's disease population.
2) The study applied standardized instruments with defined validity and reliability.
3) The study used samples with verified CAG repeat expansions, which implied publication after 1993 when the Huntington's disease mutation was identified.

Results
A total of seven original articles met the final set of strict criteria (Table 1). The other 52 articles were excluded for the following reasons: 22 articles did not cover research on the prevalence of psychopathology; one article only concerned alcohol abuse; one exclusively concerned sexual abuse; and seven others concerned suicide/suicidal behavior. In three studies, solely pre-motor symptomatic subjects were included, and in five studies subjects were offspring of Huntington's disease mutation carriers and had not been genetically verified. One article was excluded because only patients in a nursing home were examined. Of the remaining articles, 10 did not mention standardized instruments with defined validity and reliability and, in two articles, subjects were clinically suspected for Huntington's disease, but CAG repeat numbers were not verified. The remaining seven articles employed the following instruments for the assessment of behavioral and psychiatric symptoms: the Neuropsychiatric Inventory (NPI),[17,18] the Structured Clinical Interview for the DSM-III (SCID),[19] the behavioral section of the Unified Huntington Disease Rating Scale (UHDRS),[20,21] the Yale-Brown Obsessive Compulsive Symptom (Y-BOCS) scale,[22] and the more recently developed Problem Behavior Assessment Scale for Huntington's Disease (PBA),[23] which rates severity and frequency of behavioral problems in Huntington's disease.

A broad range of symptoms portraying a chronically progressive course and fluctuating clinical picture are reported as neuropsychiatric features of Huntington's disease. These neuropsychiatric phenomena are de noted by an array of terms, for example: behavioral problems or symptoms, personality changes, and psychiatric problems or disorders. The characteristic behavioral changes in early stage Huntington's disease, including depression, irritability, mental inflexibility, and apathy, have in earlier days been described as 'choreopathy'.[24] We have limited our subsequent analyses to the most frequently reported symptoms of depressed mood, anxiety, irritability, apathy, obsessive and compulsive symptoms, and psychosis. Originally, we intended to estimate the cumulative prevalences of the different neuropsychiatric phenomena. In spite of our strict inclusion criteria, however, large inconsistencies in methodology remained. This would lead to neither reliable nor valid results; studies used different assessment methods with strongly

varying definitions of neuropsychiatric phenomena. For example, the definition of depression is much stricter according to the SCID than to the UHDRS.[25,26] Also, out of two studies using the same neuropsychiatric assessment measure in populations of comparable disease duration and cognitive function, one study[17] consistently reported lower prevalences than the other.[18] This suggests a strong bias. Furthermore, the criteria for the onset of Huntington's disease are not always given, the comparability of reported disease durations is highly questionable, and finally, not all populations are well-described. We therefore assumed them to be outpatients unless otherwise noted.

Table 1. Overview of included articles on psychopathology in Huntington's disease

Year	Author	n	Disease duration*	Measure	Symptoms
2001	Anderson et al.[22]	27	Unknown	Y-BOCS	Obsessive and/or compulsive symptoms
2001	Craufurd et al.[23]	78	9 ± 5	PBA-HD	Apathy, irritability, depressed mood, anxiety, obsessive and/or compulsive symptoms, psychotic symptoms
2001	Kulisevsky et al.[17]	29	5.6 ± SEM 1.6	NPI	Apathy, irritability, depressed mood, anxiety, psychotic symptoms
2001	Murgod et al.[20]	26	5.5 ± 3.9	UHDRS	Apathy, irritability, depressed mood, anxiety, obsessive and/or compulsive symptoms, psychotic symptoms
2001	Paulsen et al.[18]	52	4.7 ± 4.4	NPI	Apathy, irritability, depressed mood, anxiety, psychotic symptoms
2002	Leroi et al.[19]	21	12.0 ± 6.6	SCID	Depressive disorder
2005	Paulsen et al.[21]	2835	7.6 ± 6.0	UHDRS	Depressed mood, anxiety

* Disease duration in years (mean ± standard deviation; SEM: Standard Error of the Mean)

Y-BOCS: Yale-Brown Obsessive Compulsive Scale; PBA-HD: Problem Behaviour Assessment for Huntington's disease; NPI: Neuropsychiatric Inventory; UHDRS: Unified Huntington Disease Rating Scale; SCID: Structured Clinical Interview for DSM

Depressed mood
Six original studies investigate the prevalence of depressed mood in motor symptomatic patients.[17-21,23] Though two studies used the UHDRS to assess the prevalence of 'low mood',[20,21] and two others used the NPI,[17,18] results vary strongly, from 33% to 69% (Figure 1). The only study using formal DSM criteria reports a prevalence of 43% for mood disorders: 29% for major depression and 14% for non-major depression.[19]
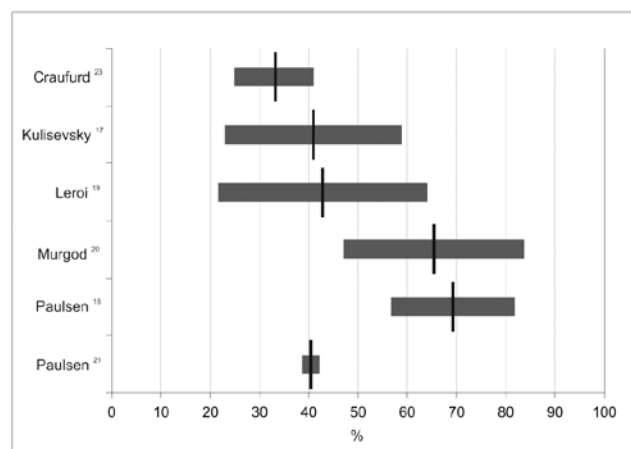
Figure 1 Prevalences of depressed mood (with 95%CI)

Anxiety

Five studies assess the prevalence of anxiety (Figure 2).[17,18,20,21,23] The lowest prevalence (34%) was reported with the NPI.[17] The prevalence almost doubled (61%) in a small study, using the UHDRS, in 26 Huntington's disease patients at their first hospital visit because of manifesting motor symptoms.[20]
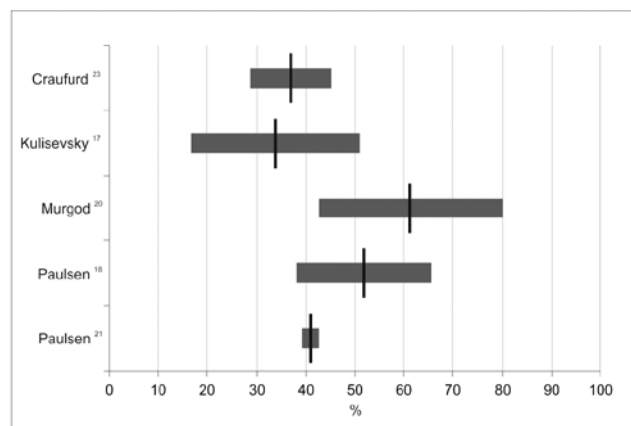
Figure 2 Prevalences of anxiety (with 95%CI)

Irritability

Irritability, varying in description from 'difficult to get along with' to 'aggression', is characterized by a reduction in control over temper that may result in verbal or behavioral outbursts.[27] In four original studies that assessed irritability as a separate behavioral phenomenon in Huntington's disease, prevalences varied between 38% and 73% (Figure 3).[17,18,20,23]
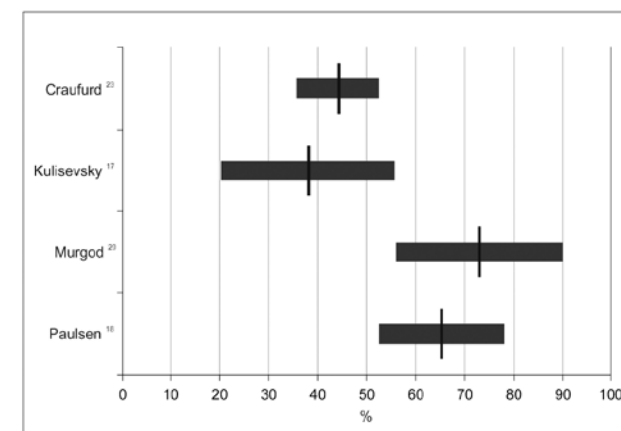
Figure 3 Prevalences of irritability (with 95%CI)

Apathy

Apathy, characterized by reduced energy and activity, lack of drive, and impaired performance of everyday tasks, may be a separate clinical entity distinct from depression, especially in neuro-psychiatric disorders.[28,29] In three original studies, prevalences of apathy in Huntington's disease patients varied from 34% to 76% (Figure 4).[17,18,23] Using the PBA, a cluster of symptoms reflecting apathy syndrome was found, with 'loss of energy' (88%), 'impaired performance of everyday life' (76%), and 'lack of initiative' (76%) as the most prevalent behavioral abnormalities.[23]
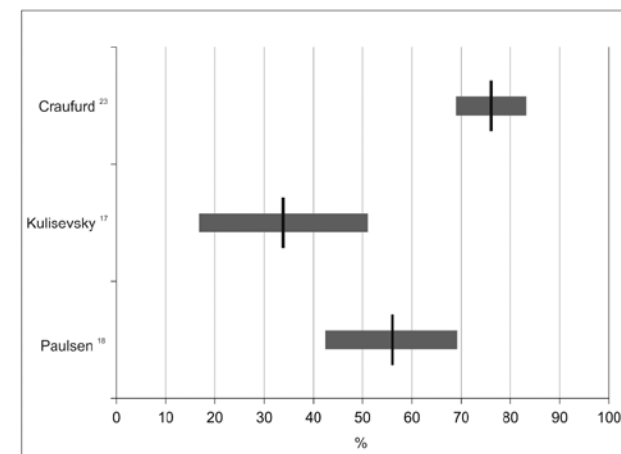
Figure 4 Prevalences of apathy (with 95%CI)

Obsessive and compulsive symptoms

The three studies investigating obsessive or compulsive behavior (Figure 5) reported prevalences of 10% to 52%.[20,22,23] Out of 27 Huntington's disease patients visiting an outpatient clinic, 52% scored either on compulsions or obsessions on the Y-BOCS.[22] The prevalence of obsessive symptoms was twice that of compulsive symptoms, while all patients with compulsive symptoms also had obsessive symptoms. Only two out of the 27 patients fulfilled formal DSM criteria for obsessive compulsive disorder. The two remaining studies reported lower prevalences in larger study populations.[20,23]
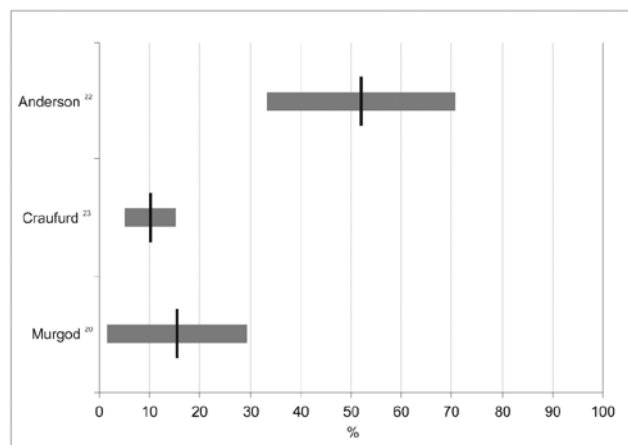
Figure 5 Prevalences of obsessive and/or compulsive symptoms (with 95%CI)

Psychotic symptoms

Prevalences of psychotic symptoms varied between 3% and 11% in four studies.[17,18,20,23] Because of small sample sizes, three of the four studies report 95% confidence intervals that include a prevalence of 0% (Figure 6).[17,20,23]

Figure 6 Prevalences of psychotic symptoms (with 95%CI)

Discussion

These results confirm that behavioral problems and psychiatric disorders are major constituents of the clinical spectrum of Huntington's disease. This is an important finding because these neuropsychiatric symptoms have a substantial impact on daily functioning,[12] possibly even more so than motor and cognitive dysfunctions.[13] Nevertheless, more and better designed studies are necessary.

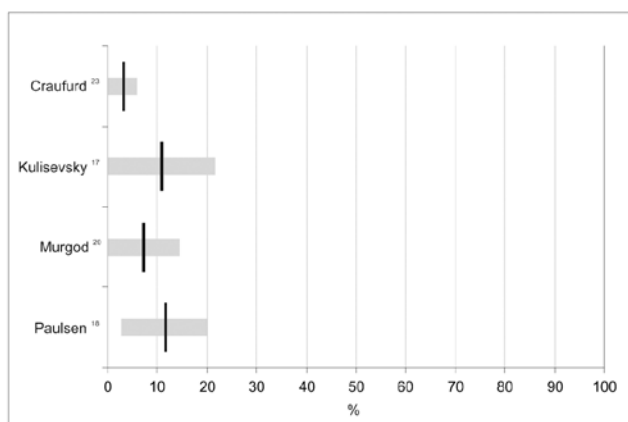The studies up to date use a variety of assessment methods in Huntington's disease populations of different disease stages. This ensures that their results are impossible to compare and that reliable prevalence estimates cannot be made. Definitions of neuropsychiatric phenomena are often unclear, and differences in definition can strongly influence the prevalences found. For example, in the UHDRS only one item refers to 'low mood', whereas the SCID uses the stringent DSM criteria for depression. These different methodologies limit the generalizability of the reported findings, which is further impaired by small sample sizes. Importantly, none of the seven studies found used a representative comparison group and, to our knowledge, no follow-up studies have been performed to relate the incidence of behavioral problems and psychiatric disorders to disease onset and disease progression.

Psychopathology

The prevalence of depressed mood in Huntington's disease, varying from 33% to 69%, may be comparable to that of anxiety, irritability, and apathy. The development of depressive symptoms in Huntington's disease could be a direct result of cerebral degeneration, for which several neuropathological mechanisms have been proposed proposed.[30,31] Depression could, however, equally well be a psychological reaction to being at risk for Huntington's disease, having grown up in an insecure and harmful environment, and/or the awareness of disease onset.

Many studies have found that depressive symptoms precede the onset of motor symptoms,[32-34] but no relation between the occurrence of depressive symptoms and disease duration has so far been reported.[35] Depression may, however, negatively correlate to cognitive decline,[23] which is possibly the result of concurrent decreasing illness awareness. Anxiety has not been a main research interest in patients with Huntington's disease. Nevertheless, 'worrying', which could be part of a generalized anxiety disorder (GAD), is often reported in Huntington's disease patients, although it is mostly limited to worries about Huntington's disease.[36] Since no studies were found that systematically investigate the prevalences of different anxiety disorders, this should be an important focus for future research.

Irritability without a prior history of short temper occurs in most Huntington's disease patients, and seems to precede motor symptoms in mutation carriers.[37-39] A tendency for irritability occurring more frequently in late stage patients whose neurological symptoms have been present for 6 to 11 years has also been described.[23] This is confirmed by a cross-sectional observational study of 27 nursing home residents with Huntington's disease (disease duration 7 to 11 years), which reports aggression in one-third of all patients over a 3-day period.[40]

We contend that increasing degeneration of the striatum and the orbito-frontal-subcortical

circuit in Huntington's disease contributes to the development of socially inappropriate behavior, which initially may be manifested as subtle irritability and, in late-stage Huntington's disease, as aggressive behavior.[41]

Of all neuropsychiatric symptoms only apathy consistently appears to be positively related to disease progression.[23,42,43] Apathy is also strongly related to the decline of everyday functioning and, once present, tends to persist or worsen.[12] Damage to structures of the anterior cingulate-subcortical circuit has in particular been associated with motivational disorders, including apathy,[41] which may also be the case in Huntington's disease.[44]

The occurrence of obsessive and compulsive symptoms in Huntington's disease is of particular interest because obsessive-compulsive disorder and Huntington's disease possibly share a similar neuropathology of the basal ganglia and (orbito)frontostriatal circuits.[45,46] Many Huntington's disease mutation carriers show personality changes with mental inflexibility in early stages,[23] possibly heralding future obsessive and compulsive symptoms. Though in certain families obsessive and compulsive symptoms have shown an early phenotype of Huntington's disease,[45] they are not often identified as a manifestation of Huntington's disease.[47]

Psychotic symptoms usually occur when movement symptoms are already clearly manifest. This could explain why in earlier days, when Huntington's disease was diagnosed at a later disease stage, psychosis was usually described as the main psychiatric feature of Huntington's disease.[48] Even so, Huntington's disease patients were often misdiagnosed with dementia praecox or schizophrenia until the first half of the 20th century. Nowadays, rather low prevalences (3% to 11%) of psychotic symptoms are reported, which is most probably due to earlier and better diagnoses of Huntington's disease and a shift in research from inpatient to outpatient populations.

Recommendations for future research
The causal pathways leading to psychopathology in Huntington's disease are unclear and should receive priority on the research agenda. Since Huntington's disease families with multiple cases of schizophrenia and schizophreniform symptoms have been described,[49,50] as well as families with obsessive-compulsive disorders,[45] and families with a high occurrence of affective syndromes in both mutation carriers and non-carriers,[51] it is highly probable that other genes than the Huntington's disease gene itself, as well as environmental factors, play a role in the development of psychopathology in Huntington's disease.[52] Previous findings indeed suggest that both neuropathology and environmental stress contribute to the occurrence of neuro-psychiatric phenomena in Huntington's disease: a case series among 37 Huntington's disease patients and 167 relatives reported significantly more psychiatric admissions and diagnoses in patients than in their relatives.[53] Thus at least some psychopathology will be due to the etiology of Huntington's disease, though not solely the Huntington's disease mutation. Since the same study showed that relatives of Huntington's disease patients also had more psychiatric diagnoses and admissions than the general population, stressors such as growing up with an affected parent and with the uncertainty about one's own disease status are also likely causes of psychopathology in Huntington's disease.

To correct for environmental stress, prevalences of psychopathology in Huntington's disease should be compared to healthy family members, particularly siblings of patients who do not carry the Huntington's disease mutation, since they share the same psychosocial family background as mutation carriers. There is need for prospective research covering all different stages of Huntington's disease with the use of such a comparison group, just as has been carried out before in pre-motor symptomatic mutation carriers.[37,39] Though this comparison group cannot correct for all potential biases affecting research in this difficult population (e.g., self-selection for genetic testing and difficulties with the staging of disease progression), use of the proposed comparison group will significantly increase the validity and interpretability of the test results. Also, a comparison of psychopathology in Huntington's disease with other neurodegenerative disorders, such as Parkinson's disease, could increase our understanding of the pathological mechanisms that affect the brain and behaviors of these patients.[17,46,54] Nevertheless, such a comparison should be explorative in nature as neither Huntington's disease patients nor patients with Parkinson's seem an adequate comparison group to the other.

As the Huntington's disease mutation does not have a full penetrance for developing specific behavioral problems or psychiatric disorders, research should also focus on the contribution of other biological factors, as well as environmental factors, to the behavioral phenotype of Huntington's disease. Identification of endophenotypes, which do not depend on what is obvious to the unaided eye, could help to resolve questions about etiological models.[55] Such an endophenotype-based approach has the potential to assist in the genetic dissection of psychopathology. These endophenotypes should be researched on the level of neurobiology, neuropsychology, and neuroradiology. An example of a possible neurobiological endophenotype is disturbance of the hypothalamic pituitary adrenal (HPA) axis functioning with hyper-cortisolism; the stress hormone cortisol plays a major role in psychiatric disorders, particularly depressive disorders that have a high prevalence in Huntington's disease. Disturbances in HPA-axis functioning have already been found in Huntington's disease patients but have not yet been linked to behavioral or psychiatric morbidity in Huntington's disease.[56,57] Another possible endophenotype is dysfunction of the immunesystem,[58] with altered secretion of cytokines. These have also been related to the presence of depression.[59] Vulnerability to psychopathology may be determined by genetic polymorphisms of the HPA-axis and the immune system, which is another important area of research in Huntington's disease.[60]

All future research should improve upon current methodologies. Some potential sources of current variation in test results, such as low incidence of Huntington's disease with resulting small sample sizes and self-selection for testing and research, are difficult to avoid; researchers should be aware of this. Other sources of variety, mainly differences in methodology, can be eliminated if consensus on terminology and staging methods, as well as standardization of instruments are achieved. This is a necessary requirement for the comparability and generalizability of results. We propose that DSM criteria are used as the gold standard for psychiatric diagnosis, and standardized instruments for other neuropsychiatric symptoms, such as apathy and irritability.

For disease progression, we propose the motor section of the UHDRS. Although the motor score is not perfectly correlated with disease progression, a functional assessment with the Total

Functional Capacity scale of the UHDRS,[61] which is related to disease progression, is not a good tool for this kind of research, as it is directly influenced by psychopathology.[12,62] Because the onset of Huntington's disease is so gradual, disease duration is also not an adequate measure, and motor assessment is therefore the most objective, reliable, and comparable method of disease staging for research.

Research should lead to an increased understanding and recognition of psychopathology in Huntington's disease and its causes. This is essential for adequate treatment of those symptoms that could improve the overall functioning and quality of life of the Huntington's disease patient and his or her direct environment.
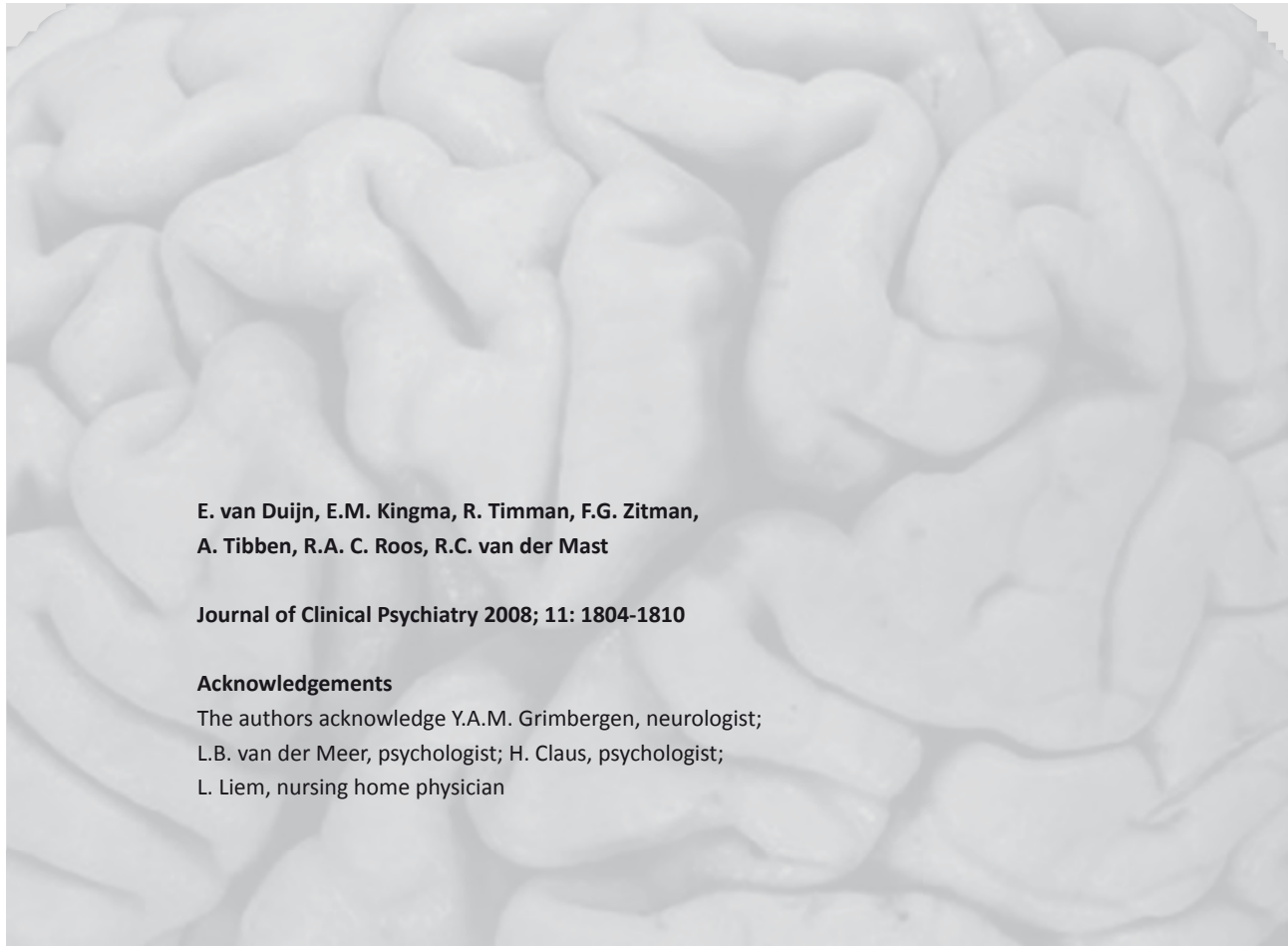
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Chapter 3

Cross-sectional study on prevalences of psychiatric disorders in mutation carriers of Huntington's disease compared with mutation-negative first-degree relatives

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Abstract

Objective: To investigate the prevalences of formal DSM-IV diagnoses in pre-motor symptomatic and motor-symptomatic mutation carriers at different stages of Huntington's disease compared to a control group of first-degree non-carriers relatives and the general population.

