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Huntington's disease: cognition and apathy

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Huntington's Disease

Cognition and Apathy

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Huntington's Disease

Cognition and Apathy

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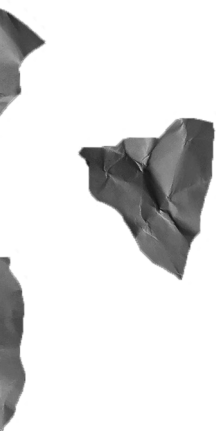
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Chapter 1

Introduction

Huntington's disease (HD) is an autosomal, dominant inherited neurodegenerative disorder, characterized by a triad of symptoms including motor abnormalities, behavioral symptoms and cognitive decline¹. The prevalence of HD varies between regions, in western countries approximately 10 per 100.000 individuals are affected by HD². The mean age of disease onset is between 30 and 50 years of age with a disease duration of 17 to 20 years¹.

In 1872, George Huntington (1850-1916) described the clinical features of, what is now called, Huntington's disease. In his essay 'On Chorea', he already described the hereditary nature, midlife onset, and the clinical symptoms³. Roughly 100 years later, in 1983, the huntingtin gene was mapped to the short arm of chromosome 4 which made linkage analysis possible⁴. Ten years later, in 1993, the mutation was identified as an abnormal expansion on the CAG (cytosine, adenine, guanine) trinucleotide on chromosome 4 in the huntingtin gene and genetic testing became an option for individuals at risk⁵. The length of the CAG repeat in the huntingtin gene can be categorized as follows: full penetrance (CAG > 39), reduced penetrance (CAG range 36-39), intermediate penetrance (CAG range 27-35), and normal (CAG < 27). An individual with a full penetrant CAG expansion will develop symptoms at some point in life, however, it cannot be predicted at what age individuals start to develop symptoms⁶. In general, a longer CAG expansion is associated with early disease onset⁷.

Clinical symptoms and measurement tools

HD symptoms can be categorized in three domains: motor, cognitive, and behavioral. Motor symptoms are the most recognized signs of HD and typically a clinical diagnosis is determined based on the occurrence of motor symptoms^{1,8}. The most characteristic motor symptom is chorea, unwanted, jerky movements, but other motor symptoms such as dystonia, rigidity, hypokinesia and bradykinesia are also often present. The symptoms worsen over the course of the disease and will eventually interfere with daily activities, such as getting dressed and walking¹. The Unified Huntington's Disease Rating Scale (UHDRS) was designed to rate the most common symptoms, including motor symptoms, and general functional capacity of daily living of HD expansion gene carriers (HDGEC)⁹. The motor part of the UHDRS is still the gold standard to rate motor abnormalities. This scale ranges from 0 to 124, with higher scores indicating more motor impairment. In research, a cut-off of 5 points on the UHDRS is used to indicate whether HDGECs have substantial motor symptoms; i.e. distinction between pre-motormanifest and motormanifest individuals. The UHDRS has a high inter-rater reliability⁹. Recently, a force transducer, the Q-motor, was developed to be able

to even detect subtle changes in motor performance and was recently used in clinical trials¹⁰.

Cognitive decline is another major HD symptom and was already recognized by George Huntington³. The last decades, the cognitive component of HD has been extensively studied, this might partially be ascribed to the fact that cognitive deterioration embodies several cognitive domains which all can be measured with different tools¹¹. This is also the challenge to identify the natural course of cognitive decline in HD with diverse studies focusing on different cognitive domains, using different measurement tools, and including different staged HDGECs. It is known that cognitive deterioration can occur before motor symptoms are present and simple psychomotor tasks seem to be sensitive in the period before motor symptoms become present¹¹⁻¹³ whereas tasks of memory and executive functioning appear to become sensitive in the early HD stages¹²⁻¹⁴. Still the exact course of cognitive decline for each domain is still unknown, but finally cognitive deterioration results in dementia in HD¹¹. Effort has been made to design cognitive batteries to track cognitive decline in HD and recently the HD cognitive assessment battery (HD-CAB)¹⁵ was designed to track cognitive decline in the early HD phase, i.e. clinically diagnosed HDGECs with still high functional capacity in daily living. However, considering the entire spectrum of the disease, no consensus exists which cognitive tasks should be used in which stage.

Besides motor disturbances and cognitive impairment, behavioral symptoms are more heterogeneously present in HD, as the presence and its severity fluctuates throughout the course of the disease^{16, 17}. The most common behavioral symptoms are depressive mood, irritability and apathy¹⁷. Other symptoms such as hallucinations, delusions and perseverations can also occur. Apathy can already mildly be present in the pre-motormanifest stage^{18, 19} and will eventually be severely present in the late stage¹⁶. It seems that apathy is the only behavioral symptom which worsens as disease progresses, suggesting a neurodegenerative cause, and is negatively related to functional capacity^{16, 20}. In addition, apathy and cognitive impairment are also connected. Apathy can occur due to disruption of cognitive processes, i.e. apathy is a result of working memory problems or executive dysfunction²¹. In HD it has been shown that apathy is associated with cognitive decline²². Several rating scales have been used in HD to track the behavioral symptoms in HD but only a few are recommended to use in HD as the behavioral symptoms are complex due to co-occurrence of different behavioral symptoms²³. The Problem Behavior Assessment – short (PBA-s), a semi-structured psychiatric interview, was developed for HD and is now commonly used to rate the presence and severity of the different behavioral symptoms²⁴.