Method: Between May 2004 and August 2006, 154 verified mutation carriers and 56 verified non-carriers were recruited from the outpatient clinics of the Neurology and Clinical Genetics departments of Leiden University Medical Center and from a regional nursing home. To assess the 12-month prevalences of DSM-IV diagnoses, the sections for depression, mania, anxiety, obsessive-compulsive disorder, and psychosis/schizophrenia of the Composite International Diagnostic Interview were used. Prevalences in the Dutch general population were extracted from the Netherlands Mental Health Survey and Incidence Study (NEMESIS).

Results: Both presymptomatic and symptomatic mutation carriers portrayed significantly more major depressive disorder (p = 0.001 and p < 0.001, respectively) and obsessive-compulsive disorder (p = 0.003 and p = 0.01, respectively) than the general population. Symptomatic mutation carriers also showed an increased prevalence (p = 0.01) of non-affective psychosis. Psychiatric disorders were more prevalent, although not significantly (p = 0.06), in mutation carriers compared to first-degree relatives who were non-carriers. Non-carriers did not differ from the general population.

Conclusion: Psychiatric disorders occur frequently in Huntington's disease, often before motor symptoms appear. In addition, first-degree non-carriers relatives do not show more psychiatric disorders compared to the general population, although they grew up in comparable, potentially stressful circumstances. Taking these findings together, psychopathology in Huntington's disease seems predominantly due to cerebral degeneration rather than to shared environmental risk factors.

Introduction

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disorder resulting from an expanded trinucleotide CAG repeat, which codes for a polyglutamine in the IT15 gene on chromosome 4p16.3.[1] The pathogenesis in relation to the CAG repeat expansion has not yet been elucidated, but several processes have been suggested.[2] The mean age at onset is between 30 and 50 years. The first signs consist of involuntary movements (chorea, hypokinesia), cognitive deterioration, behavioral problems, and psychiatric disorders. There is no curative treatment for Huntington's disease. Since 1993, presymptomatic gene testing has been available.[1] In The Netherlands, about 1200 to 1500 patients have symptoms of Huntington's disease, 6000 to 9000 persons are at 50% risk for Huntington's disease, and every year approximately 60 persons at 50% risk are tested gene-positive.

Psychiatric disorders may occur in all motor symptomatic stages of Huntington's disease and can also predate the onset of motor symptoms.[3-5] These disorders have an important negative impact on quality of life, add greatly to the suffering of patients and the burden of caregivers, increase the risk of institutionalization,[6,7] and may account for increased mortality and risk of suicide.[8,9] Little is known about true prevalences of psychiatric disorders in verified Huntington's disease mutation carriers. This lack of information is due to small sample sizes, use of different methodologies, and lack of adequate control groups.[10] We therefore aimed to investigate the 12-month prevalences of formally diagnosed psychiatric disorders in verified Huntington's disease mutation carriers compared to a control group of verified first-degree non-carriers relatives and the general population.

Since being at risk for this incurable disorder and having been raised in an Huntington's disease family is likely to have an impact on mental well-being,[11,12] we assumed that Huntington's disease family members, regardless of their genetic status, would all show increased prevalences of psychiatric disorders compared to the general population.

Methods

Subjects

Between May 2004 and August 2006, 361 subjects were recruited from 4 sources (Figure 1). First, an invitational letter was sent to 174 subjects who had attended the Department of Clinical Genetics of Leiden University Medical Center between 1999 and 2004 for Huntington's disease mutation analysis. Leiden University Medical Center is a Dutch teaching hospital and a national reference center for Huntington's disease. Next to verified Huntington's disease mutation carriers, verified first-degree non-carriers relatives — with an a priori 50% risk for Huntington's disease — were enrolled as a comparison group to control for environmental factors such as growing up with an ill parent in potentially harmful family circumstances, the knowledge of being at risk for Huntington's disease, and participating in the predictive testing procedure. Second, an invitational letter was sent to all Huntington's disease patients (n = 119) currently attending the outpatient clinic of the Department of Neurology of Leiden University Medical Center. Third, one nursing home (Overduin in Katwijk) in the area of Leiden with a specialized ward for Huntington's disease patients was visited in order to include subjects in advanced stages of Huntington's disease, both institutionalized and attending a day clinic. These

subjects (n = 50) were selected on the basis of their physical and verbal capability to participate; severe dysarthric and severely demented subjects were not approached. Fourth, a minority of the subjects, called 'spontaneous' participants (10 presymptomatic and 8 symptomatic), were included with help of the Dutch Huntington's disease patients' association after posting an announcement on their Internet site and in their quarterly.

Figure 1. Flowchart of inclusion of subjects
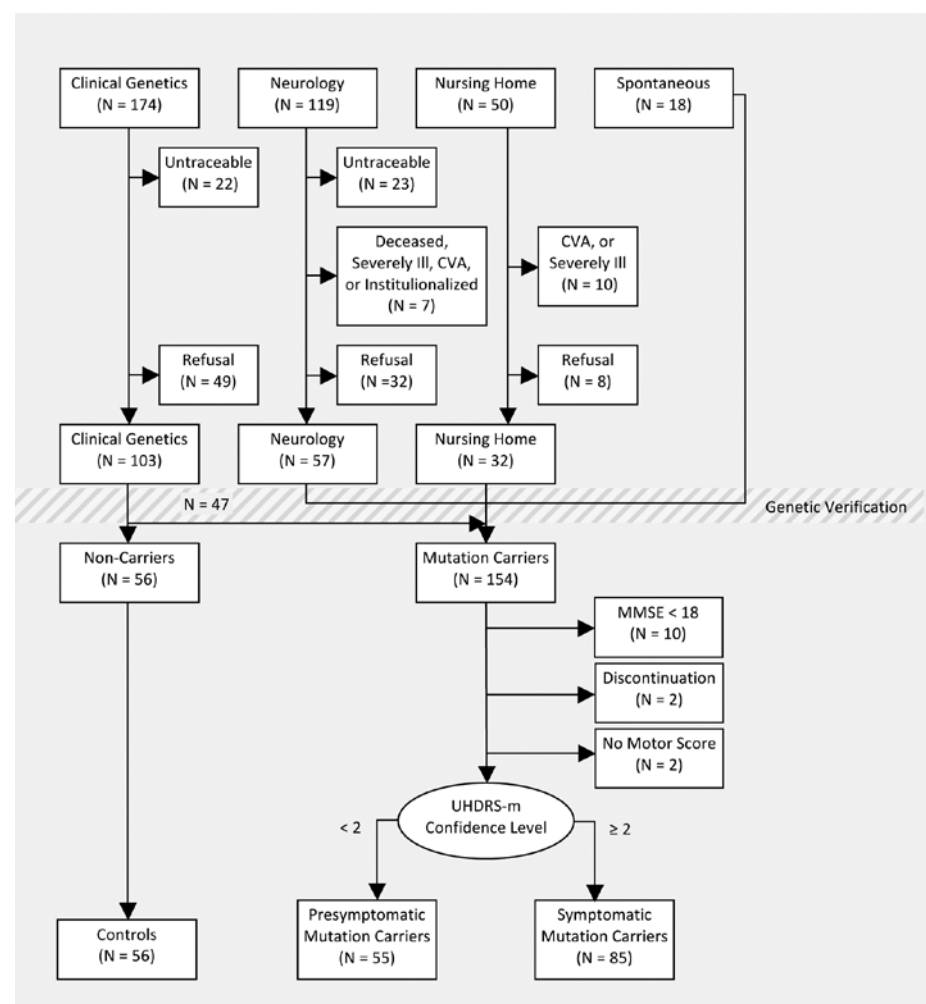
CVA = Cerebrovascular accident; MMSE = Mini-Mental State Examination; UHDRS-m = Unified Huntington's Disease Rating Scale, motor section

Subjects with juvenile-onset Huntington's disease (n = 1) or concurrent diseases of the central nervous system (e.g., cerebrovascular accident) (n = 4) were excluded, as well as mutistic subjects (n = 8) and subjects who did not have a sufficient command of the Dutch language

(n = 2). Forty-five outpatients were untraceable and 2 subjects were deceased. Of the remaining 299 subjects, 89 refused to participate because of various reasons including having no time, being too fatigued or too sick, and not wanting to be confronted with Huntington's disease (response rate 68.3%). Thus, we included 210 subjects, comprising 56 verified mutation negative subjects and 154 verified mutation carriers. After the assessment, another 10 subjects were excluded because of severe cognitive disorders, 2 subjects declined during the study, and 2 more mutation carriers were excluded because of an absent motor assessment, leaving 56 non-carriers and 140 mutation carriers (Figure 1). The study was approved by the Medical Ethics Committee of Leiden University Medical Center, and all subjects gave informed consent.

Instruments
Demographic and clinical characteristics. Information on demographic and clinical characteristics was collected using a standardized interview. Global functioning was assessed using the Total Functioning Capacity (TFC) subscale of the Unified Huntington's Disease Rating Scale (UHDRS), a widely used standardized clinical rating scale for Huntington's disease patients.[13] The TFC consists of 5 questions assessing employment; the capacity to handle financial affairs, manage domestic chores, and perform activities of daily living; and the care level provided. The TFC ranges from 0 to 13 points, with lower scores indicating poorer functional abilities.[14]

CAG repeat length
The number of CAG repeats of all subjects was verified, except for 1 symptomatic subject who died during the study. Subjects with a normal repeat length containing 26 or fewer copies and those with an intermediate repeat number between 27 and 35 were considered non-carrierss.[15] Since alleles in the 36 to 39 repeat range are unstable and are associated with the Huntington's disease phenotype, these subjects were considered positive for Huntington's disease in this study.

Assessment of motor functioning and disease stage
All subjects were examined for assessment of motor symptoms by a neurologist with experience of Huntington's disease using the motor section of the UHDRS.[13] The neurologist was blinded to the genetic status and the results of all other assessments of the subjects. On the basis of the clinical examination, the neurologist assigned a score indicating to what degree he or she was confident that the presence of an extrapyramidal movement disorder in a subject may be due to Huntington's disease. This confidence-level score ranged from 0 to 4. Mutation carriers with a confidence-level score of 0 (normal) or 1 (nonspecific motor abnormalities, < 50% confidence) were classified as presymptomatic (n = 55). The remaining mutation carriers (n = 85) with a score of 2 to 4 (2 = motor abnormalities that may be signs of Huntington's disease [50% - 89% confidence], 3 = likely signs of Huntington's disease [90% – 98% confidence], 4 = unequivocal signs of Huntington's disease [≥ 99% confidence]) were considered symptomatic. We further stratified motor symptomatic mutation carriers with confidence levels of 2 to 4 according to the total UHDRS motor scores as an 'early disease stage' group and an 'advanced disease stage' group using the median score (40 points) of the total UHDRS motor score (range, 0-124 points) as a cut-off.

Diagnosis of psychiatric disorders

The Composite International Diagnostic Interview (CIDI),[16] a fully structured, standardized psychiatric diagnostic interview for disease classification according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),[17] was administered by the interviewers after certified training and under close supervision of a psychiatrist (EvD).

The sections for depression, mania, anxiety, obsessive compulsive disorder, and psychosis of the Dutch translation of the computerized edition of the CIDI, Version 2.1, were used to assess the presence of each disorder in the past 12 months. The interrater reliability of the CIDI is excellent, and the test-retest reliability and validity are good.[18] Because of lack of reliability in subjects with severe cognitive dysfunction, the CIDI was not administered in subjects with a score < 18 points on the Mini-Mental State Examination (MMSE) (range, 0 - 30 points).[19] Raters for psychiatric and cognitive functioning were deliberately informed about the genetic status of the participants, because nondisclosure on the side of the participant could considerably influence the subjects' answers to questions about symptoms that are directly related to their genetic status.

Prevalences of psychiatric disorders in the general population were extracted from the Netherlands Mental Health Survey and Incidence Study (NEMESIS),[20] a prospective study of the prevalence, incidence, and course of psychiatric disorders using the CIDI in a representative sample of 7076 non-institutionalized Dutch adults aged 18 to 64 years.

Statistical analyses

Independent-samples t tests were used to compare group means of continuous variables, and Fisher exact tests were used for comparison of dichotomous demographic characteristics and for pair wise comparison of prevalences of psychiatric disorders. All analyses were carried out two-sided, and, because of multiple testing, a significance level of p < 0.01 was applied.

Logistic regression analysis was applied to determine possible associations between various demographic and clinical characteristics (age, sex, having a partner, having children, higher education, psychiatric family history, CAG repeat length, total UHDRS motor score, and total MMSE score) and the presence of psychiatric disorders during the past 12 months in mutation carriers. Nonlinear generalized canonical correlation analysis was conducted to determine multiple clusters and the coincidence of symptomatic and presymptomatic subjects in each of the clusters.[21]

Results

Demographic and clinical characteristics

The 56 non-carriers and 140 mutation carriers differed significantly in many demographic and clinical characteristics (Table 1). Seven non-carriers had an intermediate CAG repeat length (range, 27 to 35 repeats), and 3 mutation carriers had a CAG repeat length between 36 and 39 repeats, which is associated with a reduced penetrance. Subgroups of presymptomatic and symptomatic mutation carriers differed in age (mean = 40.8 years and 49.9 years, respectively), having any children (mean = 63.6% and 82.4%, respectively), use of psychotropic medication (mean = 21.8% and 55.3%, respectively), TFC score (mean = 12.0 points and 7.8 points, respectively), MMSE score (mean = 28.1 points and 25.9 points, respectively), and having had higher education (mean = 63.6% and 44.7%, respectively) (data not shown). Logistic regression analysis showed that only age (p = 0.003) and TFC (p < 0.001) were significant predictors, whereas the other covariates were not (p > 0.30).

12-Month prevalences of psychiatric disorders

As is shown in Table 2, mutation carriers had significantly increased prevalences of major depressive disorder and obsessive-compulsive disorder compared to the Dutch general population. Additionally, a trend of an increased prevalence of generalized anxiety disorder was found in mutation carriers compared to the general population (p = 0.02). Psychiatric disorders were more prevalent, although not statistically significant, in mutation carriers compared to non-carriers. Non-carriers did not differ from the general population in prevalences of psychiatric disorders.

The majority (n = 19, 52.8%) of the 36 mutation carriers with a psychiatric diagnosis had a single psychiatric disorder, 10 subjects had 2 psychiatric disorders, 6 subjects had 3 psychiatric disorders, and 1 subject had 4 psychiatric disorders.

Analyzing presymptomatic and symptomatic mutation carriers apart, both groups showed significantly increased prevalences of major depressive disorder (p = 0.001 and p < 0.001, respectively) and obsessive-compulsive disorder (p = 0.003 and p = 0.01, respectively) compared to the general population but not to non-carriers. In symptomatic subjects, prevalence of non-affective psychosis was also significantly increased (p = 0.01). A trend was found for an increased prevalence of generalized anxiety disorder in both presymptomatic and symptomatic mutation carriers (p = 0.03 and p = 0.02, respectively) compared to the general population (Table 3).

Symptomatic mutation carriers did not differ in prevalences of psychiatric disorders from presymptomatic mutation carriers (all p > 0.5). Discriminating symptomatic mutation carriers into 'early' and 'advanced' symptomatic subjects according to their UHDRS motor score revealed no significant differences either (data not shown, all p > 0.2).

Demographic and clinical characteristics associated with presence of psychiatric disorders

Using logistic regression analysis, we found no significant associations between demographic and clinical characteristics and the presence of psychiatric disorders among all mutation carriers. Among presymptomatic mutation carriers only, a trend was found that subjects with a psychiatric disorder were younger compared to subjects without a psychiatric disorder (mean [SD] = 37.6 [8.8] years and 42.0 [10.7] years, respectively; p = 0.04). In addition, a somewhat higher mean UHDRS total motor score was found in presymptomatic mutation carriers with a psychiatric disorder compared to presymptomatic mutation carriers without a psychiatric disorder (mean [SD] = 3.5 [3.4] points and 1.9 [2.9] points, respectively; p = 0.02).

Using nonlinear generalized canonical correlation analyses, we found no clustering of demographics, clinical characteristics, disease stage, and presence of psychiatric diagnoses.

Table 1. Sociodemographic and clinical characteristics of study subjects (n = 196)

	Mutation carriers (n = 140)		Non-carriers (n = 56)		
	n	%	n	%	p ^{a}
Male	64	45.7	25	44.6	1.00
Higher education ^{b}	73	52.1	38	67.9	0.056
Married or partner	99	70.7	46	82.1	0.108
Any children	105	75.0	30	53.6	0.006
High alcohol consumption ^{c}	18	12.9	8	14.3	0.817
Use of psychotropic medication	59	42.1	3	5.4	<0.001
- Antidepressants	37	26.4	3	5.4	<0.001
- Neuroleptics ^{d}	26	18.6	0	0	<0.001
- Benzodiazepines	29	20.7	0	0	<0.001
	mean	SD	mean	SD	t	df	p
Age (years)	46.3	11.7	39.1	11.1	3.91	194	<0.001
CAG repeats (number)	44.1 *	3.6	21.5	4.1	-40.07	194	<0.001
TFC ^{e} (points)	9.5	3.9	12.9	0.5	-10.15	150 ^	<0.001
MMSE ^{f} (points)	27.0‡	4.2	29.1	1.2	-6.97	193 ^	<0.001

^{a} Fisher's exact test (two-sided) was used for dichotomous and t-test for continuous variables; ^{b} Educational level was dichotomized into lower (<12 years) and higher (≥12 years) level; ^{c} Alcohol consumption was considered high if more than 14 glasses a week were consumed; ^{d} Including tiapridal which was primarily given as a treatment for motor symptoms; ^{e} TFC = Total Functional Capacity scale (range 0-13 points), lower scores indicating more severe functional impairment; ^{f} MMSE = Mini-Mental State Examination (range 0-30 points), lower score indicating more severe cognitive dysfunction. Only subjects with MMSE ≥ 18 were included.

* CAG repeat length of one motor symptomatic subject with a HD positive family history was not verified. Four subjects had an intermediate repeat length.

‡ One presymptomatic subject refused assessment of MMSE score.

^ Corrected for unequal variances.

Discussion

This study, using a fully standardized psychiatric interview, demonstrates that both presymptomatic and symptomatic Huntington's disease mutation carriers had significantly more formal DSM-IV diagnoses than the general population. Psychiatric disorders were also more prevalent in mutation carriers compared to non-carriers, although not statistically significant, probably due to a lack of power caused by the small groups. Contrary to our assumption, however, non-carriers did not differ from the general population, although non-carriers shared the same potentially stressful environment with mutation carriers.

Affective disorder

Our study confirms an increased prevalence of depression in mutation carriers compared to the general population. Most earlier studies, however, measured symptoms of depression and not major depressive disorder meeting formal DSM criteria.[10] Although presymptomatic mutation carriers showed a higher prevalence of major depressive disorder than did the population at large, the difference with non-carriers did not reach statistical significance (p = 0.06). This is in accordance with the only other study that used the CIDI in Huntington's disease. This study reported an increased rate of current depressive symptoms but not formal depressive disorder in presymptomatic mutation carriers compared to non-carrierss.[22]

To date, the relationship between psychiatric phenotype and disease stage is unclear. Some research indicates a decreased prevalence of depression in advanced disease stage compared to presymptomatic stage.[4,23] However, psychiatric assessment in the advanced stage of Huntington's disease may be hampered by cognitive deterioration and the increase of physical symptoms. For example, weight loss and disturbed sleeping could be symptoms of neuroendocrine disturbances in Huntington's disease as well as symptoms of depression. Therefore, in advanced symptomatic patients, other diagnostic tools like observation of behavior and relatives' information should be part of the clinical examination.

Prevalences of dysthymia, mania, or bipolar disorder did not differ between our study groups, nor has a difference been reported in earlier studies. One study using DSM criteria reported an increased prevalence of manic symptoms in presymptomatic mutation carriers compared to non-carriers, but these symptoms did not fulfill diagnostic criteria for bipolar disorder.[23]

Anxiety disorder

Several studies reported increased prevalence of anxiety,[10] but in this study we found only a non-significant trend of an increased prevalence of formal generalized anxiety disorder in Huntington's disease. Most studies, though, used measures with general questions about anxiety, worrying, and tensed feelings, e.g., the behavioral section of the UHDRS,[13] resulting in rates of anxiety symptoms as high as 34% to 61%.[10]

Obsessive-compulsive disorder

We found an increased prevalence of obsessive compulsive disorder in mutation carriers compared to the general population, both in presymptomatic and in symptomatic mutation carriers, whereas until now, occurrence of formal obsessive-compulsive disorder has been

Table 2. 12-Months prevalences of psychiatric disorders according to CIDI in mutation carriers and non-carriers, compared to the Dutch general population.

	Mutation carriers (n = 140)		Non-carriers (n = 56)		General population (n = 7076)	p^a	p^b	p
	n	%	n	%	%			
All depressive disorders [^]	25	17.9	4	7.1	-	0.07	-	-
Major depressive disorder	24	17.9	4	7.1	5.8	0.08	<0.001	0.57
Dysthymia	3	2.1	0	0	2.3	0.56	1.00	0.64
Manic episode	3	2.1	0	0	1.1	0.56	0.21	1.00
All anxiety disorders [^]	22	15.7	4	7.1	-	0.16	-	-
Panic disorder	6	4.3	2	3.6	2.2	1.00	0.14	0.35
Agoraphobia without panic	2	1.4	0	0	1.6	1.00	1.00	1.00
Generalized anxiety disorder	7	5.0	0	0	1.2	0.20	0.02	1.00
Social phobia	8	5.7	1	1.8	4.8	0.45	0.55	0.52
Obsessive-compulsive disorder	6	4.3	1	1.8	0.5	0.68	<0.001	0.25
Non-affective psychosis	2	1.4	1	1.8	0.2	1.00	0.04	0.11
Any disorder [^]	36	25.7	7	12.5	-	0.06	-	-

[^] Comparison with the general population was not possible for 'all depressive disorders' and 'all anxiety disorders', since 'all depressive disorders' was not mentioned as a separate category in the NEMESIS study; nor was it possible to compare 'all anxiety disorders' and the prevalence of 'any psychiatric disorder', since we did not assess the prevalence of specific phobias, posttraumatic stress disorder, eating disorder, and alcohol or drug abuse, which were included in the NEMESIS.

Fisher's exact test for significance (two-sided) was used: p^a: Mutation carriers versus non-carriers; p^b: Mutation carriers versus general population; p^c: Non-carriers versus general population.

Table 3. 12-Months prevalences of psychiatric disorders according to CIDI in presymptomatic mutation carriers, symptomatic mutation carriers and non-carriers, compared to the Dutch general population. [#]

	Presymptomatic mutation carriers (n = 55)		Symptomatic mutation carriers (n = 85)		Non-carriers (n = 56)		General population (n = 7076)	p^a	p^b	p^c
	n	%	n	%	n	%	%			
All depressive disorders [^]	11	20.0	14	16.5	4	7.1	-	0.06	-	-
Major depressive disorder	10	18.2	14	16.5	4	7.1	5.8	0.09	0.001	<0.001
Dysthymia	1	1.8	2	2.4	0	0	2.3	0.50	1.00	0.72
Manic episode	1	1.8	2	2.4	0	0	1.1	0.50	0.46	0.25
All anxiety disorders [^]	8	14.5	14	16.5	4	7.1	-	0.24	-	-
Panic disorder	2	3.6	4	4.7	2	3.6	2.2	1.00	0.35	0.13
Agoraphobia without panic	1	1.8	1	1.2	0	0	1.6	0.50	0.59	1.00
Generalized anxiety disorder	3	5.5	4	4.7	0	0	1.2	0.12	0.03	0.02
Social phobia	3	5.5	5	5.9	1	1.8	4.8	0.36	0.75	0.61
Obsessive-compulsive disorder	3	5.5	3	3.5	1	1.8	0.5	0.36	0.003	0.01
Non-affective psychosis	0	0	2	2.4	1	1.8	0.2	1.00	1.00	0.01
Any disorder [^]	15	27.3	21	24.7	7	12.5	-	0.06	-	-

[^] Comparison with the general population was not possible for 'all depressive disorders' and 'all anxiety disorders', since 'all depressive disorders' was not mentioned as a separate category in the NEMESIS study; nor was it possible to compare 'all anxiety disorders' and the prevalence of 'any psychiatric disorder', since we did not assess the prevalence of specific phobias, posttraumatic stress disorder, eating disorder and alcohol or drug abuse, which were included in the NEMESIS.

Fisher's exact test for significance (two-sided) was used: p^a: Presymptomatic mutation carriers versus symptomatic mutation carriers; p^b: Presymptomatic mutation carriers versus general population; p^c: Symptomatic mutation carriers versus general population.

[#] No significant differences were found comparing presymptomatic versus symptomatic mutation carriers (all p > 0.5), nor comparing symptomatic mutation carriers versus non-carriers (all p ≥ 0.09).

described only in case reports, both before[24-26] and after[27] the onset of motor symptoms. Increased prevalences of obsessive and compulsive symptoms, however, have been reported previously.[28-30] Especially in later stages of Huntington's disease, a more than 3 times greater probability of obsessive compulsive symptoms in comparison to subjects at 50% risk has been described.[31]

Psychosis
Contrary to the literature[10] and our expectations, the prevalence of non-affective psychosis in symptomatic mutation carriers in our study was rather low. This may be due to the use of strict DSM-IV criteria, our predominantly outpatient population, and the exclusion of subjects in an advanced disease stage with serious cognitive deterioration. Furthermore, symptomatic mutation carriers used much more psychotropic medication than presymptomatic mutation carriers, which could have suppressed psychiatric symptoms. In particular, the use of the neuroleptic tiapride in symptomatic mutation carriers, which is prescribed for motor symptoms, may have effectively reduced psychotic phenomena.[32,33] This fact would lead to an underestimation of psychosis, particularly in symptomatic mutation carriers.

Environmental and biological factors
We could not confirm our assumption that Huntington's disease family members who were not genetically compromised had more psychiatric disorders than the general population, although they shared a potentially stressful environment. Early life experiences, such as insecure parental binding, the stress of being at risk, and the familial disease burden, do not make them more susceptible to psychiatric disorders compared to the general population. This finding indicates a predominantly neurodegenerative origin of psychiatric disorders in Huntington's disease.

As the Huntington's disease mutation itself does not show a full penetrance for the presence of psychiatric disorders, future research should focus on the contribution of other factors, both environmental and biological. Besides playing a part in the risk profile for psychiatric disorders, biological factors may also be markers for disease progression. Since pre-motor symptomatic mutation carriers with a psychiatric disorder have a significantly higher UHDRS total motor score compared to presymptomatic mutation carriers without a psychiatric disorder, research on early neuroendocrine and neuroanatomical changes in relation to the occurrence of psychiatric disorders — before the manifestation of movement disorders — is warranted. Although imaging studies on psychopathology in Huntington's disease are rare, a decreased metabolic activity in orbital frontal-inferior prefrontal regions has been described in depressed Huntington's disease patients,[34] and disturbed anatomical connections between the basal ganglia and the limbic system have been suggested in Huntington's disease patients with obsessive-compulsive disorder,[35] all of which require further research.

To our knowledge, this is one of the largest studies among Huntington's disease mutation carriers in which a validated and fully structured instrument was used to estimate the prevalences of psychiatric disorders according to DSM-IV classification. The use of a control group of first-degree non-carriers relatives is an important strength of this study. A possible limitation of our study is that both interviewers and study subjects had knowledge of their genetic status. In a

previous study, subjects who were mostly well informed about the symptoms accompanying disease onset tended to conceal symptoms from the interviewer to avoid disclosure of their genetic status.[36] Therefore, interviewers were not blinded for the genetic status of participants, as this would potentially generate a biased response (underreport) on questions about psychiatric symptoms. This may have contributed to increased scores of psychiatric symptoms in mutation carriers. On the other hand, the prevalences of psychiatric disorders might have been underestimated, since those with psychiatric symptoms might have been more likely to refuse participation.[37] Furthermore, relatively small sample sizes and low rates of psychiatric disorders may have compromised the power to detect differences between the study groups.

This study highlights the importance of exploring the full clinical phenotype of Huntington's disease before motor symptoms arise. The presence of a potentially treatable psychiatric disorder contributes greatly to disease burden and should therefore be a constant point of attention for all who work with Huntington's disease patients and their families.

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Chapter 4

Behavioral problems in Huntington's disease using the Problem Behaviors Assessment

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Abstract

Objective: To investigate behavioral problems in Huntington's disease.

Method: In 152 Huntington's disease mutation carriers and a control group of 56 non-carriers at initial 50% risk, the Dutch version of the Problem Behaviors Assessment was administered. Mutation carriers were divided into three groups according to the motor section of the Unified Huntington's Disease Rating Scale: pre-motor symptomatic, early and advanced symptomatic subjects. The factor structure and interrater reliability of the Problem Behaviors Assessment were investigated.

Results: The clinically relevant interrater reliability of the Problem Behaviors Assessment was 0.82 for severity scores and 0.73 for frequency scores. The Problem Behaviors Assessment showed a three-factor solution: apathy, depression and irritability. Mutation carriers, including presymptomatic subjects, portrayed more apathy, depression and irritability than non-carriers. Early symptomatic subjects had more apathy, but not more depression or irritability, compared to presymptomatic subjects. Advanced symptomatic subjects had more apathy than early symptomatic subjects.

Conclusions: The Problem Behaviors Assessment is a reliable and sensitive instrument. Behavioral problems occur in all stages of Huntington's disease and arise before the onset of motor symptoms. Apathy is related to disease severity, whereas depression and irritability are not. The broad clinical phenotype of Huntington's disease therefore requires adequate service delivery with integrated and multidisciplinary patient care.

Introduction

Huntington's disease is a progressive autosomal dominant neurodegenerative disorder with an elongated CAG repeat length on chromosome 4. It has an insidious onset (mean age 40 years) and varied clinical presentation.[1] Huntington's disease is traditionally characterized by movement disturbances whilst cognitive deterioration is now well documented.[2] Increasingly, however, neuropsychiatric symptoms are recognized as much more distressing and disabling for both subjects and their caretakers, and are often the main reason for institutionalizing.[3]

A systematic review of the literature showed that the reported prevalences of depressed mood, anxiety, irritability and apathy vary from 33% to 76%, whereas obsessive compulsive symptoms and psychosis occur less often with a prevalence of 10 - 52% and 3 - 11%, respectively.[4] An evaluation of available studies on psychopathology in Huntington's disease is difficult because of different methodologies, small sample sizes and lack of control groups.[4,5] Because Huntington's disease is uncommon and complex, and behavioral symptoms are often not described as a major part of the disease process, the symptoms, course and management may be relatively unknown to health care professionals.

Some evidence exists that cognitive deterioration precedes the onset of motor symptoms in Huntington's disease.[6,7] Several retrospective studies indicate that the same might be the case for psychopathology.[8-12] Only four cross-sectional studies comparing pre-motor symptomatic mutation carriers with non-carriers have been done so far.[13-16] Although they found no difference for past or present psychiatric morbidity, they did find that presymptomatic mutation carriers differed from non-carriers on measures of irritability and anger/hostility. We therefore propose that behavioral problems, especially irritability, precede the onset of motor symptoms in Huntington's disease.

The etiology of neuropsychiatric symptoms is likely to be complex, implicating firstly direct neuropathological effects by the disease itself [17] and, secondly, social and environmental causal factors.[9-10] An appropriate control group for genetically confirmed Huntington's disease mutation carriers is therefore their mutation-negative siblings. They share the same psychosocial family background, often strongly influenced by an ill parent, as well as other risk factors that could contribute to the development of behavioral problems.[18] These include being at-risk for many years, as well as participating in the presymptomatic testing procedure until the outcome is known. We suppose that part of the behavioral problems in Huntington's disease is due to direct disease processes and therefore expect that mutation carriers portray more behavioral problems compared to their mutation-negative siblings.

The aim of our study was to investigate the prevalence of psychopathology and behavioral problems in (a) a sample of genetically and clinically confirmed Huntington's disease mutation carriers, comprising both the early and advanced stages of the disease; (b) a group of presymptomatic mutation carriers; and (c) a control group of mutation-negative subjects at initial 50% risk. Because neuropsychiatric symptoms in subjects with neurodegenerative disorders cannot often be grouped according to formal psychiatric classifications,[19] a dimensional approach may better be used to illuminate neuropsychiatric symptomatology.[20] We therefore

use the Problem Behaviors Assessment (PBA) (See: Appendix A) to assess behavioral problems in this study. The PBA is a semi-structured interview specifically designed for a more reliable assessment and better understanding of behavioral problems in Huntington's disease. Craufurd et al.[21] described three clusters of symptoms — apathy, irritability and depression — based on a factor analysis using data from 78 subjects. They also reported an interrater reliability of 0.86 for severity scores and 0.84 for frequency scores.

The PBA is a promising instrument, but Craufurd et al. did not include a sufficiently large sample in their factor analysis.[21] We therefore re-assess the factor structure and determine the interrater reliability of the Dutch translation of the PBA.

Methods

Participants

Between May 2004 and August 2006, 343 genetically tested subjects at initial 50% risk of Huntington's disease were contacted via the Departments of Neurology and Clinical Genetics of the Leiden University Medical Centre and long-term care facility 'Overduin' in the Netherlands. One hundred and ninety-two subjects were willing and able to participate in this study. Subjects with a neurological condition other than Huntington's Disease were excluded. An additional 18 subjects were recruited through other means, such as the Dutch Huntington's Disease association, but two subjects were subsequently lost to follow-up. The remaining 208 subjects were divided into four groups based on (a) their genetic test result, which was obtained from their medical records, and (b) their Unified Huntington's Disease Rating Scale (UHDRS) motor score (Figure 1).[22] The Medical Ethical Committee of the Leiden University Medical Centre approved the study. All subjects gave informed consent.

CAG repeat length

The number of CAG repeats of all subjects was verified. Subjects with a normal repeat length containing 26 or less copies and those with an intermediate repeat number between 27 and 35 were considered non-carriers.[1] Since alleles in the 36 to 39 repeat range are unstable and are associated with the Huntington's disease phenotype, these subjects were considered positive for Huntington's disease in this study.

Interview

All subjects were interviewed by trained interviewers who collected socio-demographic data and administered all measures, except for the motor section of the UHDRS. In a previous study,[6] subjects who are mostly well informed about the symptoms accompanying disease onset tended to conceal symptoms from the interviewer if they were to keep their genetic status secret. Therefore interviewers were not blinded for the genetic status of participants, as this would result in an underreporting of behavioral problems.

Assessment of motor functioning and disease stage

The motor section of the UHDRS was assessed by a neurologist who was kept blind for the genetic status of the subject. Based on the clinical examination, the neurologist expressed his confidence that the presence of motor symptoms in a study subject is a sign of clinically manifest Huntington's disease. Confidence level scores range from 0 to 4. All mutation carriers (n = 55)

with confidence level scores of 0 and 1 were classified as presymptomatic. The remaining mutation carriers (n = 97) with score 2 to 4 were all considered symptomatic. The median score (40 points) of the total UHDRS motor score (range 0 - 124 points) was used for distinguishing early symptomatic (n = 47) from advanced symptomatic subjects (n = 50) (Figure 1).

Figure 1. Flowchart of inclusion of subjects
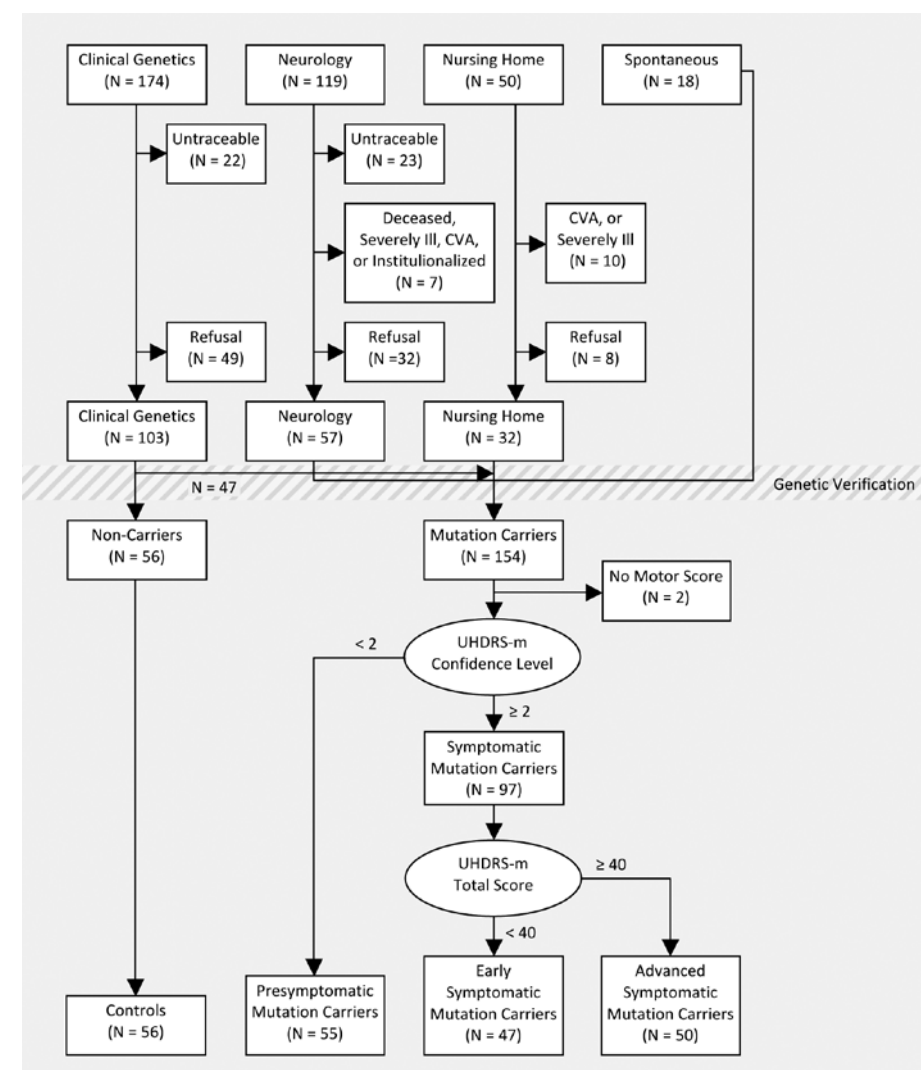
CVA = Cerebrovascular accident; UHDRS-m = Unified Huntington's Disease Rating Scale, motor section

Assessment of neuropsychiatric symptoms

Behavioral problems were assessed with the PBA which consists of 36 items covering nearly all behavioral problems present in Huntington's disease.[21] The 5-point PBA rating scales, one

subscale for severity and one for frequency, are modeled after the behavioral section of the UHDRS, using the scores 0 (absent) 1 (questionable), 2 (mild), 3 (moderate) and 4 (severe). Unlike the UHDRS, which rates behavior in the last 6 months, the PBA solely assesses behavioral problems in the 4 weeks prior to the interview.

Where possible, subjects were interviewed in the presence of a knowledgeable informant. If not, we conducted a telephone interview with an informant. Both the informant and the subject were given the opportunity to speak with the interviewer separately, in order to acquire information that might have been kept from us in the presence of the other person. Scores were determined by the interviewer based on the combination of information gathered, which included clinical observations.

In order to assess the interrater reliability of the PBA, a random subset of 63 subjects and their informants were interviewed a second time on the same day by a different interviewer. For the methodological evaluation [principal component analysis (PCA)] of the PBA, the PBAs of 152 mutation carriers only were used. These were augmented with a further group of 25 PBAs of mutation carriers who were assessed as part of ordinary monitoring. This resulted in a total of 177 PBAs for the methodological evaluation.

For this study a Dutch translation of the PBA was created. The Dutch PBA was translated back into English by a native English speaker which resulted in a few linguistic changes only.

Other clinical characteristics
Information on sociodemographic and clinical characteristics was obtained during a standardized interview. The estimated age of onset was calculated according to the following equation: log (age) = α + β (CAG number repeats), where α = 6.15 and β = −0.053.[23]

The Total Functional Capacity (TFC) scale was administered to assess general functioning. The TFC is widely used in Huntington's disease research, with scores ranging from 0 to 13 points.[24] A lower score indicates worse general functioning. The Mini-Mental State Examination (MMSE) was used to assess global cognitive functioning. A score below 25 (out of 30) is used as indication of cognitive impairment.[25]

Statistical analysis
Group differences on demographic and clinical characteristics were determined using one-way ANOVA. Post hoc comparisons were carried out with the Scheffé method for differences between groups for continuous data. Chi-square tests with adjusted standardized residuals were used for analysis of dichotomous data.

Interrater reliability of the PBA was assessed using weighted kappas. A kappa of more than 0.6 is considered acceptable and a kappa of more than 0.8 is considered good.[26] Because we only considered differences of more than 1 point between the raters as clinically relevant, a 'clinically relevant' kappa was calculated, which only included differences that were larger than 1 point.

The factor structure of the PBA was determined using PCA with varimax rotation. Items occurring in less than 10% of subjects were excluded (i.e., change in food preference, obsessions, somatization, sexually disinhibited behavior, sexually demanding behavior, delusions, jealousy and all forms of hallucinations). The PBA scores (the product of severity and frequency scores) of the resulting 28 items were entered into an analysis of 177 cases. The solution was checked for robustness by randomly deleting 10% of the cases, which was repeated five times. The quantity of factors was based on a Monte Carlo analysis and a scree plot. Based on the results of the PCA, three internally consistent subscales were computed. Alpha maximization was used as a criterion for including items in a subscale. The subscale scores were computed as the mean of the included items, resulting in a theoretical range from 0 to 16. The subscale scores of the different groups were compared using analyses of covariance (ANCOVA), with sex, education and psychiatric history as covariates, to distinguish between the groups. Because these scores are not normally distributed, a square root transformation was applied. Significance for all tests was set at p < 0.05. Kappas were computed in Microsoft Excel. All other analyses were carried out in Statistical Package for Social Sciences v. 12.0.1.

Results
Socio-demographic and clinical characteristics The main socio-demographic and clinical characteristics of the study population are given in Table 1. A significantly lower CAG repeat length was found in presymptomatic compared to symptomatic mutation carriers (p < 0.05). The calculated mean number of years to the estimated age of onset in presymptomatic mutation carriers was 8 years. Both early and advanced symptomatic mutation carriers had significantly lower mean MMSE scores than presymptomatic mutation carriers and non-carriers (p < 0.05). All groups differed significantly from each other with respect to TFC and the use of psychotropic drugs. Presymptomatic mutation carriers significantly more often reported a psychiatric history than the three other groups. This was corrected for in the subsequent analyses (ANCOVA).

Assessment of PBA
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, as measured with a 'clinically relevant kappa'.

Factor analysis revealed three components that together explained 38.6% of the variance (Table 2). Although Monte Carlo analysis allowed for four principal components, the scree plot indicated three components comprising coherent items. Based on the PCA three internally consistent subscales — apathy, depression and irritability — were computed. Alpha maximization was used as criterion for including items in a subscale. Internal consistencies expressed as Cronbach's α were 0.84 for apathy, 0.81 for depression and 0.67 for irritability. The subscales turned out to be sufficiently stable. In the five tests performing a PCA on random subsamples of 90% of the cases, the same components emerged. Some minor shifts of items to another component were observed; one or two in each test. These items included 'insomnia' (4×), 'impaired judgment' (2×), 'loss of energy' (2×), and 'self-centeredness' (1×). Only this last item was used in the construction of a subscale (irritability).

Table 1. Demographic and clinical characteristics of study subjects (n = 208)

	Non-carriers	Presymptomatic mutation carriers	Early symptomatic mutation carriers	Advanced symptomatic mutation carriers
	n = 56	n = 55	n = 47	n = 50
Demographics				
Male (n, %)	25 (45%)	24 (44%)	22 (47%)	23 (46%)
Age in years (mean, SD) [a]	39 (11.1)	41 (10.4)	47 (10.7)	54 (11.0)
Education in years (mean, SD) [b]	14 (3.5)	14 (3.9)	14 (4.1)	11 (2.3)
CAG repeat length (mean, SD) [c]	22 (4.1)	43 (2.3)	45 (3.2)	45 (3.6)
Estimated age of onset (mean, SD) [d]	N/A	49 (5.9)	45 (7.1)	43 (7.5)
Clinical Characteristics				
Psychiatric history (n, %) [e]	18 (32%)	28 (51%)	19 (40%)	16 (32%)
Use of psychopharmaca, (n, %) [f]	3 (5%)	12 (22%)	19 (40%)	38 (76%)
High alcohol consumption (mean, %) [g]	8 (14%)	10 (18%)	5 (11%)	3 (6%)
MMSE (mean, SD) [a]	29.1 (1.2)	28.7 (1.4)	26.9 (2.7)	21.5 (6.9)
TFC (mean, SD) [f]	12.9 (0.5)	12.0 (1.8)	10.1 (2.8)	4.1 (3.4)
UHDRS-motor score (mean, SD) [a]	2.2 (2.6)	2.3 (3.1)	19.3 (11.1)	61.1 (15.1)

MMSE = Mini-Mental State Examination; TFC = Total Functional Capacity; UHDRS = Unified Huntington's Disease Rating Scale; NA = not-applicable.
[a] Non-carriers and presymptomatic mutation carriers versus early symptomatic versus advanced symptomatic mutation carriers: p < 0.05.
[b] Advanced symptomatic mutation carriers compared to all other groups: p < 0.05.
[c] Non-carriers compared to all other groups: p < 0.001; and presymptomatic mutation carriers versus early and advanced symptomatic mutation carriers: p < 0.05.
[d] Presymptomatic mutation carriers versus early and advanced symptomatic mutation carriers: p < 0.005.
[e] Presymptomatic mutation carriers compared to all other groups: p < 0.05.
[f] Difference between all groups: p < 0.05.
[g] Alcohol consumption was considered high if more than 14 glasses a week were consumed.

Table 2. Principal Component Analysis on PBA items *

	Component loadings		
	Apathy	Depression	Irritability
Lack of perseverance	*.80*	.16	.02
Poor quality of work	*.79*	.12	.03
Lack of initiative	*.72*	.28	-.07
Poor self-care	*.71*	.01	.01
Blunting of affect	.53	.27	-.06
Bolting food	.49	-.20	.12
Los of energy	.43	.31	.23
Loss of libido	.42	.20	.01
Sleeping or drowsy during day	.41	.06	.26
Pathological preoccupations	.40	.09	.26
Depressed mood	.21	*.79*	.10
Depressive cognitions	.30	*.73*	-.02
Anxiety	.08	*.70*	.11
Tension	-.02	*.67*	.14
Suicidal ideation	.23	*.64*	-.02
Reduced appetite	.19	.45	.00
Early wakening	-.09	.38	.06
Loss of volition	.28	.38	-.04
Impaired judgment	.30	.31	.27
Irritability	.28	.22	*.67*
Aggression	-.08	.06	*.65*
Verbal outbursts	.03	.10	*.60*
Inflexibility	.40	.03	*.50*
Disturbed temperature regulation	-.04	.06	.48
Self centered, demanding	.42	.11	*.45*
Increased appetite	-.03	-.11	.43
Compulsive behaviors	.20	-.04	.41
Initial insomnia	-.05	.34	.37
% Variance	15.6	13.2	9.8
Cronbach's alpha [#]	0.84	0.81	0.67

* For the Principal Component Analysis (PCA) data from the Problem Behaviors Assessments of another 25 subjects were added (42% males; mean age: 46 years, SD 7.7 years) resulting in a group of 177 genetically confirmed mutation carriers. The items that are used for the subscales are in **bold italics**.
[#] Alpha maximization was used as a criterion for including items in a subscale.

Table 3. Subscale scores for the different study groups*

| | Non-carriers | Mutation carriers | | | p values | | | |
| | | Pre-symptomatic | Early symptomatic | Advanced symptomatic | Non-carriers vs. all mutation carriers | Non-carriers vs. presymptomatic | Presymptomatic vs. early symptomatic | Early vs. advanced symptomatic |
	n = 56	n = 55	n = 47	n = 50				
Apathy (mean, SD)	0.11 (0.40)	1.01 (1.86)	2.07 (3.07)	5.76 (5.10)	< 0.001	< 0.001	0.01	< 0.001
Depression (mean, SD)	1.32 (1.94)	2.54 (2.71)	2.79 (2.92)	2.65 (3.17)	0.002	0.04	0.25	0.64
Irritability (mean, SD)	0.68 (1.21)	1.53 (1.88)	1.52 (1.63)	2.41 (2.74)	< 0.001	0.02	0.41	0.50

Analysis of variance, with psychiatric history, sex and education as covariates.

* Subscale scores were computed as the mean (SD) of the included items, resulting in a theoretical range from 0 to 16 points.

Behavioral problems in Huntington's disease

Comparison of the subscale scores of the different study groups revealed significantly more apathy, depression and irritability in all mutation carriers than in non-carriers (Table 3). Presymptomatic mutation carriers showed more apathy, depression and irritability compared to non-carriers, whereas they differed from early symptomatic mutation carriers on measures of apathy only. Advanced mutation carriers revealed more apathy than the earlier disease stage groups, but not more depression and irritability (Table 3).

No significant relationships were found between the three subscale scores and the estimated age of onset of motor symptoms in mutation carriers.

Discussion

The PBA appears to be a promising instrument for the assessment of behavioral symptoms in Huntington's disease. The instrument shows a good interrater reliability, is easy to administer and covers a broad range of behavioral problems. The PBA also facilitates a dimensional approach, which seems appropriate for the assessment of behavioral problems in Huntington's disease.[19]

The PCA conducted on this instrument gives a robust solution. It features three subscales: apathy, depression and irritability. Our subscales are roughly similar to the factors found by Craufurd et al.,[21] although their sample was rather small for a reliable factor analysis.[27] Measuring the correlation between external measures of apathy, depression, irritability and the relevant factors on the PBA could provide further evidence for the existence of different neuropsychiatric syndromes in Huntington's disease.

A disadvantage of the PBA is its comparative length, but the instrument can be considerably reduced whilst retaining most of the advantages listed. We recommend leaving out all the items that have been excluded from the factor analysis, which reduces the amount of items from 36 to 28. If necessary the PBA could be reduced to the 14 items that constitute the three factors. Because the PBA does not generate formal psychiatric diagnoses, the instrument may be used alongside traditional psychiatric measures. The PBA is very likely to have a greater sensitivity for behavioral problems in Huntington's disease, whereas formal psychiatric diagnostic instruments provide greater specificity.