The last decades, tremendous effort has been made in neuroimaging studies to understand the relationship between HD symptoms and the underlying neurodegenerative process. Magnetic resonance imaging (MRI) technique was often used to map symptoms to structural and/or functional changes in the brain in HD²⁵. These studies showed that atrophy of the putamen is correlated to motor symptoms^{26,27}, atrophy of the caudate is correlated to cognitive deficits¹⁴, and that striatal atrophy already starts before symptoms become apparent¹⁹. But still a lot is unknown about the development of symptoms and the neurodegenerative process.

As there is no cure of HD, many individuals take medication to manage HD symptoms. In a large European study about 85% received symptomatic treatment, the majority for depression²⁸. Unfortunately, there is only low level of evidence on the effects and side effects of medication use in HD and most decision making on prescription is based on clinical practice²⁹⁻³¹.

Aims

As exact knowledge of the course of cognitive decline and the underlying cause of developing apathy is still lacking in HD, the primary aim of this thesis was to gain further insight into the cognitive profile and apathy in Huntington's disease (HD). This information is incredible useful to advice future clinical trials about their design if cognitive decline and/or apathy is targeted.

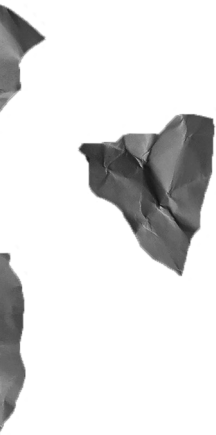
As HD is a rare disease, research heavily relies on collaboration between HD centers. In 2004, the European Huntington's Disease Network (EHDN) launched the European, multicenter, observational REGISTRY study³². We aimed to evaluate whether the most commonly used participant classification makes a useful distinction between HDGECs and whether these groups are homogeneous by giving an overview of the participants' characteristics at the largest REGISTRY HD center (**chapter 2**). Secondly, using the entire European REGISTRY cohort, we aimed to map the cognitive profile in different disease stages, ranging from pre-motormanifest to advanced HD stages, and to evaluate whether CAG length mediates cognitive decline in HD (**chapter 3**). In addition, we explored whether there is a difference in cognitive performance between individuals taking medication targeting non-cognitive neuropsychiatric signs or/and tetrabenazine and non-users in HD (**chapter 4**). The following two chapters focus on apathy, we aimed to relate apathy to the neurodegenerative process in HD (**chapter 5**). In **chapter 6**, we evaluated whether HDGECs and their proxies agree on the degree of apathy by using a self-report questionnaire. General discussion of our findings and future perspectives are outlined in **chapter 7**.

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Chapter 2

Participants at the Leiden site of the REGISTRY study: a demographic approach

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Abstract

Background: REGISTRY is the largest European observational study of Huntington's disease (HD). The Leiden University Medical Center (LUMC) in The Netherlands is the largest recruiting site.

Objective: The aim of this paper is to give an overview of the baseline characteristics of all Leiden participants from the start of the study in 2005 until the close of REGISTRY at the LUMC in September 2014.

Methods: The Leiden cohort is described in two different ways: CAG repeat length and presence of motor signs.

Results: Division into groups based on prolonged CAG length revealed that the cohort consists of 4 intermediate - (27 – 35 CAG), 22 reduced penetrance - (36-39 CAG), 465 full penetrance - (> 39 CAG) and 60 control participants (< 27 CAG). The second way of dividing the participants based on present or absent of motor signs, showed that 170 pre-motormanifest - and 317 motormanifest participants were enrolled.

Conclusion: The Leiden REGISTRY cohort at baseline is mainly characterized by full penetrance gene expansion carriers who have been clinically diagnosed with HD but who remain relatively functionally independent. For the majority of these participants, disease onset was based on motor signs followed by psychiatric and cognitive signs.

Introduction

Huntington's disease (HD) is a devastating neurodegenerative disease with autosomal dominant inheritance, affecting approximately 10 per 100,000 people in Western countries^{1, 2}. It is characterized by a triad of symptoms: progressive motor abnormalities, behavioral signs and cognitive deterioration³. HD is caused by an unstable trinucleotide repeat expansion which codes for mutant huntingtin on chromosome 4⁴. With the discovery of the expanded gene and its exact location⁴ individuals who are at risk of developing this disorder can be tested for the expanded HD gene before any clinical signs become apparent. The fully penetrant nature with a CAG repeat of >39 means that a person will inevitably develop symptoms and signs of HD during their normal life span⁵. Over a course of, on average, 15 years, signs will gradually worsen, severely debilitate the patient, resulting in premature death⁶. Currently, symptomatic treatment is available, but as yet no cure or disease modification. Study of the expanded gene carriers over time provides valuable insights into disease progression which in turn might identify underlying disease mechanisms.