A comparison of symptomatic and presymptomatic mutation carriers and a control group consisting of non-carriers at initial 50% risk shows that all mutation carriers portray more apathy, depression and irritability than the control group. This difference is apparent even before motor symptoms arise. Although some psychopathology in the mutation carrier group may be due to knowledge of a Huntington's disease positive test result, a negative result also produces psychological problems, such as survivors' guilt. No substantial long-term effects of test results have been found.[28] Therefore the difference between mutation carriers and the control group is directly due to neuropathology, rather than to psychosocial stressors such as a disturbed childhood and anxiety about test results.

These findings give strong evidence that behavioral problems are amongst the first disease

symptoms in Huntington's disease and, in keeping with our hypothesis, can precede the onset of motor symptoms. Since our presymptomatic group also had reduced total functional capacity compared to non-carriers, clinically manifest Huntington's disease can present itself before the onset of motor symptoms. This contradicts previous literature, which only found a difference between presymptomatic and non-carriers for irritability.[13-15] The PBA, facilitating a multidimensional approach, may have been more sensitive than the instruments used in other studies.

Recognition and acknowledgement of these behavioral changes as part of the clinical phenotype of Huntington's disease will help carriers and their families cope with this disease. General practitioners should be aware of these specific characteristics in subjects at risk for Huntington's disease, because in many carriers the negative impact of Huntington's disease may start long before the first motor symptoms occur. Possible interventions in general practice are family support and psycho-education about the broad spectrum of disorders in Huntington's disease. Furthermore, multidisciplinary treatment with general practitioners, psychiatrists, psychologists, neurologists, nurses and social workers will contribute to the care of these patients and the quality of their lives.[29]

Presymptomatic and early symptomatic mutation carriers differed on measures of apathy only, as do early and advanced symptomatic mutation carriers. This confirms earlier evidence that apathy is strongly correlated to disease progression.[21,30-34] Depression and irritability appear to be not related to disease stage at all, with consistent levels found in pre-, early and advanced symptomatic subjects.

A possible limitation of our study is that both interviewers and study subjects had knowledge of their mutation status. This may have contributed to increased scores of behavioral problems in mutation carriers. Blinding interviewers to the genetic status of the participant requires subjects to keep their status secret. Experience has shown that this would generate a biased response on questions about emotional problems which could be related to genetic status or be perceived by the subject or informant as related to disease onset. The interviewers were aware of this limitation, and in order to guarantee objectivity, frequent interrater sessions were held and disease progression was assessed separately, and blindly, by a neurologist.

This is the first study that incorporates various Huntington's disease stages and a control group of non-carriers at initial 50% risk and gives clear evidence for the early emergence of behavioral problems in Huntington's disease. These symptoms are at least partly due directly to neuropathological processes. Since behavioral problems are amongst the most distressing symptoms for caregivers and patients,[3] recognition and multidisciplinary treatment are vital. The PBA seems to be an appropriately sensitive instrument for assessment of behavioral problems. Overall, these findings provide strong support for increasing the emphasis on neuropsychiatric symptoms in Huntington's disease in both research and clinical care.

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Chapter 5

Measurement of psychopathology in Huntington's disease: the critical role of caregivers
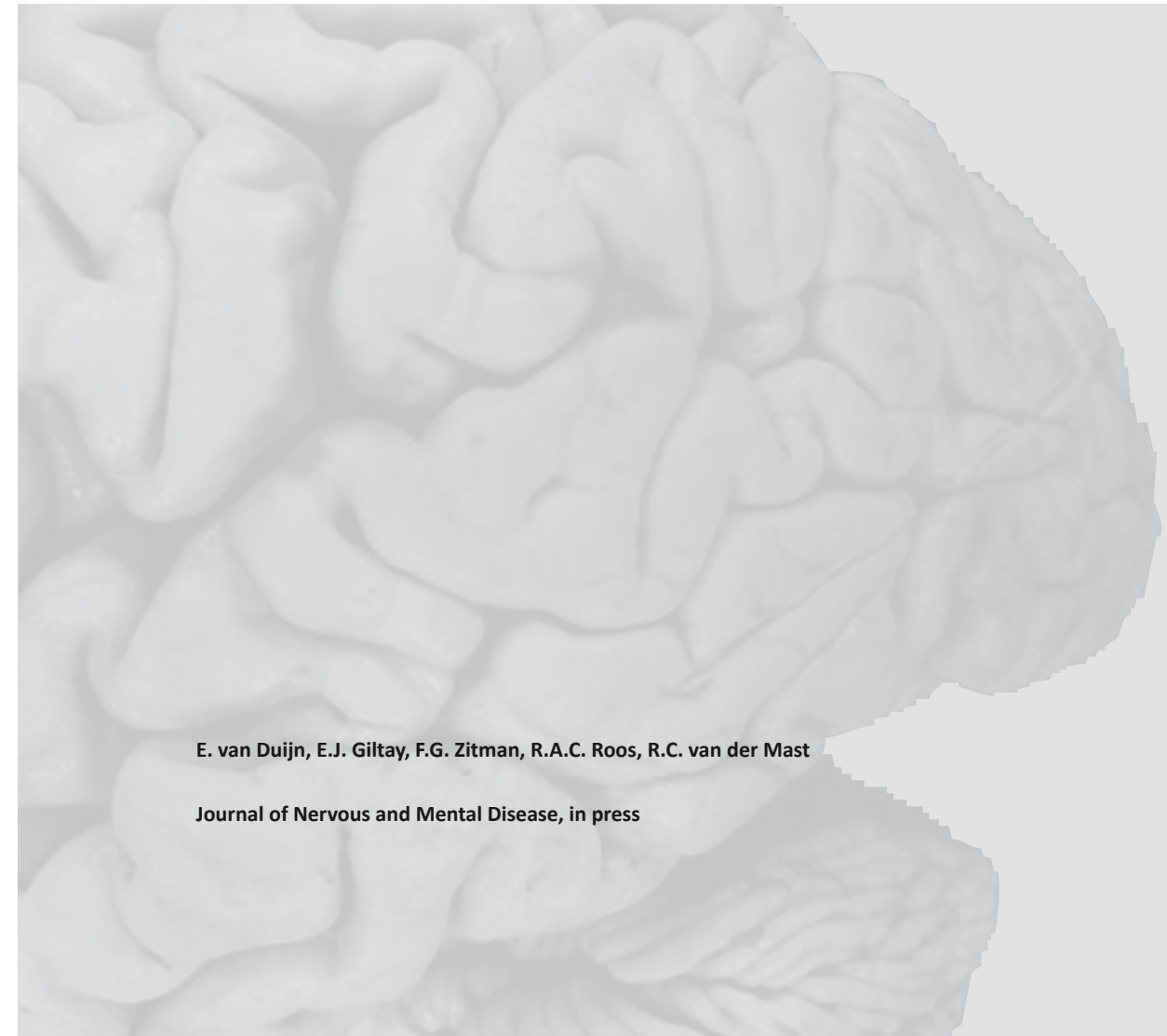
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Abstract

Objective: To investigate the concurrent validity of two dimensional rating scales that were designed for assessment of psychopathology in Huntington's disease, with categorical DSM-IV diagnoses.

Background: Assessment of psychopathology in Huntington's disease using formal criteria is complex due to the co-morbid somatic and cognitive disturbances, and diminished disease awareness.

Method: In 152 Huntington's disease mutation carriers, test scores on the Problem Behaviors Assessment scale (PBA) and the behavioral section of the Unified Huntington's Disease Rating Scale (UHDRS-b) were associated with DSM-IV diagnoses according to the Composite International Diagnostic Interview (CIDI).

Results: Both high PBA and UHDRS-b scores corresponded with presence of DSM-IV diagnoses. Receiver operating characteristic curves showed an area under the curve of 0.87 for the PBA and 0.91 for the UHDRS-b, demonstrating moderate to strong discriminatory power. Using caregiver information, subjects who were too cognitively impaired for CIDI assessment showed similar high PBA and UHDRS-b scores, with both a negative predictive value of 96% and a positive predictive value of 40% and 44% respectively, for the presence of formal psychiatric disorders.

Conclusion: The use of dimensional rating scales and caregiver information allows for the assessment of psychopathology in advanced stage Huntington's disease, also in the presence of cognitive impairment.

Introduction

Huntington's disease is a progressive neurodegenerative disorder with an autosomal dominant hereditary pattern, caused by an elongated CAG repeat on chromosome 4.[1] Huntington's disease is clinically characterized by progressive motor dysfunction, psychiatric disorders and cognitive dysfunction. Typically, first clinical symptoms appear between the age of 30 and 50 years, showing a progressive course and disease duration of 15 to 20 years.

The presence of psychiatric disorders in Huntington's disease is associated with poor quality of life and increased caregiver distress, and it hastens admission to nursing homes.[2-4] Depression is the most frequently reported psychiatric disorder, but neuropsychiatric symptoms such as irritability and apathy are also highly prevalent in Huntington's disease.[5,6] Because some of the non-emotional symptoms of psychiatric disorders overlap with the typical symptoms of Huntington's disease, these may influence the validity of psychiatric assessment, e.g. weight loss may be a symptom of depression, but can also be an isolated symptom of Huntington's disease.[7] Besides, Huntington's disease patients frequently show lack of insight in advanced stages, and may not be able to communicate.[8,9] Assessment of psychiatric disorders may thereby be considerably hampered and even impossible, although in fact patients may suffer from gross psychopathology leading to severe functional impairments.

The current generally accepted diagnostic classification of psychiatric disorders is the Diagnostic and Statistical Manual, Fourth edition (DSM-IV-TR).[10] The DSM utilizes a non-etiological, categorical approach according to a subset of strict criteria to assign a psychiatric diagnosis at a certain time. This approach is useful in physically healthy subjects, but has major limitations in patients with a neurodegenerative disorder.

These limitations raise the question whether diagnostic classification of psychiatric disorders according to the DSM is reliable and valid in Huntington's disease. For that reason, the use of dimensional rating scales that use caregiver information for the assessment of psychopathology has been suggested as more appropriate in clinically affected Huntington's disease patients.[11,12] Such an approach may better reflect the range of symptoms across the spectrum of psychopathology than a DSM diagnosis.

In this study, we hypothesized that dimensional measurement using caregiver information is appropriate to detect psychopathology in advanced Huntington's disease. We assessed the concurrent validity of two dimensional rating scales that were specifically designed for the assessment of psychopathology in Huntington's disease, compared to a categorical assessment of psychiatric disorders as defined by DSM-IV criteria.

Methods

Subjects

Between May 2004 and August 2006, 152 consecutive Huntington's disease mutation carriers with a repeat length of 36 or more were recruited from the out-patient departments of Clinical Genetics and Neurology of the Leiden University Medical Center (LUMC), and from a regional nursing home. The design of the study has been described in detail elsewhere.[13] All subjects

gave written informed consent. The study was approved by the Medical Ethical Committee of the LUMC.

Instruments
Demographic and clinical characteristics
Information on demographic and clinical characteristics was collected using a standardized interview. CAG repeat length of all subjects was known, except for one subject who died during the study. 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)].[14] Global functioning was assessed using the Total Functioning Capacity (TFC; range 0-13 points, with lower scores indicating worse performance) of the Unified Huntington's Disease Rating Scale (UHDRS).[15] Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE; range 0-30 points, with lower scores indicating worse performance).[16] Subjects were examined for assessment of motor symptoms by a neurologist with experience of Huntington's disease using the motor section of the UDHRS (range 0-124 points, with higher scores indicating worse performance).[17]

General assessment of psychopathology
Composite International Diagnostic Interview
The Composite International Diagnostic Interview (CIDI) is a fully structured standardized psychiatric diagnostic interview for disease classification.[18] The CIDI aims to identify the extent to which endorsed symptoms satisfy diagnostic criteria for one of the mental disorders according to DSM-IV. The sections for depression, mania, anxiety, obsessive-compulsive disorder and psychosis of the interviewer administered version of the CIDI Version 2.1 were used to assess the presence of these Axis I disorders in the month prior to the interview. The inter-rater reliability of the CIDI is excellent, and the test-retest reliability and validity are good.[19] Subjects with an MMSE score < 18 points were considered too cognitively impaired for a reliable formal assessment with the CIDI.

Huntington's disease specific rating scales for psychopathology
Problem Behaviors Assessment
The Problem Behaviors Assessment (PBA) (See: Appendix A) is a recently developed instrument for the assessment of the severity and frequency of behavioral problems in Huntington's disease.[20] The PBA is a semi-structured interview designed for use with both patients and their caregivers. The severity and the frequency of each of the 36 items are scored on a scale from 0 to 4, with higher scores indicating more psychopathology. The severity and the frequency scores are multiplied to assess the total score for each item. The sum of these scores is called the PBA score (range 0 - 576). Previously, we performed a factor analysis on the 36 items of the PBA,[21] and distinguished three underlying symptom dimensions: 'apathy' (consisting of four items: lack of perseverance, poor quality of work, lack of initiative, and poor self-care; range 0 - 64 points), 'depression' (five items: depressed mood, depressive cognitions, anxiety, tension, and suicidal ideation; range 0 - 80 points), and 'irritability' (five items: irritability, aggression, verbal outbursts, inflexibility, and self-centered, demanding behavior; range 0 - 80 points). The interrater reliability of the PBA in a mixed population of Huntington's disease mutation carriers was 0.82 for severity scores and 0.73 for frequency scores.[21]

Behavioral section of the Unified Huntington's Disease Rating Scale
The behavioral section of the UHDRS (UHDRS-b) (See: Appendix B) consists of 11 items for the assessment of neuropsychiatric symptoms in a four weeks period.[17] Severity and frequency of these symptoms are scored on a scale from 0 to 4, with higher numbers indicating more psychopathology. The sum of the product of severity and frequency scores of all items is the UHDRS-b score (range 0 - 176).

Caregivers
Ratings of the PBA and the UHDRS-b are based on the reports of the subject and his/her caregiver, together with the clinical impression of the interviewer. Caregivers of the subjects who were too cognitively impaired for the CIDI consisted of nurses (58%), partners (25%), and children (17%). Caregivers of the other subjects were partners (60%), siblings (13%), parents (10%), children (7%), and the remaining 10% were assessed in the absence of a caregiver.

Statistical analyses
The three study groups were compared using independent samples t-tests for continuous variables and chi-square (χ^2) tests for dichotomous variables and for pair-wise comparison. All analyses were carried out two-sided with a significance level of $p < 0.05$. Non-parametric Kruskal-Wallis one-way analysis of variance was applied for testing differences between the groups for variables with skewed distributions.

Receiver operating characteristic (ROC) analysis was done to compare the results with the PBA as well as the UHDRS-b to classification of subjects according to DSM-IV diagnosis as assessed with the CIDI, and to select optimal cut-off scores for screening and diagnostic purposes of these two scales.[22] ROC curves were plotted for Huntington's disease patients with a DSM-IV diagnosis, as well as for the combined group of Huntington's disease patients with a DSM-IV diagnosis and Huntington's disease patients in whom formal CIDI assessment was not possible. These curves yielded the 'sensitivity' versus '1 minus the specificity' for each possible cut-off point. Optimal cut-off points were determined by assessing which score combined maximum sensitivity and specificity. The area under the ROC curve (AUC) was used as an indicator of diagnostic test's discriminatory power to distinguish between subjects with and without a DSM-IV diagnosis.[23] An AUC < 0.75 was considered not clinically useful.

Results
Demographic and clinical characteristics
Nineteen (13.6%) of the 140 subjects had one or more psychiatric disorders according to the CIDI (Table 1). Ten of them (52.6%) of the 19 subjects with a psychiatric diagnosis had a single psychiatric disorder; five subjects (26.3%) had two psychiatric disorders, three subjects (15.8%) had three psychiatric disorders, and one subject (5.3%) had even four. Most frequently reported psychiatric disorders were major depressive disorder (n = 8) and obsessive-compulsive disorder (n = 7).
Table 1 shows the demographic and clinical characteristics of 121 subjects without a formal DSM-IV diagnosis, 19 subjects with a formal DSM-IV diagnosis, and 12 subjects that were too cognitively impaired. These latter subjects showed characteristics of advanced Huntington's

Table 1. Sociodemographic, clinical, and functional characteristics of the three study groups among 152 HD mutation carriers

	Subjects without DSM-IV diagnosis (n = 121)	Subjects with DSM-IV diagnosis (n = 19)	Subjects in whom CIDI was not possible ‡ (n = 12)	p value (3 groups comparison)
Sociodemographics				
Male (n, %)	57 (47.1)	7 (36.8)	5 (41.7)	0.68
Age (mean, SD)	47 (11.7) a	44 (12.3) a	57 (10.0) b	0.008
Married or partner (n, %)	87 (71.9)	12 (63.2)	7 (58.3)	0.50
Any children (n, %)	89 (73.6)	16 (84.2)	11 (91.7)	0.26
Clinical characteristics				
Estimated age of onset [1] (mean, SD)	45 (7.9)	47 (4.7)	45 (6.0) ^	0.64
CAG repeats [2] (mean, SD)	44 (3.5)	43 (2.2)	44 (2.5) ^	0.55
High alcohol consumption [3] (n, %)	18 (14.9)	0	0	0.07
Use of psychotropic medication (n, %)	46 (38.0) a	13 (68.4) b	10 (83.3) b	0.001
- Antidepressants	26 (21.5) a	11 (57.9) b	6 (50.0)	0.001
- Neuroleptics [4]	23 (19.0) a	3 (15.8) a	7 (58.3) b	0.006
- Benzodiazepines	17 (14.0) a	12 (63.2) b	7 (58.3) b	<0.001
Functional measures				
TFC (median, IQR)	11 (7-13) a	8 (4-10) b	1 (1-2) c	<0.001
MMSE (median, IQR)	28 (25-29) a	26 (23-30) a	14 (7-17) b	<0.001
UHDRS-m (median, IQR)	13 (2-44) a	5 (2-31) a	80 (67-88) b	<0.001

CIDI = Composite International Diagnostic Interview. DSM-IV = Diagnostic Statistical Manual, Fourth edition. TFC = Total Functional Capacity scale. MMSE = Mini-Mental State Examination. UHDRS-m = Unified Huntington's Disease Rating Scale, motor section.

[1] Estimation of the age of onset was calculated according to the equation of Vassos et al.: ln [age of onset (years)] = 6.18 - 0.054 * [CAG repeats (number)]. [2] CAG repeat length of one motor symptomatic subject with a HD positive family history was not verified. Four subjects had an intermediate repeat length. [3] Alcohol consumption was considered high if more than 14 glasses a week were consumed. [4] Including tiapride which was primarily given as a treatment for motor symptoms. ‡ CIDI was not possible because of severe cognitive dysfunction (ten subjects with MMSE score <18 points and two subjects who did not understand the questions, though MMSE scores were 19 and 20 points, respectively).

^ These calculations are based on n = 11.

Because of their skewed distributions, median and Interquartile Range (IQR: P_{25} - P_{75}) are given for TFC, MMSE, and UHDRS-m. P values are calculated by non-parametric Kruskal-Wallis tests.

a b c Values in the same row with different superscript letters are significantly different at p < 0.05 by post hoc tests with Bonferroni correction.

Table 2. Median PBA (sub)scores and UHDRS-b scores for the three study groups among 152 HD mutation carriers

	Subjects without DSM-IV diagnosis (n = 121)	Subjects with DSM-IV diagnosis (n = 19)	Subjects in whom CIDI was not possible ‡ (n = 12)	p value (3 groups comparison)
PBA score (median, IQR)	46 (26-85) a	134 (92-164) b	126 (78-166) b	<0.001
PBA subscores				
- Apathy (median, IQR)	1 (0-12) a	15 (6-32) b	40 (13-56) b	<0.001
- Depression (median, IQR)	8 (1-16) a	38 (10-46) b	10 (1-30)	<0.001
- Irritability (median, IQR)	5 (0-14) a	12 (6-28) b	7 (0-21)	0.01
UHDRS-b score (median, IQR)	9 (2-22) a	48 (28-72) b	27 (10-70) b	<0.001

PBA = Problem Behaviors Assessment; UHDRS-b = Unified Huntington's Disease Rating Scale, behavioral section; DSM-IV = Diagnostic Statistical Manual, fourth edition. CIDI = Composite International Diagnostic Interview.
‡ CIDI was not possible because of severe cognitive impairment (ten subjects with MMSE score <18 points and two subjects who did not understand the questions, though with MMSE scores 19 and 21 points).

PBA score ranges from 0 - 576 points, with higher scores indicating more behavioral problems; Apathy subscore ranges from 0 - 64 points; depression subscore ranges from 0 - 80 points; irritability subscore ranges from 0 - 80 points; UHDRS-b score ranges from 0 - 76, with higher scores indicating more behavioral problems.

Because of their positively skewed distributions, median and Interquartile Range (IQR: P_{25} - P_{75}) are given.

a b: Values in the same row with different superscript letters are significantly different at p < 0.05 by non-parametric Kruskal-Wallis tests.

disease stage including decreased TFC score, increased total UHDRS-motor (UHDRS-m) score, and the use of significantly more neuroleptics, in comparison with the two other study groups.

PBA and UHDRS-b scores in relation to presence of DSM-IV diagnoses
There was a significant difference between the three study groups for both the PBA (sub) scores and the UHDRS-b score (Table 2). All median PBA (sub) scores and the UHDRS-b score were significantly higher in subjects with a DSM-IV diagnosis compared to subjects without a DSM-IV diagnosis (all p < 0.05). Also, subjects to whom the CIDI could not be administered because of severe cognitive dysfunction showed a significantly higher total PBA score, PBA apathy subscore, and UHDRS-b score compared to those without a DSM-IV diagnosis. No statistically significant differences were found between the cognitively compromised group and subjects with a DSM-IV diagnosis. As is shown in Figure 1A, high PBA and UHDRS-b scores indicate severe and frequent psychopathology in the cognitively compromised group.

Figure 1. Histograms and ROC curves for the PBA and UHDRS-b scores of the three study groups among 152 Huntington's disease mutation carriers
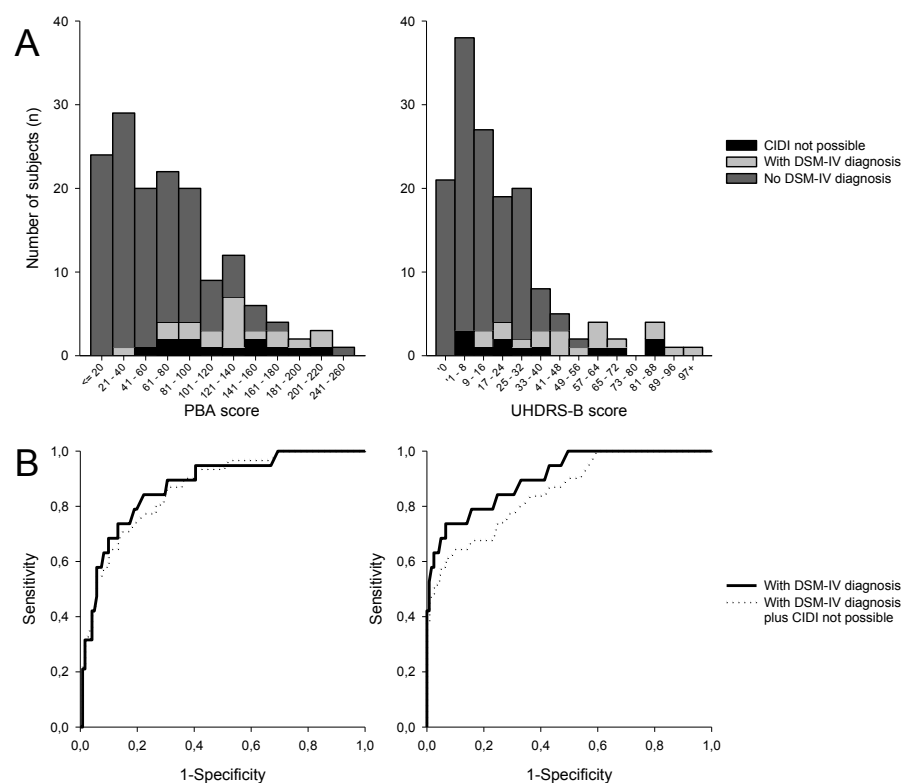
PBA = Problem Behaviors Assessment; UHDRS-b = Unified Huntington's Disease Rating Scale, behavioral section; CIDI = Composite International Diagnostic Interview

Validity of PBA and UHDRS-b compared to DSM-IV
To assess the concurrent validity of the two Huntington's disease specific rating scales, the CIDI was considered to be the gold-standard. The ROC curves showed an AUC for the group with a DSM-IV diagnosis of 0.87 for the PBA and 0.91 for the UHDRS-b (Figure 1B), demonstrating moderate to strong discriminatory power. Next, adding the group without a CIDI assessment due to cognitive impairment to the group of subjects with a formal DSM-IV diagnosis, the AUC remained almost equal (0.86) for the PBA, but slightly decreased (0.86) using the UHDRS-b. The discriminatory power was therefore considered to be moderate and of similar strength for both rating scales in cognitively impaired subjects with Huntington's disease.

Sensitivity and specificity of the PBA and UHDRS-b for the presence of DSM-IV psychopathology
The PBA demonstrated an optimal sensitivity and specificity (respectively 79% [95% confidence interval (CI): 61 - 97%] and 81% [95% CI: 74 - 88%]) for psychopathology according to DSM-IV at a cut-off of 91 points for the total PBA score. The corresponding negative and positive predictive values were 96% [95% CI: 92 - 100%] and 40% [95% CI: 24 - 55%], respectively. The optimal sensitivity and specificity of the UHDRS-b (respectively 79% [95% CI: 61 - 97%] and 84% [95% CI: 78 - 91%]) was at a cut-off of 27 points for the total UHDRS-b score. The corresponding negative and positive predictive values were 96% [95% CI: 93 - 100%] and 44% [95% CI: 27 - 61%], respectively.

Discussion
We showed that both high PBA and UHDRS-b scores corresponded with the presence of a psychiatric disorder according to DSM-IV criteria as assessed with the CIDI. Importantly, making use of caregiver information, subjects in whom formal assessment of DSM-IV diagnosis according to the CIDI was impossible because of cognitive impairment also showed high PBA and UHDRS-b scores. This finding confirms the face validity of these instruments suggesting severe and frequent psychopathology in patients in advanced disease stage.

Our finding that assessment using the PBA and UHDRS-b with caregiver information, was able to encompass psychopathology in all disease stages of Huntington's disease, is in line with the suggestions done by others.[11,12] The use of formal DSM diagnosis, instead of a dimensional measure, may explain why in some earlier studies the published rates of psychiatric disorders in the advanced stage of Huntington's disease were relatively low compared to earlier disease stages. Especially in advanced stage of Huntington's disease, when communication and insight may become so impaired that subjects are no longer able to express or to judge their symptoms, reported rates of psychiatric disorders appeared to decrease.[9] In this stage, the PBA and the UHDRS-b may be particularly useful, since they include caregiver information. This contributes to a more accurate assessment of psychopathology than a patient assessment alone.

Furthermore, the PBA and the UHDRS-b showed similar psychometric performances, with similar negative and positive predictive values. The positive predictive values were rather low, due to the relative high number of subjects in whom the CIDI assessment was not possible.

The PBA has already shown an interrater reliability of 0.82 for severity scores and 0.73 for frequency scores.[21] Although the UHDRS is widely used, we are not aware of any study on

the interrater reliability of the UHDRS-b which is a possible limitation of our study. A second limitation is that we did not assess the degree of insight, next to cognitive functioning, whereas lack of insight may already have been present before severe cognitive impairment. This may have compromised outcomes of the CIDI, since the use of the CIDI does not require information of the caregivers. A third limitation is that there is no agreement on the concept of psychopathology in patients with advanced neurodegenerative disorders. Consequently, high PBA and UHDRS-b scores may not represent the presence of DSM-IV disorders, though they indicate the presence of psychopathology. Finally, the number of patients with a formal DSM diagnosis was rather small, and therefore our results should be confirmed in other larger and therefore international cohorts of Huntington's disease patients.

Whereas the assessment of psychopathology in advanced stages of Huntington's disease is difficult, it may be even more difficult to measure the effectiveness of pharmacotherapy of neuropsychiatric symptoms. Still, monitoring the effect of a pharmacological treatment is compulsory to avoid the use of various non-indicated psychotropic medications. In our study, a high percentage of the patients used different psychotropic medications, especially those with cognitive impairments. Although the high PBA and UHDRS-b scores among these patients seem to justify the use of psychotropic medication, medication interactions and side effects may at the same time worsen motor symptoms. Furthermore, despite the frequent use of psychotropic medication, neuropsychiatric symptoms were still highly prevalent in this group.

In conclusion, the use of dimensional rating scales allows for the assessment of psychopathology, and for regular evaluation of psychiatric pharmacotherapy, making use of information of patients, caregivers and clinical parameters. The PBA and the UHDRS-b are particularly useful in the advanced stage of Huntington's disease being indicative for initiation and (dis)continuation of psychiatric pharmacotherapy.

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Chapter 6

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 benzo-diazepines.

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 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 Huntington's disease 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 Huntington's disease.[2-4] Reported prevalences of apathy in Huntington's disease 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 Huntington's disease mutation carriers and control non-carriers. Furthermore, we investigated sociodemographic, clinical and neuropsychiatric correlates of apathy comparing Huntington's disease mutation carriers with apathy to those without apathy.

Methods

Subjects

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

Instruments

Assessment of apathy

Apathy was assessed using the semi-structured Apathy Scale (AS) (Figure 1; Appendix C).[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

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1. Are you interested in learning new things?
2. Does anything interest you?
3. Does someone have to tell you what to do each day?
4. Are you concerned about your condition?
5. Are you indifferent to things?
6. Do you put much effort into things?
7. Are you always looking for something to do?
8. Do you have plans and goals for the future?
9. Do you have motivation?
10. Do you have energy for daily activities?
11. Are you unconcerned with many things?
12. Do you need a push to get started on things?
13. Are you neither happy nor sad, just in between, no matter what happens?
14. Would you consider yourself to be apathetic?

Scoring:

Questions 1, 2, 4, 6-10 :   Not at all = 3; Slightly = 2; Some = 1; A lot = 0
Questions 3, 5, 11-14:   Not at all = 0; Slightly = 1; Some = 2; A lot = 3

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Dutch version: see Appendix C

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 Huntington's disease, 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 of the UHDRS-m was used to define subjects as pre-motor symptomatic (Confidence Level score = 0 or 1 points) or motor symptomatic (Confidence Level score = 2 - 4 points).

Assessment of depression
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. χ^2-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).

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 < 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.

Results

Sociodemographic and clinical characteristics of mutation carriers versus non-carriers

The sociodemographic, clinical, and neuropsychiatric characteristics of 152 Huntington's disease 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 < 0.05) (Figure 2).

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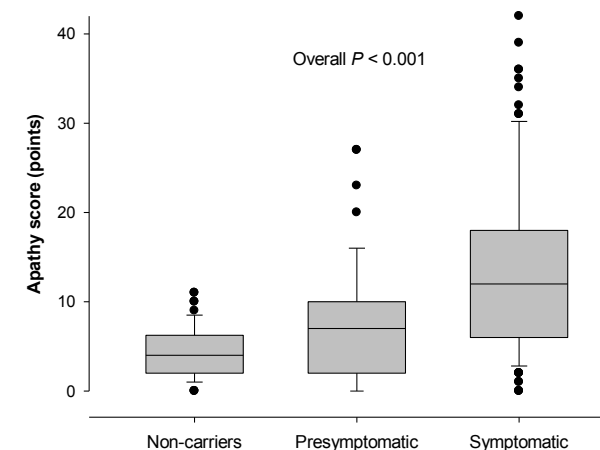
Table 1. Sociodemographic, clinical, and neuropsychiatric characteristics of Huntington's disease mutation carriers and non-carriers

	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	< 0.00
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.

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 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.

Independent correlates of apathy in Huntington's disease 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 benzo-diazepines (Table 3b).

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 41 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	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.

Discussion

The results of our study confirm that apathy frequently occurs in Huntington's disease 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 Huntington's disease 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 Huntington's disease, apathy has been shown to be associated with the presence of depressed mood,[3] but inconsistently.[11,26,27] 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 Huntington's disease, 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 disease stage. Therefore, apathy may be a sign of disease progression in Huntington's disease, 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 Huntington's disease, 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 Huntington's disease 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 Huntington's disease patients due to selection bias, as subjects who did not respond to the invitation to participate in the study may have been more apathetic.
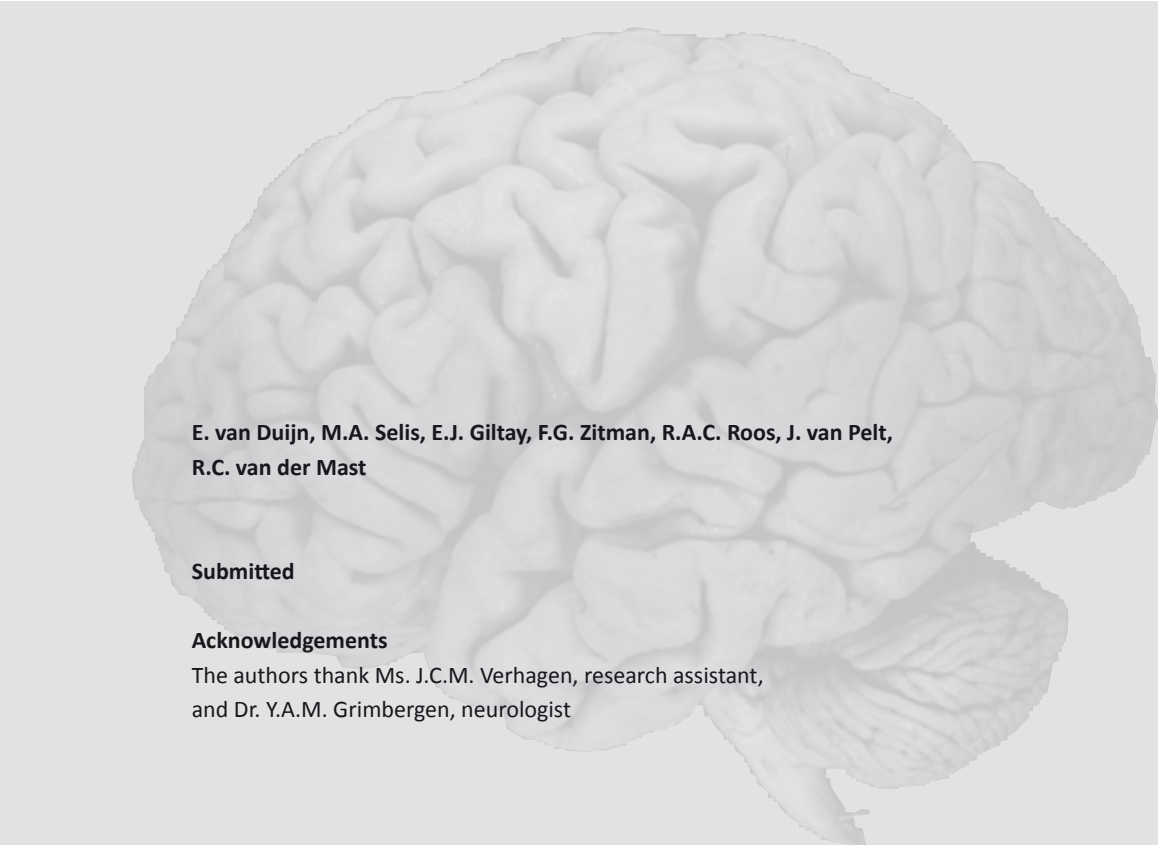
We conclude that apathy is highly prevalent in Huntington's disease and is strongly associated with the presence of depression, worse global functioning, and the use of psychotropic medication (especially neuroleptics and benzodiazepines). Therefore, we advise to evaluate the use of all psychotropic medications to exclude an iatrogenic cause of apathy.

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Chapter 7

Differences in the response of the hypothalamic-pituitary-adrenal axis in presymptomatic mutation carriers of Huntington's disease in comparison to symptomatic mutation carriers and controls

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Abstract

Neurodegeneration in Huntington's disease occurs in various brain regions including the hypothalamus. In this cross-sectional study, hypothalamic-pituitary-adrenal axis functioning was studied in 26 presymptomatic and 58 symptomatic Huntington's disease mutation carriers, and 28 controls. Hypothalamic-pituitary-adrenal axis functioning was measured through salivary cortisol in the day curve, the cortisol awakening response (CAR), the area under the curve (AUC), the morning rise, and the dexamethasone suppression test (DST).The CAR was statistically different (p = 0.046) between the three groups, being explained by higher cortisol concentrations at 45 and 60 minutes post-awakening for presymptomatic mutation carriers compared to both symptomatic mutation carriers and controls. The morning rise was also higher for presymptomatic mutation carriers (p = 0.005). No differences were found for the AUC, evening and post-DST cortisol concentrations. Our study indicates a delicate disturbance in morning cortisol secretion in Huntington's disease mutation carriers that precedes the onset of motor symptoms.

Introduction

Huntington's disease is a progressive autosomal dominant neurodegenerative disorder characterized by motor symptoms, cognitive decline, behavioral problems and psychiatric disorders.[1] Huntington's disease is caused by a trinucleotide expansion on chromosome 4 (4p16.3), coding for the mutant protein huntingtin.[2] Neurodegeneration primarily occurs in the striatum and cerebral cortex. Atrophy has also been found in hypothalamic areas,[3,4] with neuronal loss up to 90% in the nucleus tuberalis lateralis.[5,6] Direct involvement of huntingtin and pathological mechanisms, such as decreased hypocretin neurotransmission,[7] loss of hypothalamic D_2 receptors and microglia activation,[8] may play a role in hypothalamic dysfunctioning in Huntington's disease. Consequently, malfunctioning of the hypothalamic-pituitary-adrenal axis might occur.[9]

The hypothalamic-pituitary-adrenal axis regulates the stress response.[10] Corticotropin-releasing hormone, being released in a circadian, pulsatile rhythm in the hypothalamus with an increase in amplitude in the early morning hours, stimulates the anterior pituitary to produce adrenocorticotropic hormone that triggers the secretion of glucocorticoids from the adrenal cortex.

Previous studies have reported a hyperactivation of the hypothalamic-pituitary-adrenal axis in mutation carriers with increased corticotropin-releasing hormone in cerebrospinal fluid (CSF),[11] and increased cortisol concentrations in plasma,[12,13] and urine.[14] However, none of these studies, except for one,[12] took into account the circadian rhythm of the hypothalamic-pituitary-adrenal axis. Sample sizes varied from 10 to 82 Huntington's disease mutation carriers, while potential confounders of the hypothalamic-pituitary-adrenal axis were inconsistently taken into account. Our study therefore aimed to investigate the functioning of the hypothalamic-pituitary-adrenal axis as assessed with a cortisol day curve and dexamethasone suppression test (DST) in presymptomatic and symptomatic Huntington's disease mutation carriers, compared to controls.

Experimental procedures

Subjects

All 210 participating subjects (154 Huntington's disease mutation carriers and 56 controls) of an ongoing follow-up study on behavioral problems and psychiatric disorders in Huntington's disease,[15] were invited to participate. These persons had been recruited at the start of the study from the outpatient clinics of Neurology and Clinical Genetics of the Leiden University Medical Center, a nursing home with a specialized ward for Huntington's disease patients and the Dutch Huntington's disease patients association. Verified non-carriers with a CAG repeat < 36 were included as a control group because they had been exposed to the same stressful family circumstances as mutation carriers. Severely dysarthric and mutistic patients were excluded, as well as patients with juvenile onset Huntington's disease, concurrent diseases of the central nervous system or an insufficient command of the Dutch language. All subjects were Caucasian.

Twenty-five subjects refused to participate in this follow-up study, four subjects were untraceable, two were deceased, and one subject had become too severely affected to communicate. The remaining 178 subjects participated in this part of the study. The study was approved by the Medical Ethical Committee of the Leiden University Medical Center and all subjects gave their informed consent.

Demographic and clinical characteristics
Demographic and clinical characteristics, including potential confounders for hypothalamic-pituitary-adrenal axis functioning, like sex, age, smoking status, high alcohol consumption (> 14 consumptions a week), body mass index (BMI), presence of depressive disorder, and use of corticosteroid and psychotropic medication were assessed during a standardized interview. In addition, global cognitive functioning and general functioning were measured.

The presence of a depressive disorder (major depressive or dysthymic disorder) in the past two weeks was assessed with the Composite International Diagnostic Interview (CIDI), computerized version 2.1.[16] The CIDI is a fully structured psychiatric interview for disease classification of psychiatric disorders according to the Diagnostic and Statistical Manual of mental disorders (DSM).[17] Global cognitive functioning was measured using the Mini-Mental State Examination (MMSE).[18] Because of lack of reliability in subjects with severe cognitive dysfunction, the CIDI was not administered to subjects with a MMSE score < 18 points. Global general functioning was assessed using the Total Functioning Capacity (TFC) of the Unified Huntington's Disease Rating Scale (UHDRS).[19] The TFC consists of 5 questions assessing employment, the capacity to handle financial affairs, to manage domestic chores, to perform activities of daily living, and the care level provided. The TFC ranges from 0 - 13 points, with lower scores indicating poorer functional abilities.[20]

Assessment of motor functioning and disease stage
Subjects were examined for assessment of motor symptoms by a neurologist with experience of Huntington's disease using the motor section of the UHDRS. The neurologist was blinded to the genetic status of the subjects and the results of all other assessments. Based on the clinical examination, 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 Huntington's disease. Mutation carriers with confidence level score 0 (normal) or 1 (nonspecific motor abnormalities; < 50% confidence) were considered presymptomatic (n = 26). The remaining mutation carriers (n = 58) with score 2 (motor abnormalities that may be signs of Huntington's disease; 50 - 89% confidence), 3 (likely signs of Huntington's disease; 90 - 98% confidence), or 4 (unequivocal signs of Huntington's disease; ≥ 99% confidence) were considered symptomatic.

Measurement of hypothalamic-pituitary-adrenal axis functioning
Functioning of the hypothalamic-pituitary-adrenal axis was assessed by the use of cortisol concentrations in saliva, reflecting the free fraction of plasma cortisol.[21] Advantages of salivary cortisol above plasma cortisol measurement are the easy collection of saliva by the subjects at their homes, the possibility of repeated sampling to yield a day curve, the stability of cortisol at room temperature during the time required for this study, the absence of stress induction

by a venapuncture, and the lower costs.[22] After oral and written instruction, subjects were asked to collect saliva by themselves on two consecutive days. For this, they had to place cotton wads from a saliva collection tube (Salivette; Sarstedt, Newton, NC) in their mouth and chew on them until they were saturated. The wads were restored in the tube labeled with date and time. Subjects were asked to refrain from eating, drinking, and brushing their teeth before the morning sampling to avoid contamination of the saliva with food or blood. They were free to wake up according to their normal schedule, but were asked to record their time of awakening because the cortisol response may be influenced by the time of awakening.[22]

The circadian rhythm of the hypothalamic-pituitary-adrenal axis was taken into account by assessing a cortisol day curve. On day 1 six samples were taken: at the time of awakening, 30, 45, and 60 minutes post-awakening, at 22:00 h, and at 23:00 h. The cortisol awakening response (CAR) is a distinctive measurement of the cortisol circadian cycle. In healthy adults salivary cortisol concentrations increase by 50% to 160% in the first 30 minutes post-awakening.[23] The CAR is defined as the mean of the two cortisol concentrations at 45 minutes and at 60 minutes post-awakening, minus the cortisol concentration at the time of awakening on day 1.[24] The area under the curve (AUC) with respect to ground was calculated according to the trapezoid formula using the first four time points.[25]

The DST is a measure of hypothalamic-pituitary-adrenal axis regulation and normally shows a decrease of morning cortisol concentrations due to inhibition of adrenocorticotropic hormone secretion after dexamethasone administration the night before.[26] A low dose of dexamethasone (0.5 mg) had to be taken orally after the last sample on day 1, and the final sample was taken at the time of awakening on day 2. After collecting all seven samples, the subjects were asked to return the tubes through regular postal service. After centrifugation of the cotton wad, salivary cortisol concentrations were measured with a competitive electrochemiluminescence immunoassay (ECLIA), using a Modular Analytics E170 immunoassay analyzer (Roche Diagnostics, Mannheim, Germany) by the Central Laboratory for Clinical Chemistry of the Leiden University Medical Center. The functional detection limit was 2.0 nmol/l and the intra- and inter-assay variability coefficients in the measuring range were less than 10%. We assumed concentrations ≥ 100 nmol/l to be physiologically unlikely.

Statistical analyses
Categorical variables are presented as numbers and percentages, and continuous variables as means ± standard deviations (SD) or medians with percentiles P_{10} - P_{90}, when appropriate. Differences between the three groups were assessed by one-way analysis of variance (ANOVA). Post-hoc intergroup comparisons were performed for those variables with significant test results. All subjects with four or more missing salivary cortisol concentrations on day 1 were excluded (n = 5). All other missing cortisol data (n = 21 of 672; 3.1%) were intrapolated by using the subject's preceding and following salivary cortisol values, and modeling the average curve from all subjects over these values for that point in time. For positively skewed variables, natural log-transformed values were used in statistical analyses, and back-transformed geometric mean values are presented in tables. The cortisol awakening response (CAR) was analyzed by repeated measurements general linear models (GLM), with time as within-subject factor and

group as between-subject factor. Next, three markers of salivary cortisol were calculated. The total area under the curve of the morning rise (AUC) was calculated using trapezoid formula. The morning rise during the CAR was calculated as the maximum of the two cortisol concentrations at 30 minutes and at 45 minutes post-awakening, minus the cortisol concentration at time of awakening on day 1. The cortisol suppression ratio was calculated as the salivary cortisol at the time of awakening on the first day / post-DST salivary cortisol. Differences in cortisol levels and markers between the three groups were assessed by ANOVA. The covariates sex, age, the use of psychotropic medication, and the time of awaking were added to multivariable models using ANOVA, to adjust for potential confounding effects. Significance levels were set at $p < 0.05$. Statistical analysis was performed using the Statistical Package for the Social Sciences 16.0 for Windows.

Results

Demographic and clinical characteristics

Forty subjects (22%) declined saliva collection, 24 subjects (13%) collected insufficient saliva, and two subjects (1%) were excluded because of physiologically unlikely high salivary cortisol concentrations. One subject was excluded because of the use of oral corticosteroid medication at the time of the study. None of the female subjects reported pregnancy, that potentially may affect cortisol concentrations. This resulted in available saliva of 58 symptomatic and 26 presymptomatic mutation carriers, and 28 controls. Demographic and clinical characteristics of these subjects are presented in Table 1; as is shown, data of the potential confounders smoking status, alcohol consumption, BMI, and use of psychotropic medication were incomplete. Further, the presence of a depressive disorder could not be assessed in five symptomatic mutation carriers because of a MMSE score < 18 points.*Hypothalamic-pituitary-adrenal axis functioning*

Since we assumed cortisol concentrations ≥ 100 nmol/l to be physiologically unlikely, measurements at seven time points (1.0%) of a total of 672 measurements in 112 subjects were excluded.

On day 1, using repeated measurements GLM there was a time effect for the CAR ($p < 0.001$, indicating an increase at 30 minutes post-awakening), a time * group effect ($p = 0.04$, indicating that the dynamics of the curve were dissimilar between the groups), and a group effect ($p = 0.046$). Post-hoc tests showed that the mean cortisol concentration of the presymptomatic mutation carriers was higher compared to the symptomatic mutation carriers ($p = 0.035$), largely due to higher mean cortisol concentrations at 45 minutes and 60 minutes post-awakening (Table 2 and Figure 1). For the mean evening cortisol concentrations there was no time effect ($p = 0.29$), no time * group effect ($p = 0.95$), and no group effect ($p = 0.21$). The AUC showed a trend towards significance ($p = 0.09$).

On day 2, using ANOVA after the DST, there were no statistically significant differences between the groups for morning salivary cortisol concentrations ($p = 0.39$) nor for the cortisol suppression ratio ($p = 0.92$) (Table 2).

Effect of potential confounders

The three groups did not differ for smoking status, alcohol consumption, BMI, and the presence

Table 1. Demographic and clinical characteristics of all study subjects (n = 112)

	n	Presymptomatic mutation carriers (n = 26)	Symptomatic mutation carriers (n = 58)	Controls (n = 28)	p value
Demographic characteristics					
Male (n, %)	112	12 (46.2)	29 (50.0)	14 (50.0)	0.94
Age (mean ± SD)	112	44.2 ± 11.0 [a]	52.7 ± 10.7 [b]	44.0 ± 11.3 [a]	< 0.001
Clinical characteristics					
Smoker (n, %)	106	6 (24.0)	11 (20.8)	9 (32.1)	0.53
High alcohol consumption (n, %)	100	2 (10.5)	5 (8.9)	0 (0.0)	0.28
BMI (mean ± SD)	95	25.6 ± 3.6	25.2 ± 4.5	25.6 ± 4.7	0.90
Depressive disorder (n, %)	112	3 (11.5)	5 (8.6)	3 (10.7)	0.90
Psychotropic medication (n, %)	110	6 (23.1)	33 (57.9)	0 (0.0)	< 0.001
MMSE (median, P_{10} - P_{90})	111	29 (26 - 30) [a]	28 (18 - 30) [b]	29 (28 - 30) [a]	< 0.001
TFC (median, P_{10} - P_{90})	112	13 (8 - 13) [a]	7 (1 - 13) [b]	13 (12 - 13) [c]	< 0.001

Alcohol consumption was considered high if more than 14 glasses a week were consumed; BMI = Body Mass Index (= kilograms per square meter of height); Depressive disorder consists of major depressive disorder or dysthymic disorder in the past two weeks according to the Composite International Diagnostic Interview; MMSE = Mini-Mental State Examination (range 0 - 30 points with lower score indicating more severe cognitive dysfunction);

TFC = Total Functional Capacity scale (range 0 - 13 points with lower scores indicating more severe functional impairment). For MMSE and TFC the median and 10th and 90th percentiles are given (P_{10} - P_{90}) because of their skewed distributions.

[a,b]; Values in the same row with different superscript letters are significantly different: $p < 0.05$ (post-hoc test).

Table 2. Mean salivary cortisol concentrations and derived cortisol day curve parameters of all study subjects (n = 112)

	n	Presymptomatic mutation carriers (n = 26)	Symptomatic mutation carriers (n = 58)	Controls (n = 28)	p value (crude)	p value (adjusted)[d]
Cortisol day curve (nmol/l)						
Time of awakening	112	18.6 (10.0 - 31.6)	18.8 (11.2 - 33.1)	16.5 (9.2 - 29.3)	0.57	0.23
+ 30 minutes	112	23.6 (13.0 - 37.5)	18.7 (9.2 - 36.9)	19.4 (7.5 - 35.0)	0.14	0.22
+ 45 minutes	112	24.6 (13.4 - 56.3) *	17.6 (8.1 - 37.4) ^	18.0 (8.5 - 30.8) ^	0.03	0.04
+ 60 minutes	112	19.8 (8.3 - 48.7) *	14.0 (6.2 - 28.0) ^	14.1 (4.9 - 24.3) ^	0.04	0.02
22:00 hours	112	5.4 (2.6 - 13.7)	4.7 (2.1 - 12.4)	3.9 (1.2 - 11.2b)	0.24	0.34
23:00 hours	112	5.7 (1.9 - 19.0)	4.9 (2.2 - 11.7)	4.2 (1.3 - 14.3)	0.31	0.27
Morning rise (nmol/l)[a]	112	9.5 (4.2 - 14.7) *	2.0 (-0.5 - 4.6) ^	6.8 (2.1 - 11.4)	0.01	0.005
AUC (minutes * nmol/l)	112	2.75 (1.63 - 4.69)	2.20 (1.23 - 3.92)	2.22 (1.35 - 3.62)	0.09	0.12
Post-DST (nmol/l)	104[c]	6.6 (1.3 - 2.5)	7.6 (1.1 - 2.7)	6.3 (0.9 - 2.6)	0.39	0.34
Cortisol suppression ratio[b]	104[c]	2.9 (2.3 - 3.5)	2.8 (2.3 - 3.4)	3.0 (2.4 - 3.6)	0.92	0.96

AUC = Area Under the Curve for the CAR with respect to ground (minutes * nmol/l); Post-DST = cortisol concentration after the Dexamethasone Suppression Test.

Geometric mean and back-transformed 95% confidence intervals of the mean are given, except for the CAR and the cortisol suppression ratio for which the mean and 95% confidence intervals of the mean are given.

[a] Morning rise: the maximum of the two cortisol concentrations at 30 minutes and 45 minutes post-awakening, minus the cortisol concentration at time of awakening on day 1.

[b] The cortisol suppression ratio is defined as the salivary cortisol at the time of awakening on the first day / post-DST salivary cortisol.

[c] Cortisol concentration after DST was not assessed in one presymptomatic and seven symptomatic mutation carriers because they refused to take dexamethasone.

[d] P value was adjusted for sex, age, psychotropic medication, and time of awakening (on day 1 for the cortisol day curve, CAR, and AUC; and on day 2 for the post-DST cortisol and the cortisol suppression ratio) by analysis of variance.

* , ^ : Values in the same row with different superscript letters are significantly different: p < 0.05 (post-hoc test).

of depression. Therefore, we did not adjust for these variables as potential confounders in subsequent multivariable models. However, a significant difference between the three groups was found for age, use of psychotropic medication and time of awakening, which may have had influenced cortisol concentrations. Symptomatic mutation carriers woke up later than controls (7:52 ± 1:22 h versus 7:07 ± 1:06 h; p = 0.03), whereas the presymptomatic group woke up in between (7:22 ± 1:02 h). After adjustment for age, sex, psychotropic medication and the time of awakening, the morning rise during the CAR between the three groups was still significantly different (p = 0.005). The AUC between the three groups however was not significantly different (p = 0.12; Table 2). Moreover, after exclusion of subjects with time of awakening after 9:00 h, the morning rise during the CAR still showed a statistical trend of being different between the three groups (p = 0.07).

Figure 1. Salivary cortisol concentrations of the day curve and post-DST
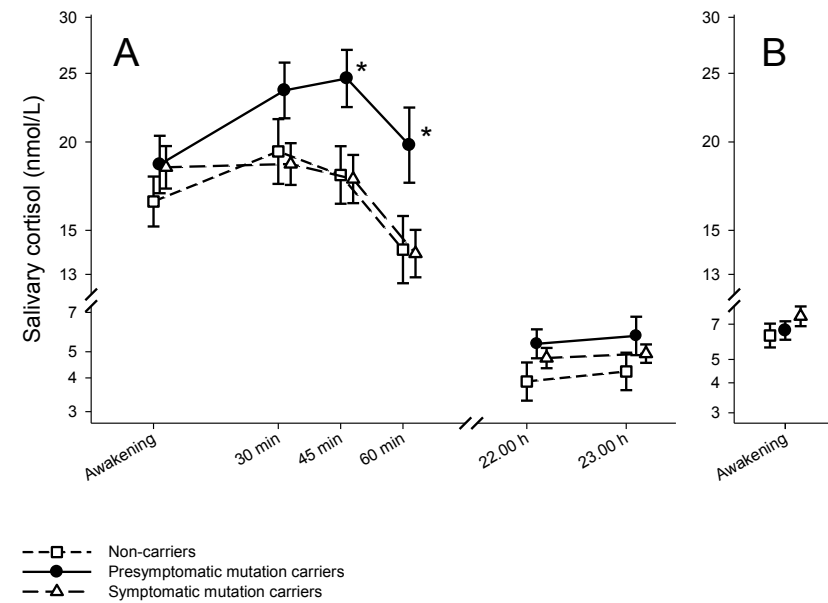
Panel A shows the basal salivary concentrations of day 1 on a logarithmic scale. Panel B shows the post-dexamethasone suppression test (DST) cortisol concentrations of day 2 on a logarithmic scale.

* Mean cortisol concentrations at 45 and 60 minutes after time of awakening in presymptomatic Huntington's disease mutation carriers were significantly higher, compared to non-carriers, as well as compared to symptomatic mutation carriers.

Discussion

The differences in the CAR of the three study groups were explained by higher salivary cortisol concentrations at 45 and 60 minutes post-awakening and a higher morning rise for presymptomatic mutation carriers compared to both symptomatic mutation carriers and controls. These differences persisted after adjustment for potential confounders.

Increased basal plasma cortisol concentrations have previously been reported in two small studies including only 10,[12] and 11 symptomatic Huntington's disease patients,[13] whereas no difference was found in a single morning sample between 8:00 h and 10:00 h in a study comparing 41 symptomatic and 18 presymptomatic female Huntington's disease mutation carriers as well as healthy controls.[27] Similar to our findings, no significant difference was found for post-DST cortisol concentrations between 10 Huntington's disease patients and 10 controls.[12] In a large study among 82 moderate and advanced Huntington's disease mutation carriers, higher urinary cortisol concentrations have been described, compared to 68 healthy controls.[14] However, in the latter study, measurement of cortisol concentrations was done in urine samples that were collected during a short time period (between 14:00 and 17:00 h), and disease stage was defined according to the TFC instead of the motor section of the UHDRS. Thus, except for one small study,[12] the circadian rhythm was not taken into account. Moreover, potential confounders of hypothalamic-pituitary-adrenal axis functioning such as smoking status, alcohol consumption, BMI, use of psychotropic medication and presence of depression, was inconsistently adjusted for in the four studies that examined hypothalamic-pituitary-adrenal axis functioning in Huntington's disease.

Different hypotheses exist concerning hyperactivation of the hypothalamic-pituitary-adrenal axis in Huntington's disease. First, psychosocial life stress from growing up in families with members suffering from Huntington's disease might induce chronic hypothalamic-pituitary-adrenal axis hyperactivation. Second, following disclosure of being mutation carrier, presymptomatic mutation carriers may experience stress due to continuous self-observation for the onset of symptoms, causing hyperactivity of the hypothalamic-pituitary-adrenal axis. Third, hyperactivation of the hypothalamic-pituitary-adrenal axis could be the result of hypothalamic degeneration disrupting its delicate feedback mechanisms.[9] Fourth, degeneration of the hippocampus and the frontal cortex in Huntington's disease may indirectly cause a diminished feedback inhibition of the hypothalamic-pituitary-adrenal axis, leading to hyperactivation.[28] There are indications that increased cortisol concentrations may cause further degeneration of the hippocampus.[29,30] Fifth, it has been suggested that the loss of GABA neurons in Huntington's disease induces an endogenous corticotropin-releasing hormone overdrive, resulting in higher cortisol levels.[11] Also, increased cortisol concentrations may in turn contribute to an increased susceptibility for emotional disturbances, which may further induce hypothalamic-pituitary-adrenal axis activity.[31]

These hypotheses would lead one to expect a further hyperactivation of the hypothalamic-pituitary-adrenal axis during disease progression, but this is not supported by the data from our cross-sectional study. In contrary to an earlier report,[14] we found diminished activation of the hypothalamic-pituitary-adrenal axis in subjects with prevalent motor symptoms reflecting more advanced disease stage. In our opinion, this might be the result of either decreased responsiveness or exhaustion of the hypothalamic-pituitary-adrenal axis, which is supported by a postmortem study that reported a decreased concentration of corticotropin-releasing hormone immunoreactivity in the striatum of 11 Huntington's disease patients.[32]

Alternatively, the impact of psychosocial stress may be reduced once the disease is clinically manifest, as a result of the acceptance of the disease, whereas in advanced disease stage, subjects may have a diminished awareness of current stress factors.

Several limitations of the present study need to be addressed. First, the data are cross-sectional, and therefore do not allow for causal inferences. Second, the saliva collection was unsupervised; to improve compliance with respect to the time instructions, controlled collection using devices with electronic time registration is advised but expensive. Also, some subjects in an advanced stage of the disease had difficulties in collecting sufficient saliva, possibly as a result of disturbed osmoregulation or impaired saliva production in Huntington's disease.[33] Third, missing cortisol concentrations were intrapolated, but potential effect of bias is likely to be small as only 3% of time points were missing. Fourth, disease stage was defined according to the confidence level of the motor section of the UHDRS that depends on the experience and knowledge of the clinician, and solely assesses the presence of motor symptoms. Finally, we found differences between the groups for the CAR, but it is unclear whether other exogenous factors such as season, day of the week and sleep regulation have confounded this association.

Despite these shortcomings our study indicates a delicate disturbance in morning cortisol secretion in Huntington's disease mutation carriers that precedes the onset of motor symptoms, and possibly plays a role in the progression of the disease. Hyperactivity of the hypothalamic-pituitary-adrenal axis may play a role in the development of the first subtle symptoms of Huntington's disease, including psychiatric phenomena. The use of more refined rating scales might increase our insight into a potential relationship between hypothalamic-pituitary-adrenal axis activation and the early manifestation of Huntington's disease.

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Chapter 8

General discussion and future perspectives
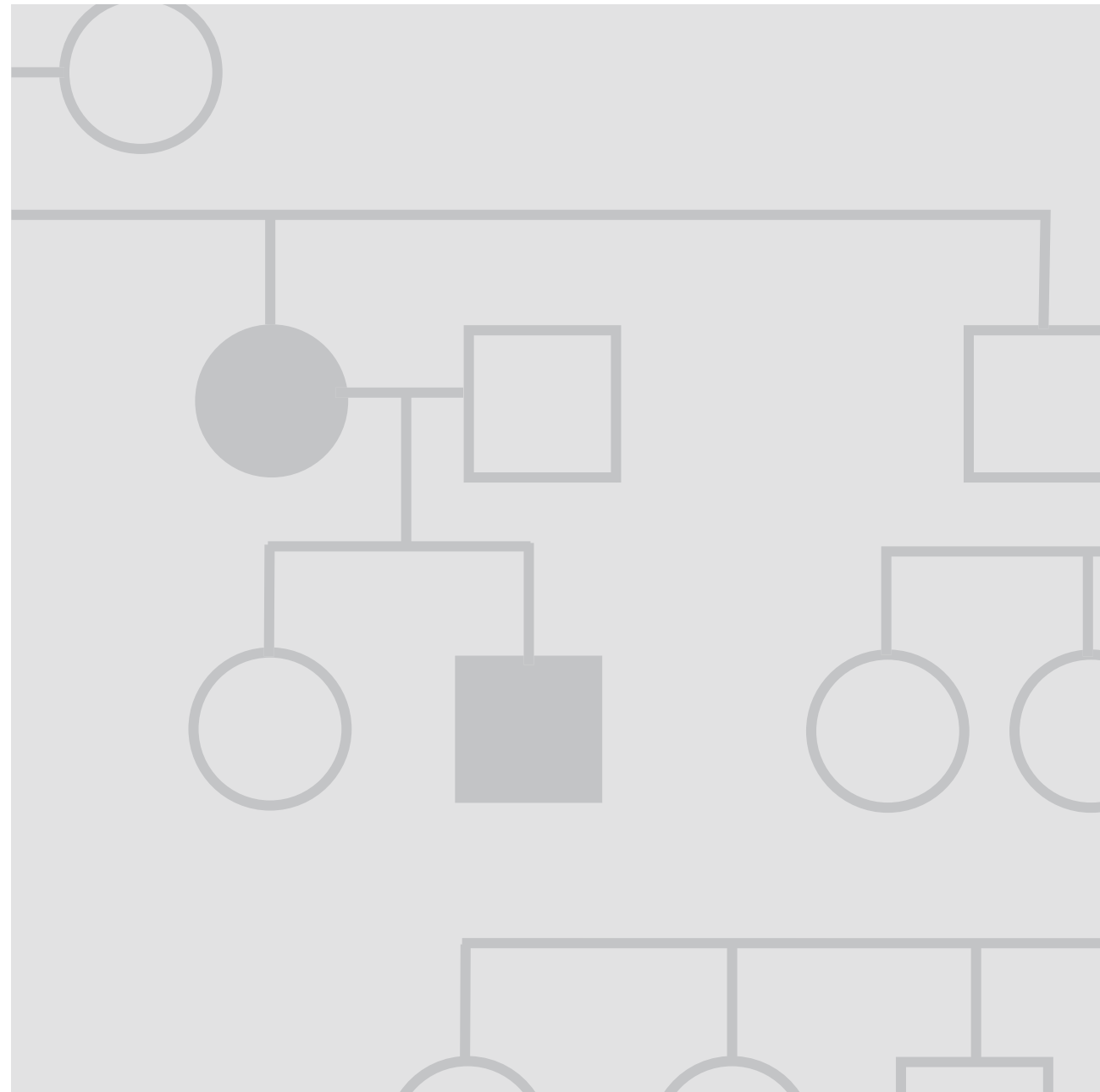
This thesis confirms that psychiatric disorders and behavioral problems are major constituents of the clinical spectrum of Huntington's disease. The prevalence of the different psychiatric disorders and behavioral problems vary, but overall mutation carriers are at major risk of developing psychiatric disorders and behavioral problems in all disease stages. This is an important finding because the presence of psychopathology has a substantial negative impact on quality of life and daily functioning of patients, possibly even more so than motor and cognitive symptoms.[1]

Assessment

In our review, we demonstrated that prevalences of psychiatric disorders and behavioral problems in Huntington's disease depend on definition of the disease stages and the measurement tools applied.

Definition of disease stages

In this thesis, the motor section of the Unified Huntington's Disease Rating Scale (UHDRS-m) was used for the definition of disease stages.[2] Although the motor score does not correlate perfectly with disease stage, the use of a functional assessment (e.g., the Total Functional Capacity (TFC)[3] scale of the UHDRS) for disease staging was not preferable in our study, as it is directly influenced by the presence of psychiatric disorders and behavioral problems.[4] For that reason, we assume that the assessment of motor function by a blinded experienced neurologist is the most objective and reliable method of disease staging for psychiatric research in Huntington's disease.

Measurement tools

Diagnostic classification according to the Diagnostic Statistical Manual of mental disorders, Version IV (DSM-IV),[5] is currently the gold standard for assessing psychiatric disorders in general psychiatry. Yet, this diagnostic classification insufficiently takes into account co-morbid and overlapping physical symptoms of Huntington's disease. Furthermore, cognitive impairments may complicate the assessment of a psychiatric diagnosis. Particularly in an advanced stage of Huntington's disease, when communication and insight may become so impaired that patients are no longer able to express their emotions or to judge their symptoms correctly. Therefore, a structured interview using formal DSM-IV criteria seems less applicable in an advanced stage, since it will result in an underestimation of the prevalences of psychiatric disorders.[6] In this stage, dimensional measures of neuropsychiatric symptoms are necessary to capture the full range of psychopathology in Huntington's disease. The semi-structured Problem Behaviors Assessment (PBA) is especially useful, since other diagnostic information sources such as clinician`s observation of behavior and caregivers' information are being used.[7]

Symptomatology

Both with the Composite International Diagnostic Interview (CIDI),[8] assessing DSM-IV diagnoses, and the PBA, assessing neuropsychiatric behavioral problems, an increased prevalence of depression was found in mutation carriers. Despite a threefold increase of formal depression in the group of mutation carriers (18%) compared to the general population (6%), this prevalence is considerably lower than the 33% to 69% prevalences reported in earlier studies in Huntington's

disease.[9-14] This can be explained by the fact that most earlier studies measured symptoms of depression such as 'low mood' or 'dysphoria', and not major depressive disorder meeting formal DSM-IV criteria. Also, some studies assessed the prevalence of psychiatric symptoms during a longer time period, e.g., prevalence since the occurrence of motor symptoms or life time prevalence.

Depression is equally present in presymptomatic and symptomatic disease stages, as assessed with the CIDI, as well as with the PBA. The difference in prevalence of depression between presymptomatic mutation carriers and non-carriers did not reach statistical significance when formal DSM-IV criteria were used. However, using the PBA, we found a significant increase of depression in presymptomatic carriers compared to non-carriers. This could be a reflection of higher sensitivity of the PBA for depression in Huntington's disease, but may also be due to increased power as the PBA is a continuous measure whereas the CIDI is not.

Apathy is also a common neuropsychiatric behavioral problem in Huntington's disease, with prevalences varying from 34% to 76%.[9,10,14] Of all psychiatric symptoms, only apathy consistently appears to be positively related to disease progression.[14] In our study, using the Apathy Scale, 32% of all mutation carriers showed apathy in the previous two weeks, compared to none of the non-carriers. We found that male sex was independently associated with apathy, together with higher use of both antidepressants and neuroleptics, and the presence of depression. As apathy may be an expression of depression, we excluded all subjects with depression (n = 10). Then, male sex, higher use of neuroleptics, higher use of benzodiazepines, and a decline of everyday functioning – that was quantified with the TFC scale – were independently associated with apathy. Since this study has a cross-sectional design, we cannot conclude whether the use of psychotropic medication is a cause or a consequence of apathy, but it is plausible that the use of psychotropic medication may at least worsen apathy.

In earlier studies increased prevalences of anxiety (34% - 61%) have been reported,[9,10,12-14] with higher prevalences in studies that used general questions about anxiety, worrying, and tensed feelings. In this thesis, we report a non-significant trend of an increased prevalence of generalized anxiety disorder in Huntington's disease. We also found a twofold increased prevalence of panic disorder in mutation carriers, compared to the general population, but this difference was – presumably due to small numbers – non-significant. Factor analysis of the PBA revealed that anxiety and tensed feelings often co-occur with depressed mood, depressed cognitions and suicidal ideation, and may therefore be a symptom of an affective syndrome in Huntington's disease, that is not covered by one DSM-IV diagnosis. Since no other studies are known that systematically investigated the prevalence of anxiety disorders in Huntington's disease, this should be an important focus for future research.

Many patients with Huntington's disease show personality changes with obsessive-like mental inflexibility in an early disease stage,[15] though only a minority will get a formal diagnosis of obsessive-compulsive disorder. The few studies investigating obsessions and compulsions in verified mutation carriers, reported prevalences of 10% to 52% for the presence of obsessive or compulsive symptoms.[13-15] We found a significantly increased prevalence of formal obsessive-compulsive disorder in mutation carriers compared to the general population, both in presymptomatic (6%) and in symptomatic (4%) mutation carriers, although their numbers were small.

Irritability occurs in most patients with Huntington's disease, and may also precede motor symptoms.[9,10,12,14] We found an increased prevalence of irritability according to the PBA in mutation carriers, compared to non-carriers, whereas no significant differences were found between disease stages. Given that irritability is a frequent neuropsychiatric symptom, consensus on a distinct definition is warranted for the assessment and clinical follow-up during treatments.

Prevalences of psychotic symptoms in verified mutation carriers vary from 3% to 11%.[9,10,12,14] However, we found only two mutation carriers (1%) with psychosis. Although it may be delicate to draw conclusions from this small number of affected patients, the prevalence of psychosis may have been overestimated in earlier days when psychosis was considered to be a more prevalent psychiatric feature of Huntington's disease. Next to the use of strict DSM-IV criteria, this can be explained by the relatively advanced disease stage at the time of diagnosis before genetic testing became available. In fact, our two psychotic patients were also advanced symptomatic patients.

Environmental and biological factors
Although family members with a prior 50% risk of Huntington's disease, who were not genetically compromised, had a shared environment during two to three decades of their lives, they had no more psychiatric disorders than the general population. In contrast to our assumption, the presence of a familial disease burden, did not make them more susceptible to psychiatric disorders than the general population.

It is unlikely that the mutation on its own has a full penetrance for the presence of psychiatric disorders; other factors probably contribute to the risk of developing psychopathology. Future research should focus on the contribution of both environmental and biological factors to the presence of psychopathology, that may enable early (preventive) interventions.

In this thesis, we examined the function of the hypothalamic-pituitary-adrenal axis in mutation carriers and controls. The hypothalamic-pituitary-adrenal axis function was measured through salivary cortisol in a day curve and after a dexamethasone suppression test. We found an increased salivary cortisol concentration in pre-motor symptomatic mutation carriers, indicating a hyperactivation of the hypothalamic-pituitary-adrenal axis in mutation carriers before the onset of motor symptoms. Increased cortisol concentrations may in turn contribute to an increased susceptibility for emotional disturbances, but we could not demonstrate this in our cross-sectional study.

Strengths and weaknesses
The strengths of this study are the rather large study population with Huntington's disease, the use of a control group consisting of mutation-negative first-degree relatives, and the use of

specific, reliable and validated measurement tools in a standardized interview setting.

Some potential sources of variation in test results as found in our study, such as low incidence of Huntington's disease with resulting small sample sizes and self-selection for testing and research, were difficult to avoid. Also, since this is a cross-sectional and first assessment of a follow-up study, no conclusions can be drawn on changes in time or causal relations.

A weakness of our study is that many patients in mid and advanced disease stages used psychotropic medications. A medication-free population would have been better for the assessment of psychopathology, though it is nearly impossible to include patients in these disease stages who do not use psychotropic medications. This may have confounded our results, with most likely an overestimation of apathy due to the use of neuroleptics and benzodiazepines, and an underestimation of other psychopathology.

Final remarks

This thesis confirms the observation of George Huntington that there is 'a tendency to insanity' in Huntington's disease,[16] characterized by a variety of psychopathology, already before the onset of motor symptoms. These psychiatric manifestations of Huntington's disease have major influences on the daily functioning of patients and the lifes of caregivers.

Since recognition and treatment of psychopathology is often complicated by co-morbid cognitive and motor symptoms, a multidisciplinary approach is recommended to provide the optimal patient care. Then, collaboration between clinical and pre-clinical researchers is needed for further research involving multiple disciplines, to bridge the gap between promising basic research and solutions for clinical manifestations of Huntingtons's disease.

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Summary
Samenvatting
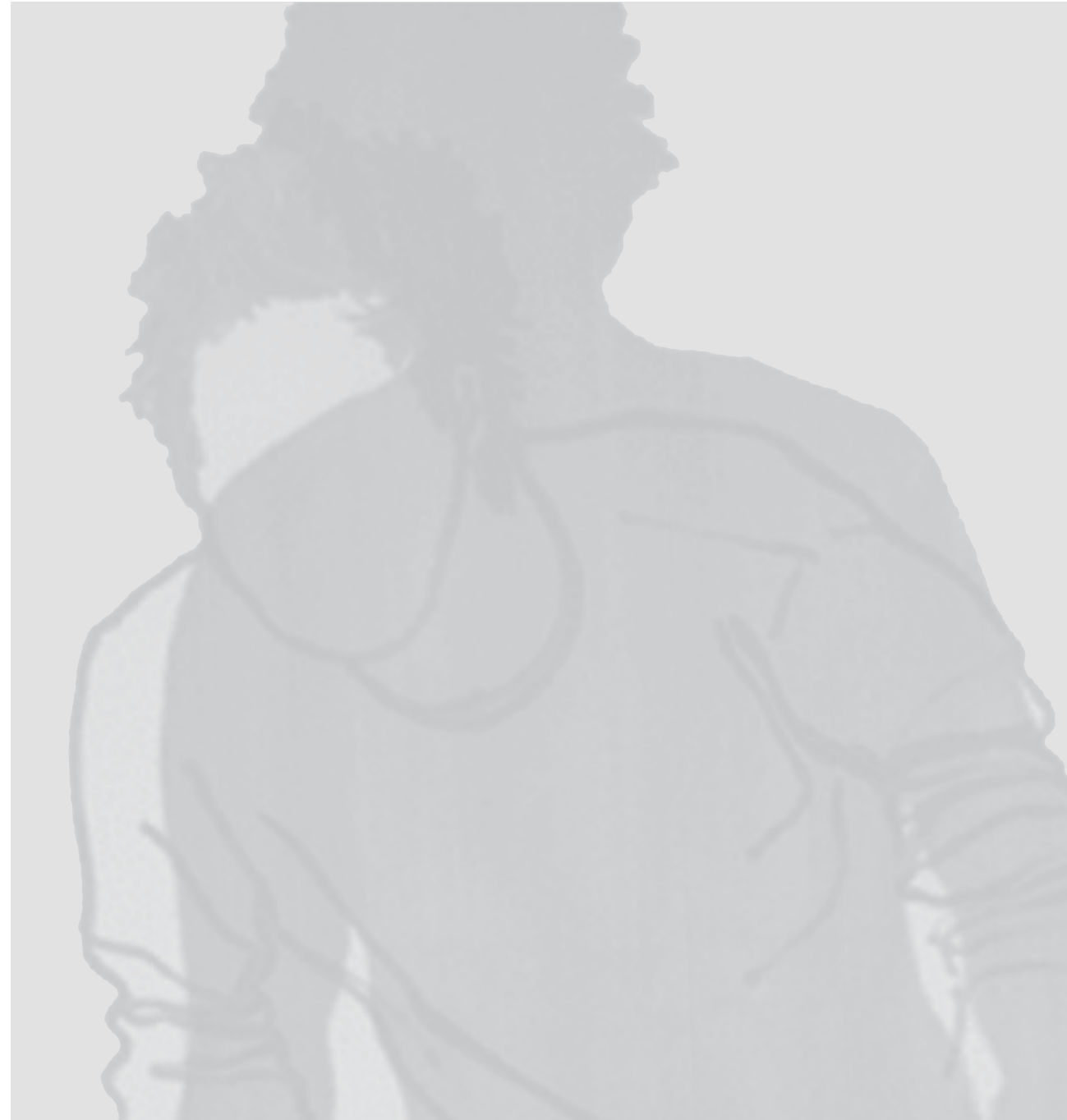
This thesis starts with a review of original research on psychopathology in Huntington's disease that used standardized instruments in verified mutation carriers (Chapter 2). Frequently reported neuropsychiatric symptoms are depressed mood, apathy, anxiety, obsessive and compulsive symptoms, irritability, and psychosis. However, many studies are hampered by small sample sizes and the lack of a control group, whereas different methodologies had been used.

Between May 2004 and August 2006, we started a large cohort study to assess psychopathology in verified Huntington's disease mutation carriers in different disease stages, in comparison with first-degree non-carriers and the general population.

Twenty-five percent of all mutation carriers had at least one formal psychiatric disorder according to the Diagnostic Statistical Manual of mental disorders, Version IV (DSM-IV), with a significantly increased prevalence of depression, obsessive-compulsive disorder, and psychosis. Although first-degree non-carriers grew up in comparable, potentially stressful circumstances, they did not show more psychiatric disorders than the general population (Chapter 3).

Besides a formal diagnostic classification using the criteria of the DSM-IV, the prevalences of behavioral problems were assessed with the Problem Behaviors Assessment (PBA), that has especially been developed for the assessment of behavioral problems in Huntington's disease. After a factor analysis, the PBA showed a three factor solution: apathy, depression and irritability. Apathy was related to disease stage, whereas depression and irritability were not (Chapter 4).

The use of general diagnostic criteria for the assessment of psychopathology in Huntington's disease is complicated when co-morbid and overlapping physical and cognitive symptoms, or diminished disease awareness are present. Since the PBA and the behavioral section of the Unified Huntington's Disease Rating Scale (UHDRS-b) use observation of behavior and caregivers' information, these instruments allow for the assessment of psychopathology in advanced stages of Huntington's disease (Chapter 5).

Of the mutation carriers forty-nine (32%) showed apathy, compared to none of the non-carriers. After exclusion of all patients with a depression, apathy was independently associated with male sex, worse global functioning and higher use of neuroleptics and benzodiazepines. Therefore, the use of psychotropic medication should critically be evaluated when apathy is present (Chapter 6).

Since neurodegeneration in Huntington's disease occurs in various brain regions, including the hypothalamic areas, we finally investigated the function of the hypothalamic-pituitary-adrenal axis in relation to Huntington's disease. A higher post-awakening salivary cortisol concentration was found in presymptomatic mutation carriers compared to both symptomatic mutation carriers and controls, indicating a hyperactivation of the hypothalamic-pituitary-adrenal axis in presymptomatic mutation carriers (Chapter 7).

Dit proefschrift begint met een overzichtsartikel van oorspronkelijk onderzoek naar psychopathologie bij bewezen mutatiedragers voor de ziekte van Huntington, waarbij gestandaardiseerde instrumenten werden gebruikt (Hoofdstuk 2). Van de neuropsychiatrische symptomen komen depressieve stemming, apathie, angst, obsessieve en compulsieve symptomen, prikkelbaarheid en psychose voor. Veel van de studies hebben beperkingen zoals een kleine onderzoekspopulatie en het ontbreken van een controlegroep, met bovendien een uiteenlopende methodologie.

Tussen mei 2004 en augustus 2006 hebben wij een grote cohortstudie opgezet om de aanwezigheid en ernst van psychopathologie vast te stellen bij bewezen mutatiedragers voor de ziekte van Huntington in verschillende ziektestadia. Deze mutatiedragers werden vergeleken met eerstegraads niet-dragers en de algemene bevolking.

Vijfentwintig procent van alle mutatiedragers heeft tenminste één formele psychiatrische stoornis volgens de criteria van de Diagnostic Statistical Manual voor psychiatrische stoornissen, versie IV (DSM-IV), met een significant verhoogde prevalentie van depressie, obsessieve-compulsieve stoornis en psychose. Eerstegraads niet-dragers hebben niet meer psychiatrische stoornissen dan de algemene bevolking, hoewel zij zijn opgegroeid in vergelijkbare, potentieel stressvolle omstandigheden (Hoofdstuk 3).

Naast een formele diagnostische classificatie volgens de criteria van de DSM-IV werd het vóórkomen van gedragsproblemen ook vastgesteld met de Problem Behaviors Assessment (PBA), die is ontwikkeld voor de beoordeling van gedragsproblemen bij de ziekte van Huntington. Na een factoranalyse van de PBA werden er drie factoren gevonden: apathie, depressie en prikkelbaarheid. Apathie was gerelateerd aan het ziektestadium, maar depressie en prikkelbaarheid niet (Hoofdstuk 4).

Het gebruik van algemene diagnostische criteria voor de beoordeling van psychopathologie bij de ziekte van Huntington is gecompliceerd wanneer co-morbide en overlappende somatische en cognitieve symptomen aanwezig zijn of als er sprake is van een verminderd ziektebesef. Omdat de PBA en de gedragsschaal van de Unified Huntington's Disease Rating Scale (UHDRS-b) ook de observatie van gedrag en informatie van verzorgers gebruiken, zijn deze instrumenten geschikt voor de beoordeling van psychopathologie in gevorderde stadia van de ziekte van Huntington (Hoofdstuk 5).

Van de mutatiedragers hadden er negenenveertig (32%) apathie, terwijl geen van de niet-dragers apathisch was. Na exclusie van alle depressieve patiënten, was apathie onafhankelijk geassocieerd met mannelijke geslacht, slechter algemeen functioneren en het gebruik van meer antipsychotica en benzodiazepines. Om deze reden moet het gebruik van psychotrope medicatie kritisch worden beoordeeld wanneer apathie aanwezig is (Hoofdstuk 6).

Omdat neurodegeneratie bij de ziekte van Huntington in verschillende hersengebieden voorkomt, waaronder hypothalame gebieden, werd tenslotte de relatie tussen het functioneren van de hypothalamus-hypofyse-bijnier-as en de ziekte van Huntington onderzocht. Bij pre-

symptomatische mutatiedragers werd een hogere cortisolconcentratie in het speeksel na het ontwaken gevonden ten opzichte van zowel symptomatische mutatiedragers als controles, wat wijst op een mogelijke hyperactivatie van de hypothalamus-hypofyse-bijnier-as bij pre-symptomatische mutatiedragers (Hoofdstuk 7).

Appendices
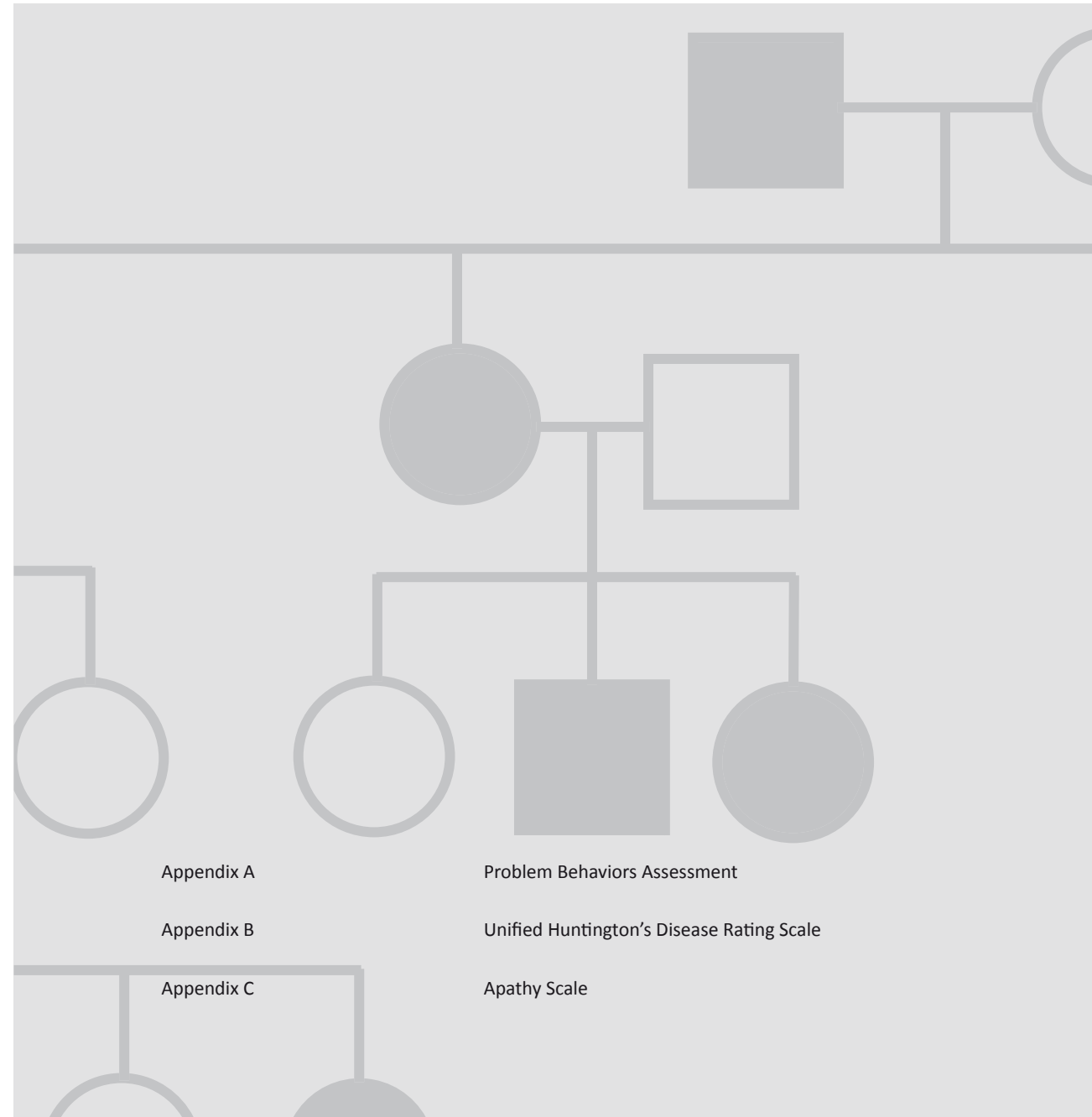
APPENDIX A

Problem Behaviors Assessment
(Beoordelingsschaal voor Probleemgedrag bij de Ziekte van Huntington)

Origineel: D. Craufurd, J.C. Thompson, J.S. Snowden: Behavioral Changes in Huntington Disease (2001)
Vertaling: E.M. Kingma, R.C. van der Mast, R.A.C. Roos

Instructie

De beoordelingsschaal van probleemgedrag (PBA) bij de ziekte van Huntington is een instrument voor het scoren van de aanwezigheid, frequentie en ernst van abnormaal gedrag bij patiënten met de ziekte van Huntington. Het is bedoeld voor gebruik door getrainde psychiaters met ervaring in het beoordelen van patiënten met neuropsychiatrische aandoeningen. Scores moeten worden gebaseerd op informatie van (a) patiënt, (b) een goed ingelichte informant en (c) de observaties van de onderzoeker tijdens het onderzoek van de psychische functies van de patiënt. Probeer, als dat mogelijk is, ook de informant te interviewen zonder dat patiënt daarbij aanwezig is en voordat de scores ingevuld worden. Scoor, tenzij anders is aangegeven, het gemiddelde gedrag van patiënt over de afgelopen 4 weken met behulp van de criteria die nader zijn gespecificeerd. Dit instrument is niet bedoeld om te gebruiken als vragenlijst.

Symptomen worden gescoord op frequentie en ernst met behulp van dezelfde 5-puntsschaal als in de Unified Huntington's Disease Rating Scale. De hierna volgende richtlijnen zijn ontwikkeld om het gebruik ervan verder te verduidelijken en de inter-beoordelaars-betrouwbaarheid van het instrument te vergroten.

Instructies voor het invullen van de frequenstiescores

Frequentiescores zijn dezelfde als in de UHDRS behalve dat code 1 (zelden) wordt gedefinieerd als minder dan een keer per week optredend, en code 3 (herhaaldelijk) als 'de meeste dagen optredend'. De frequentiescores worden dus consequent gebruikt voor frequentie in de zin van aantal dagen per week (duidelijk geschikt voor symptomen zoals slaapproblemen en agressieve uitbarstingen), terwijl de duur van symptomen zoals piekeren of depressieve gedachten expliciet is opgenomen in de ernstscores (die het, onvermijdelijk, toch al beïnvloedt).

Code 0	Nooit of bijna nooit
Code 1 (zelden)	Minder dan een keer per week optredend
Code 2 (soms)	Ten minste een keer per week optredend
Code 3 (herhaaldelijk)	De meeste dagen van de week optredend
Code 4 (vaak)	Bijna altijd

Instructies voor het invullen van de ernstscores

De gedetailleerde beschrijvingen hieronder zijn alle gebaseerd op dezelfde algemene principes: de ernst wordt bepaald door de hoeveelheid leed die het veroorzaakt voor de patiënt of diens familie, de mate waarin het de dagelijkse routine verstoort, en de hoeveelheid tijd die het symptoom in beslag neemt of de mate waarin het symptoom het denken van de patiënt beheerst. Als algemene regel geldt:

Code 1 (twijfelachtig)	Wordt gebruikt als de beoordelaar niet helemaal overtuigd is dat het symptoom aanwezig is of als het symptoom van weinig belang is.

Code 2 (licht)	Symptoom is aanwezig, maar veroorzaakt geen ongemak. Symptoom is aanwezig, maar verstoort normale activiteiten niet. Symptoom is vluchtig of slechts af en toe aanwezig.
Code 3 (matig)	Symptoom veroorzaakt aanmerkelijk ongemak. Symptoom verstoort duidelijk het dagelijks leven. Symptoom neemt een substantieel deel van de aandacht van patiënt in beslag.
Code 4 (ernstig)	Symptoom veroorzaakt ernstig of ondraaglijk leed. Symptoom maakt normaal leven onmogelijk. Symptoom is continu aanwezig en alle psychische activiteit van de patiënt is ervan doordrongen.

Vragenlijst

1. Depressieve stemming:
0 Afwezig.
1 Twijfelachtig of van weinig belang.
2 Gedrukte stemming is met tussenpozen aanwezig, maar verstoort het dagelijks functioneren niet.
3 Patiënt is een groot gedeelte van de tijd somber en heeft geen plezier meer in wat hij/zij gewoonlijk leuk vindt, maar kan soms nog met veel moeite in een betere stemming komen.
4 Patiënt voelt zich voortdurend diep ongelukkig.

2. Inslaapstoornis:
0 Afwezig.
1 Twijfelachtig of van weinig belang.
2 Heeft maximaal één uur nodig om in slaap te vallen.
3 Heeft tussen één en twee uur nodig om in slaap te vallen.
4 Heeft meer dan twee uur nodig om in slaap te vallen.

3. Vroeg wakker worden:
Houdt bij het scoren er rekening mee of patiënt eerder dan normaal gaat slapen en wat de gebruikelijke tijd van wakker worden is.
0 Afwezig.
1 Twijfelachtig of van weinig belang.
2 Wordt tot maximaal één uur eerder wakker dan gewoonlijk.
3 Wordt tussen één en twee uur eerder wakker dan gewoonlijk.
4 Wordt meer dan twee uur eerder wakker dan gewoonlijk.

4. Slaapt of is overdag slaperig:
0 Afwezig.
1 Twijfelachtig of van weinig belang.
2 Slaperig gedurende enige tijd overdag, maar slaapt niet en het symptoom verstoort het normale functioneren niet in belangrijke mate (één dutje wordt nog beschouwd als normaal).
3 Slaperig gedurende het grootste gedeelte van de dag, en slaapt overdag wat het normale functioneren verstoort.
4 Slaapt het grootste gedeelte van de dag.

5. Depressieve cognities:
Laag gevoel van eigenwaarde, pessimistisch, zelfbeschuldigend zonder dat daarvoor een reden is, zelfdevaluerend, heeft het idee tekort te schieten.
0 Afwezig.
1 Twijfelachtig of van weinig belang.
2 Patiënt heeft de neiging alles van de zwarte kant te zien, maar het symptoom is niet ernstig genoeg om dagelijkse activiteiten te verstoren.
3 Depressieve cognities beïnvloeden het gedrag, maar patiënt kan daar nog steeds afstand van nemen als dat nodig is (bijvoorbeeld in gezelschap).
4 Depressieve cognities zijn constant aanwezig en het hele denken van de patiënt is ervan doordrongen.

6. Angst:
Gebruik dit onderdeel om de cognitieve aspecten van gepieker en angst te scoren.
0 Afwezig.
1 Twijfelachtig, onbestemd gevoel van je niet op je gemak voelen (scoor ook 1 als de patiënt zich alleen zorgen maakt over de prognose van de ziekte van Huntington).
2 Patiënt heeft met enige regelmaat last van gepieker en angst, maar het symptoom is niet ernstig genoeg om aanmerkelijk ongemak te veroorzaken of dagelijkse activiteiten te verstoren.
3 Angst en/of ongerustheid is het grootste gedeelte van de tijd aanwezig, en heeft een aanmerkelijke invloed op het gedrag van de patiënt (bijvoorbeeld: vermijdt plaatsen die geassocieerd zijn met het uitlokken van angst).
4 Angst is constant aanwezig en heeft een zeer grote invloed op de manier van leven van patiënt (bv. agorafobie is dusdanig dat patiënt het huis niet meer kan verlaten zonder begeleiding); regelmatige paniekaanvallen zijn ook voldoende reden om een 4 te scoren.

7. **Spanning:**

Dit onderdeel is bedoeld om niet alleen de fysiologische aspecten van angst weer te geven, maar ook het gevoel van innerlijke spanning (gewoonlijk geassocieerd met spanningshoofdpijn, pijnlijke schouders, en spierpijn) dat vaak voor lijkt te komen bij patiënten met de ziekte van Huntington.

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt ervaart met tussenpozen gevoelens van spanning, maar het symptoom is niet ernstig genoeg om aanmerkelijk ongemak te veroorzaken of dagelijkse activiteiten te verstoren.

3 Patiënt kan het grootste gedeelte van de tijd niet ontspannen en ziet dit symptoom als een oorzaak van aanmerkelijk ongemak.

4 Patiënt is constant gespannen, kan zich helemaal niet ontspannen, heeft frequent hoofdpijn, en ondervindt duidelijk leed door dit symptoom.

8. **Suïcidale gedachten:**

0 Afwezig.

1 Twijfelachtig; scoor ook 1 als patiënt van plan is om zich te suïcideren als de ziekte ernstiger zal zijn, maar daar troost van ondervindt als een manier om controle te behouden over zijn/haar toekomst.

2 Patiënt is soms erg pessimistisch met vluchtige suïcidale gedachten.

3 Patiënt heeft indringende en kwellende gevoelens van hopeloosheid en frequente suïcidale gedachten, maar heeft daar nog niet naar gehandeld.

4 Patiënt heeft een suïcidepoging gedaan of heeft daar de voorbereidingen toe getroffen zoals het sparen van pillen en het plannen van manieren om ontdekking te voorkomen als het zover zou zijn.

9. **Energieverlies:**

Bij het scoren van dit onderdeel moet rekening gehouden worden met zowel de premorbide toestand van de patiënt als die van een "normaal" persoon.

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt klaagt dat hij zich na normale activiteiten uitgeput voelt, maar dit heeft geen merkbaar effect op de hoeveelheid activiteiten die hij onderneemt.

3 Er is sprake van een duidelijke vermindering in de mate van activiteit van de patiënt.

4 Patiënt doet niet zo veel meer.

10. **Zelfverzorging:**

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt en/of verzorger heeft een verandering bemerkt (bijv. verzorgt uiterlijk niet meer in dezelfde mate of neemt de moeite niet meer om zich op te maken) maar die blijft binnen sociaal-acceptabele grenzen.

3 De zelfverzorging van de patiënt is verslechterd tot onder sociaal-acceptabele grenzen (bijv. verzorger moet patiënt soms aansporen om zich te scheren of schone kleren aan te trekken).

4 Patiënt wast of doucht zich niet meer tenzij hij/zij daartoe wordt aangespoord.

11. **Verlies van eetlust:**

Beoordeel dit onderdeel en het volgende vooral in vergelijking met de premorbide toestand van de patiënt.

0 Geen verandering, symptoom afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt en/of verzorger heeft een vermindering van eetlust bemerkt, maar niet voldoende om enigermate zorgwekkend te zijn.

3 Patiënt eet duidelijk minder dan voorheen.

4 Het verlies van eetlust van de patiënt is zo ernstig dat de verzorger moet zorgen voor een adequate voedselinname van de patiënt.

12. **Toename van eetlust:**

0 Geen verandering, symptoom afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt en/of verzorger heeft een toename in eetlust bemerkt, maar niet voldoende om enigermate zorgwekkend te zijn.

3 Patiënt eet duidelijk meer dan voorheen.

4 De toename in eetlust van de patiënt is zo ernstig dat de verzorger overmatige voedselinname moet beperken.

13. **Schrokken van voedsel:**

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt heeft de neiging om te snel te eten, maar niet in die mate dat het de verzorger zorgen baart.

3 Verzorger moet patiënt soms berispen voor te snel eten.

4 Patiënt slikt het eten door zonder te kauwen en propt het eten in zijn mond voor de vorige hap is doorgeslikt.

14. **Verandering in voedselvoorkeur:**

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Duidelijke verandering in voedselvoorkeur (bijv. patiënt heeft een voorliefde voor zoet eten ontwikkeld), maar niet in die mate dat het de verzorger zorgen baart.

3 Grote verandering in voedselvoorkeur wat resulteert in een ongepast/ongezond dieet.

4 Patiënt beperkt zijn dieet tot een paar hoogst ongepaste etenswaren (bv. wil niets anders eten dan chocoladebonbons).

15. **Initiatiefverlies:**

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Moet af en toe aangespoord worden om de gewone dagelijkse taken te doen.

3 Heeft regelmatig/bijna altijd aansporing nodig om gewone dagelijkse taken te doen.

4 Doet niets, zelfs niet bij herhaaldelijke aansporing.

16. **Onvermogen om dagelijkse taken af te maken:**

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Slaagt er af en toe niet in om de gewone dagelijkse taken af te maken.

3 Slaagt er regelmatig niet/bijna nooit in om gewone dagelijkse taken af te maken.

4 Doet niets meer.

17. **Kwaliteit van werk:**

Deze scores refereren aan dagelijkse routine taken (bv. huishoudelijk werk of eenvoudige klusjes) waarvan van iedereen verwacht mag worden dat die dat kan. Scoor geen beperkingen van beroepsmatig werk.

0 Geen beperking.

1 Twijfelachtig of van weinig belang.

2 Er is sprake van een duidelijke verandering, maar de kwaliteit van het werk is nog steeds binnen normale grenzen.

3 Er is sprake van een aanmerkelijke verandering en de kwaliteit van het werk is nu beslist beneden peil.

4 De taak komt niet af, of het resultaat is geheel onbruikbaar, of patiënt doet helemaal niets meer.

18. **Oordeelsvermogen en zelfkritisch vermogen:**

0 Geen beperking.

1 Twijfelachtig of van weinig belang.

2 Patiënt is soms impulsief, denkt niet na over de gevolgen van acties, maakt inschattingsfouten, maar zonder dat die een belangrijke invloed hebben op het leven van patiënt.

3 Patiënt schat de uitkomst van acties of beslissingen regelmatig verkeerd in wat soms leidt tot praktische problemen voor de patiënt zelf of zijn/haar verzorgers.

4 Patiënt is niet in staat om op de uitkomsten van acties of beslissingen te anticiperen wat ernstige sociale of praktische gevolgen heeft; heeft constante begeleiding nodig voor zijn/haar eigen bescherming.

19. **Affectvervlakking:**

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Er is sprake van een merkbare vermindering in emotionele gevoeligheid.

3 Afstomping van het affect is ernstig genoeg om enig ongemak bij verzorgers, familie

of vrienden te veroorzaken.

4 Volslagen afwezigheid van interactie met anderen; patiënt vertoont alleen nog emotionele reacties als het hemzelf betreft.

20. **Egocentrisch, veeleisend:**

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt is merkbaar meer egocentrisch dan voor zijn/haar ziekte, maar dit veroorzaakt geen praktische problemen voor de verzorger of familie.

3 Patiënt vertoont zelfzuchtig en /of veeleisend gedrag op verschillende gebieden van het dagelijks leven; veroorzaakt praktische problemen of aanmerkelijk ongemak voor andere leden van het gezin.

4 Zelfzuchtig en/of veeleisend gedrag is constant aanwezig en onverdraaglijk voor verzorger of andere gezinsleden, wat het risico creëert dat patiënt zal worden afgewezen.

21. **Inflexibel, niet coöperatief:**

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt is merkbaar minder flexibel of coöperatief dan voor zijn/haar ziekte, maar dit heeft geen aanmerkelijke praktische problemen voor de verzorger of familie veroorzaakt.

3 De tegenzin van patiënt om van de routine af te wijken of de weigering om zich te schikken naar redelijke wensen van andere gezinsleden veroorzaakt aanmerkelijke praktische problemen voor verzorgers.

4 Patiënt kan niet omgaan met afwijkingen van de vaste dagelijkse routine.

22. **Wilszwakte:**

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt is merkbaar meer passief dan voor zijn/haar ziekte, maar dit veroorzaakt geen praktische problemen.

3 Gebrek aan wilsuiting is zodanig dat patiënt kwetsbaar is voor uitbuiting.

4 Patiënt laat geen eigen wil zien.

23. **Obsessionele ideeën, gedachten, angsten, overpeinzingen, beelden:**

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Er zijn af en toe obsessionele gedachten, maar deze verstoren het dagelijks leven niet en veroorzaken voor de patiënt geen aanmerkelijk ongemak.

3 Er is sprake van obsessionele symptomen zodanig dat deze het dagelijks leven verstoren of aanmerkelijk ongemak veroorzaken voor de patiënt.

4 De obsessionele verschijnselen beheersen bijna het gehele denken van patiënt en veroorzaken ernstige praktische problemen of leed.

24. Dwangmatig gedrag:

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Er is sprake van dwangmatige neigingen maar patiënt kan deze gewoonlijk weerstaan en het symptoom verstoort het dagelijks leven niet en veroorzaakt geen aanmerkelijk ongemak.

3 Dwangmatig gedrag komt regelmatig voor en patiënt is niet in staat om dit te weerstaan; de dwanghandelingen verstoren het dagelijks leven of veroorzaken bij de patiënt aanmerkelijk ongemak.

4 Dwanghandelingen nemen een groot gedeelte van de tijd in beslag en veroorzaken serieuze praktische problemen of leed.

25. Pathologische preoccupaties:

Dit zijn vaste ideeën of thema's die de aandacht van de patiënt overmatig of op de verkeerde momenten in beslag nemen (bijv voortdurende preoccupatie met de behoefte om naar de wc te gaan wat het denken en het gesprek domineert) zoals vaak voorkomt bij patiënten met de ziekte van Huntington. Patiënt beschouwt deze niet als ongepast, noch ervaart hij/zij een drang om deze te weerstaan, en ook zijn ze niet noodzakelijkerwijs geassocieerd met subjectieve angst of ongerustheid; ze vertegenwoordigen waarschijnlijk eerder een aandachtsstoornis dan een echt obsessioneel verschijnsel.

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Er is sprake van abnormale preoccupaties, maar deze verstoren het dagelijks leven niet en veroorzaken voor patiënt of verzorgers geen aanmerkelijk ongemak.

3 De abnormale preoccupaties nemen een aanmerkelijk deel van de aandacht van patiënt in beslag en veroorzaken aanmerkelijk ongemak voor patiënt of praktische problemen voor verzorgers.

4 De abnormale preoccupaties nemen het grootste gedeelte van de aandacht van patiënt in beslag en veroorzaken zeer grote problemen en leed voor patiënt en verzorgers.

26. Prikkelbaarheid:

Op dit item wordt het gemak gescoord waarmee patiënt kwaad wordt; niet de mate waarin patiënt de zelfbeheersing verliest als hij/zij eenmaal boos is (het laatste wordt gescoord in de volgende twee items).

0 Niet prikkelbaarder dan een normaal persoon.

1 Twijfelachtig of van weinig belang; binnen de grenzen van het normale maar sneller geprikkeld dan vroeger.

2 Patiënt is beslist prikkelbaarder dan redelijk is, maar niet in die mate dat het aanmerkelijke problemen of ongemakvoor andere gezinsleden veroorzaakt.

3 Patiënt is erg prikkelbaar en wordt kwaad over onbelangrijke zaken; gezinsleden moeten voorzichtig zijn met wat zij zeggen en doen om problemen te voorkomen.

4 Patiënt is voortdurend erg prikkelbaar en wordt kwaad zonder dat daar een duidelijke reden voor is; met hem/haar samenleven is als lopen op eieren.

27. Opvliegendheid, verbale uitvallen:

Op dit item (en het volgende) wordt het gebrek aan zelfbeheersing gescoord als patiënt kwaad is. De twee items (verbale uitvallen en gewelddadig gedrag) worden op de UHDRS schaal als één item gescoord; gebruik de hoogste score.

0 Normaal.

1 Twijfelachtig of van weinig belang; binnen de grenzen van het normale, maar erger dan hij/zij gewoonlijk was.

2 Er is af en toe sprake van verbale uitbarstingen die buiten sociaal-acceptabele grenzen zijn, maar die geen aanmerkelijke problemen of ongemak veroorzaken voor de andere gezinsleden.

3 De driftbuien zijn ernstig genoeg om aanmerkelijk ongemak te veroorzaken voor de andere gezinsleden en/of praktische problemen bij het verzorgen van patiënt.

4 De patiënt heeft zulke ernstige driftbuien dat de relatie met verzorgers bedreigd wordt. Daarmee loopt patiënt het risico dat hij/zij afgewezen zou kunnen worden.

28. Dreigend gedrag, geweld:

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Geweld gericht op objecten (bijv schopt tegen meubels, smijt met deuren).

3 Er is sprake van bedreiging met geweld jegens personen, of meer extreme schade aan objecten wat een gerede angst veroorzaakt bij de overige gezinsleden voor tegen personen gericht geweld.

4 Er is sprake van daadwerkelijke lichamelijk geweld, of bedreigingen met een dodelijk wapen (bijv mes, geweer).

29. Somatisatie:

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Er zijn nu en dan hypochondrische zorgen die het gedrag van patiënt niet beïnvloeden.

3 Er is sprake van hypochondrische preoccupaties die het grootste gedeelte van de tijd aanwezig zijn en een aanmerkelijke invloed op het gedrag van patiënt hebben (bijv frequente bezoeken aan de dokter).

4 De hypochondrische preoccupaties nemen de aandacht van patiënt in beslag en verstoren de dagelijkse routine aanzienlijk.

30. Verlies van libido:

Scores op dit onderdeel weerspiegelen voornamelijk een verandering van de premorbide toestand van patiënt.

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt is minder geïnteresseerd in seks dan voordat de ziekte begon.

3 Er is sprake van een aanmerkelijk verlies van seksueel verlangen en activiteit, wat problemen kan veroorzaken in de relatie met echtgenoot/partner.

4 Patiënt heeft geen enkel seksueel verlangen of seksuele activiteiten meer.

31.   Seksuele ontremming:

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt is merkbaar meer ontremd wat betreft seksuele zaken dan voor de ziekte, maar het gedrag blijft binnen sociaal acceptabele grenzen.

3 Er is sprake van sociaal onacceptabel ontremd seksueel gedrag.

4 Het seksuele ontremde gedrag van patiënt zou hem/haar in de problemen kunnen brengen met politie, of zou afwijzing door partner, familie of andere verzorgers kunnen veroorzaken.

32.   Seksueel veeleisend gedrag:

Dit onderdeel wordt gebruikt om veranderingen in/afwijkingen van seksueel gedrag te scoren binnen de context van de relaties van patiënt in plaats van de openlijke manifestaties van seksualiteit. Tenzij het gedrag van patiënt buitengewoon abnormaal is, is het waarschijnlijk dat de scores vooral veranderingen ten opzichte van de premorbide gedragspatronen van de patiënt zullen weerspiegelen.

0 Afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt is merkbaar seksueel actiever dan voor zijn/haar ziekte, maar het gedrag blijft voor de partner binnen acceptabele grenzen.

3 Patiënt stelt buitensporig frequente, grove, ongevoelige of agressieve seksuele eisen die voor de partner onacceptabel zijn.

4 Er is sprake van zodanig veeleisend of pervers seksueel gedrag dat het zeer veel leed veroorzaakt voor de partner en de relatie kapot dreigt te maken.

33.   Wanen:

0 Symptoom afwezig.

1 Twijfelachtig of van weinig belang.

2 Er is af en toe sprake van overwaardige ideeën (géén wanen) maar deze beïnvloeden het gedrag van patiënt niet.

3 De overwaardige ideeën zijn een groot gedeelte van de tijd aanwezig ofschoon patiënt (met moeite) ervan overtuigd kan worden dat hij/zij het mis heeft; patiënt gedraagt zich alsof deze ideeën echt zouden zijn.

4 Er is sprake van wanen: niet te corrigeren onjuiste denkbeelden, die niet worden gedeeld door andere leden van de sociale en culturele groep van patiënt en die min of meer continu aanwezig zijn geweest gedurende tenminste 7 dagen.

34.   Jaloezie:

0 Symptoom afwezig.

1 Twijfelachtig of van weinig belang; scoor ook 1 als er een duidelijke basis is voor de jaloezie van patiënt.

2 Patiënt lijkt jaloers, vindt het moeilijk om echtgenoot/partner alleen uit te laten gaan, en koestert wrok als hij/zij dat wel doet.

3 Patiënt is openlijk jaloers, beschuldigt zijn/haar partner onterecht van ontrouw wat aanzienlijke ruzies veroorzaakt, en aanmerkelijk ongemak voor de partner.

4 Patiënt is er onwankelbaar van overtuigd (onterecht) dat zijn/haar partner hem/haar ontrouw is en gedraagt zich om deze reden onredelijk (bijv volgt partner, huurt detectives etc.).

35.   Hallucinaties:

0 Symptoom afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt meldt (desgevraagd) dat hij/zij hallucinaties ervaart, maar deze lijken geen ongemak te veroorzaken of het gedrag van patiënt te beïnvloeden.

3 Er is sprake van hallucinaties die het gedrag van patiënt beïnvloeden (bijv zoeken naar de bron van verborgen stemmen of watten in de oren stoppen), maar geen verder leed lijken te veroorzaken.

4 Patiënt wordt duidelijk gekweld door hallucinaties en is ermee gepreoccupeerd.

36.   Gedrag geassocieerd met verstoorde temperatuurregulatie:

0 Symptoom afwezig.

1 Twijfelachtig of van weinig belang.

2 Patiënt heeft een verstoring van de temperatuurregulatie bemerkt of heeft gemerkt dat hij/zij overvloedig zweet, maar dit heeft geen significant leed veroorzaakt, noch heeft het diens gedrag beïnvloed.

3 Patiënt wordt gekweld door verstoorde temperatuurregulatie en onderneemt acties (bijv het openen van ramen als het koud is) die lastig zijn voor andere gezinsleden.

4 Het gedrag door de verstoorde temperatuurregulatie veroorzaakt aanmerkelijke praktische problemen, (bv. staat erop dat alle ramen de hele nacht open blijven ondanks veiligheidsrisico's).

APPENDIX B

Unified Huntington's Disease Rating Scale (UHDRS): behavioral section (Gedragsproblemen)

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Instructie

Beoordeel de frequentie en de ernst van het gedrag. Deze beoordeling moet op alle beschikbare informatie worden gebaseerd, gebruik makend van de indruk van de clinicus, het rapport over de patiënt en de informatie over de afgelopen maand.

1. Depressieve stemming:

Frequentie:

0 = nooit of bijna nooit
1 = zelden, minder dan eenmaal per week
2 = soms, minstens eenmaal per week
3 = regelmatig, meerdere keren per week
4 = erg vaak, bijna altijd

Ernst:

0 = geen stemmingsstoornissen
1 = twijfelachtig
2 = licht, reageert op geruststelling
3 = matig depressief, geeft uiting van lijden
4 = ernstig, duidelijk lijden en verlies van functioneren

2. Laag zelfvertrouwen/schuldgevoelens:

Frequentie:

0 = nooit of bijna nooit
1 = zelden, minder dan eenmaal per week
2 = soms, minstens eenmaal per week
3 = regelmatig, meerdere keren per week
4 = erg vaak, bijna altijd

Ernst:

0 = geen aanwijzingen
1 = twijfelachtig
2 = licht, duidelijk aanwezig
3 = matig, enige mate van lijden
4 = ernstig

3. Angst:

Frequentie:

0 = nooit of bijna nooit
1 = zelden, minder dan eenmaal per week
2 = soms, minstens eenmaal per week
3 = regelmatig, meerdere keren per week
4 = erg vaak, bijna altijd

Ernst:

0 = geen aanwijzingen
1 = twijfelachtig
2 = licht, reageert op geruststelling
3 = matig, beïnvloedt dagelijks functioneren
4 = ernstig, belemmert activiteiten

4. Suïcidale gedachten:

Frequentie:

0 = geen gedachten over suïcide of zelfbeschadiging
1 = zelden suïcidegedachten, minder dan eenmaal per maand
2 = soms gedachten over suïcide, minstens eenmaal per week
3 = regelmatig gedachten over suïcide, minstens eenmaal per week
4 = vaak gedachten over suïcide, soms dagen of weken achter elkaar

Ernst:

0 = geen suïcidale gedachten
1 = op dit moment geen gedachten, maar praat over suïcide als mogelijkheid
2 = vluchtige gedachten over suïcide
3 = serieus suïcide overwogen, maar heeft geen plannen
4 = heeft een plan en is bezig met voorbereidingen

5. Opvliegend of agressief gedrag:

Frequentie:

0 = nooit of bijna nooit

1 = zelden, minder dan eenmaal per maand

2 = soms, minstens eenmaal per maand

3 = regelmatig, minstens eens per week

4 = erg vaak, elke dag

Ernst:

0 = gedrag is goed onder controle

1 = verbale bedreigingen of intimiderend gedrag

2 = duidelijk fysiek of verbaal dreigend gedrag

3 = duidelijk fysieke dreiging (matige agressie), stoten, schuiven, verbale uitbarstingen

4 = duidelijke fysieke dreiging (ernstige agressie), slaan, of duidelijke intentie om iemand pijn te doen

6. Prikkelbaarheid:

Frequentie:

0 = nooit of bijna nooit

1 = zelden, minder dan eenmaal per week

2 = soms, minstens eenmaal per week

3 = regelmatig, meerdere keren per week

4 = erg vaak, bijna altijd

Ernst:

0 = gedrag is goed onder controle

1 = twijfelachtig

2 = duidelijk, maar licht

3 = matig, anderen veranderen hun gedrag om te vermijden dat patiënt geïrriteerd wordt

4 = ernstige irritatie

7. Persevererend/obsessioneel denken:

Frequentie:

0 = nooit of bijna nooit

1 = zelden, minder dan eenmaal per week

2 = soms, minstens eenmaal per week

3 = regelmatig, meerdere keren per week

4 = erg vaak, bijna altijd

Ernst:

0 = denken is altijd flexibel

1 = twijfelachtig

2 = blijft hangen op bepaalde ideeën, maar deze kunnen wel worden gewijzigd

3 = matig, blijft hangen op bepaalde ideeën, moeilijk om deze bij te sturen

4 = ernstig, blijft hangen op bepaalde ideeën, laat zich niet bijsturen

8. Compulsief gedrag:

Frequentie:

0 = nooit of bijna nooit

1 = zelden, minder dan eenmaal per week

2 = soms, minstens eenmaal per week

3 = regelmatig, meerdere keren per week

4 = erg vaak, bijna altijd

Ernst:

0 = gedrag is goed onder controle

1 = twijfelachtig, heeft lichte impulsen, handelt daar nog niet naar

2 = licht, heeft impulsen, handelt ernaar, maar kan stoppen

3 = matig, heeft impulsen, handelt ernaar, en kan het soms niet stoppen

4 = ernstig, heeft impulsen, handelt ernaar en kan niet stoppen

9. Wanen:

Frequentie:

0 = geen aanwijzingen

1 = zelden, minder dan eenmaal per maand

2 = soms, minstens eenmaal per maand

3 = regelmatig, minstens eenmaal per week

4 = erg vaak, soms dagen achtereen

Ernst:

0 = geen aanwijzingen

1 = heeft waanachtige denkbeelden, weet niet zeker of het waar is

2 = overtuigd van idee(ën), maar accepteert dat het niet waar is

3 = volledig overtuigd van idee(ën)

4 = volledig overtuigd van idee(ën), gedrag wordt er door bepaald

10. Hallucinaties:

Frequentie:

0 = geen aanwijzingen of hallucinaties

1 = zelden, minder dan eenmaal per maand

2 = soms, minstens eenmaal per maand

3 = regelmatig, minstens eenmaal per week

4 = erg vaak, soms dagen achtereen

Ernst:

0 = geen aanwijzingen

1 = heeft hallucinaties, maar twijfelt of ze echt zijn

2 = overtuigd van de realiteit ervan, maar houdt er rekening mee dat ze onjuist zijn

3 = volledig overtuigd dat ze echt zijn, maar handelt er niet naar

4 = ernstig, heeft levendige hallucinaties, overtuigd van het feit dat ze waar zijn en ze verstoren het gedrag in ernstige mate

11. Apathie:

Frequentie:

0 = nooit

1 = zelden, minder dan eenmaal per week

2 = soms, minstens eenmaal per week

3 = regelmatig, meerdere keren per week

4 = erg vaak, bijna altijd

Ernst:

0 = geen aanwijzingen

1 = twijfelachtig

2 = lichte apathie, initieert geen gesprek of activiteit, maar reageert wel

3 = matige apathie, reageer soms op initiatieven om betrokken te worden bij gesprek/ activiteit

4 = ernstige apathie, over het algemeen niet responsief op pogingen om betrokken te worden bij activiteiten of gesprekken

Apathy Scale (Apathieschaal)

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Instructie

Lees de vragen voor en laat de deelnemer het antwoord kiezen. De deelnemer mag de partner of verzorger om raad vragen en de beoordelaar moet ook het oordeel van de partner/verzorger en zijn/haar eigen indruk laten meewegen. Omdat het een semi-gestructureerd interview is, kan bij onduidelijkheden een toelichting gegeven worden of om verheldering gevraagd worden.

Mogelijke antwoorden:
- in het geheel niet aanwezig
- weinig aanwezig
- aanwezig
- sterk aanwezig

1. Heeft u belangstelling om dingen te leren?
2. Heeft iets uw interesse?
3. Is het nodig dat een ander u zegt wat u op een dag moet doen?
4. Bent u bezorgd om uw gezondheid?
5. Maakt het u allemaal niet uit wat er gebeurt?
6. Steekt u veel energie in de dingen die u doet?
7. Bent u altijd op zoek naar dingen die u kunt doen?
8. Heeft u plannen en stelt u zichzelf doelen voor de toekomst?
9. Bent u gemotiveerd?
10. Heeft u voldoende energie voor uw dagelijkse bezigheden?
11. Bent u niet meer betrokken bij veel dingen?
12. Hebt u een aanzet nodig om ergens aan te beginnen?
13. Voelt u zich niet opgewekt of verdrietig, maar iets daartussenin?
14. Zou u zichzelf apathisch noemen?

Berekening

Vragen 1, 2, 4, 6-10 :
in het geheel niet aanwezig = 3; weinig aanwezig = 2; aanwezig = 1; sterk aanwezig = 0.

Vragen 3, 5, 11-14:
in het geheel niet aanwezig = 0; weinig aanwezig = 1; aanwezig = 2; sterk aanwezig = 4.

Als afkapwaarde tussen lage en hoge scores voor apathie wordt 13-14 punten gehanteerd.

Dankwoord

Het is een bijzonder moment in mijn leven om mijn promotietraject met dit proefschrift af te kunnen ronden. Uiteraard is dit het resultaat van een project van velen en mijn dank gaat dan ook uit naar allen die aan dit proefschrift hebben meegewerkt. Een aantal van hen wil ik in het bijzonder bedanken:

Allereerst alle deelnemers die geheel belangeloos aan dit onderzoek hebben meegedaan. Dit onderzoek is door hen en voor hen gedaan. Hun bereidwilligheid om mee te werken aan onderzoek wordt zeer gerespecteerd.

De Raad van Bestuur van Rivierduinen en de directie van GGZ Duin- en Bollenstreek ben ik zeer erkentelijk voor de geboden mogelijkheden om dit onderzoek uit te voeren.

De medewerkers van verpleeghuis 'Overduin', in het bijzonder Lani Liem, Hans Claus en het verzorgend personeel, die allen zeer behulpzaam zijn geweest bij het werven en het onderzoeken van deelnemers.

Ook ben ik dank verschuldigd aan de student-stagiaires zonder wie dit onderzoek niet gedaan kon worden: Elselijn Kingma, Annelieke Willemsen, Rosalinde Poortvliet, Marjan Steenweg, Maaike van Herpen, Yvonne Ruijsink, Hanneke Nijendijk, Cigdem Ozturk, Dirk-Jan Bruijn, Tansel Yilmaz, Laura Reisma, Sevim Orhan, Nienke Pannekoek, Fang-Yuh Hsia en Mieke Bevers.

Voor het laboratoriumonderzoek waren Hans van Pelt en Jolanda Verhagen onmisbaar, waarvoor dank.

Collega onderzoekers Marie-Noëlle Witjes-Ané, Caroline Jurgens, Lucienne van der Meer, Reinier Timman, Nanda Reedeker, Erik Giltay en Mischa Selis wil ik bedanken voor hun hulp en vriendschap.

Mijn collega psychiaters bij GGZ Duin- en Bollenstreek dank ik voor hun bereidheid om de patiëntenzorg voor mij waar te nemen.

Ik ben mijn ouders – helaas is mijn vader veel te vroeg overleden – zeer dankbaar voor alle kansen en aanmoedigingen die ik heb mogen krijgen.

Lieve Jan Willem, op deze plaats wil ik jou, ook officieel, bedanken voor je geduld en de ruimte die je mij hebt gegeven om tot dit moment te komen. *Te quiero*.

Haarlem, februari 2010

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Curriculum Vitae

Erik van Duijn werd op 4 december 1971 in Katwijk geboren. Na het behalen van het VWO diploma in 1990 aan het Pieter Groen College te Katwijk, studeerde hij geneeskunde aan de Rijksuniversiteit te Leiden. Tijdens zijn studie volgde hij een wetenschappelijke stage bij prof. dr. W. Bergman. Hij bestudeerde erfelijke aspecten van het dysplastisch naevus syndroom; een erfelijke huidaandoening die evenals de ziekte van Huntington relatief vaak in Katwijk voorkomt. Aan het eind van zijn studie volgde hij gedurende een jaar diverse keuzevakken aan de Rijksuniversiteit te Leiden en aan de Vrije Universiteit te Amsterdam. In 1998 ontving hij de artsenbul. Aansluitend werkte hij ruim een jaar als arts-assistent op de afdelingen interne geneeskunde, longziekten en cardiologie van het Spaarne Ziekenhuis te Haarlem en Heemstede. In 1999 werkte hij nog enkele maanden als arts-assistent in het psychiatrisch ziekenhuis Duin en Bosch te Castricum. Vervolgens startte hij in 2000 met de keuzestage consultatieve en liaison-psychiatrie zijn opleiding tot psychiater in het Leids Universitair Medisch Centrum. Daarna volgde de basisopleiding binnen het Haags-Leids Opleidingsconsortium met prof.dr. F.G. Zitman als hoofdopleider. Sinds 2004 is hij geregistreerd psychiater. In de laatste fase van zijn opleiding startte hij met zijn promotieonderzoek naar psychopathologie bij de ziekte van Huntington, wat hij voortzette nadat hij in 2004 bij GGZ Duin- en Bollenstreek te Voorhout, onderdeel van Rivierduinen, ging werken. Hij werkte op poliklinische en klinische afdelingen en werkte als consultatief psychiater onder andere in het gespecialiseerde Huntingtoncentrum 'Overduin'. Hij is actief binnen het European Huntington's Disease Network en hij werkt samen met collega's van de Huntington Study Group. Hij is lid van de wetenschappelijke adviesraad van de Vereniging van Huntington en van de Parkinson adviesraad zorg. Sinds 2009 werkt hij als psychiater bij GGZ Delfland te Delft.