The relative rarity of HD poses challenges to the study of this disease. As substantial numbers of participants are needed to investigate the multimodal progression of HD, research relies heavily on international, multicenter studies, such as REGISTRY⁷, COHORT⁸, PREDICT-HD⁹ and TRACK-HD¹⁰.

The REGISTRY study is a European, multicenter, observational study coordinated by the European Huntington's Disease Network (EHDN)⁷. It was initiated in 2004 and 17 European countries have recruited or are still recruiting asymptomatic, symptomatic, at risk, and control participants. Assessments of motor, cognitive, behavior, and daily functioning are administered according to standard procedures and participants are asked to donate blood and urine samples annually. All data are rigorously monitored. At present, over 12,000 participants are included in the database with both cross-sectional and longitudinal data.

The Leiden University Medical Center (LUMC) in The Netherlands, with 589 participants enrolled, is the largest site in the REGISTRY followed by Madrid (Spain; 497 participants) and Münster (Germany; 464 participants). In Europe, the REGISTRY sites are being closed one by one in the transition to the worldwide, observational Enroll-HD study (for more information see www.enroll-hd.org). The REGISTRY site in Leiden was closed in September 2014, thus providing an opportunity to present an overview of the demographic and disease-specific characteristics of all enrolled REGISTRY participants at baseline visit.

In this paper, the Leiden population is described in two different ways. Clinical features are described according to CAG length categorization and presence of motor

signs. Using these classifications allows us to evaluate whether the most commonly used classification makes a useful distinction between participants and whether participants within these groups are homogeneous. Describing the large Leiden population thoroughly provides particularly useful information for designing future clinical trials and their target population. This paper can give guidance as to which variables should be taken into account for recruiting participants in order to answer specific research questions.

Methods

The Leiden University Medical Center (LUMC) is the largest national HD referral center in the Netherlands. Between 2005 and 2014, all individuals consulting the HD outpatient clinic were asked to participate in the REGISTRY study. About 2% did not participate for various reasons: non-Dutch speaking, refusal, attended outpatient clinic only once for second opinion. In Leiden, data from patients participating in other locally performed studies were also included in the REGISTRY database: CAPIT-HD¹¹, Riluzole¹², HD-project¹³, PEP-HD¹⁴, Track-HD¹⁰, PADDINGTON¹⁵, and local studies by the Department of Psychiatry¹⁶. Study assessments were administered by trained professionals and all data were monitored. All studies mentioned have been approved by the LUMC Medical Ethics Committee and all participants gave written informed consent.

Participants

The REGISTRY study included asymptomatic and symptomatic HD expansion mutation carriers, at risk participants and healthy controls (either negatively tested participants or community controls). The data extraction included first baseline visit on January 15th, 1998 (retrospective data) and last baseline visit on June 12th, 2014 (closing of REGISTRY), resulting in 589 baseline visits. In total, 42 participants were excluded from analysis because of missing CAG length (n=16), missing motor score on the UHDRS (n=9), at risk participant (n=10), juvenile HD (n=3) or intermediate CAG length (CAG repeats between 27 and 35; n=4). The intermediates were excluded because of the low number of participants and the lack of consensus about whether intermediate gene carriers develop HD or HD-like phenotype¹⁷⁻¹⁹. This resulted in 547 individuals taking part in the analysis, 60 of whom were controls.

First, the 487 HD expansion mutation carriers were divided according to the prolonged CAG allele. Participants with CAG repeats between 36 and 39 were classified as reduced penetrance and CAG repeats of ≥ 40 as full penetrance²⁰.

Second, the cohort was divided on the basis of the presence of motor signs according to the total motor score (TMS) of the Unified Huntington's Disease Rating Scale (UHDRS)²¹ where a TMS of ≤ 5 was considered pre-motormanifest (PMHD) and TMS > 5 motormanifest (MHD)¹⁰. Other possible HD signs were not taken into consideration for this division.

Variables

General demographic data consisted of date of birth, gender, handedness, ethnicity, education (total years), employment, and marital status (partner: yes/no). HD-specific variables included number of CAG repeats of both the smaller and larger allele, information on family history (e.g. affected parent), and personal HD history. The personal history consisted of: age at onset, signs at onset, date of diagnosis and disease duration before baseline visit. These data were collected through an amnestic interview with participant and if possible partner/caregiver. Notably, age at onset is defined as age at which, for the first time, any HD related signs have occurred independent of a clinical diagnosis.

Clinical variables included items of the UHDRS: total motor score (TMS), total functional capacity (TFC), functional assessment score, independence score, total behavior score (TBS) and total cognitive score (TCS). The TCS consisted of the total correct score of the Stroop-Colour-Word-Interference test, the Symbol Digit Modalities test and verbal fluency test.

Statistical analysis

None of the reported variables proved to be normally distributed. Therefore, nonparametric tests were used to identify differences between groups: Mann-Whitney U test (U) or Kruskal-Wallis test (H). If multiple testing was performed, a conservative significance level was used: $p=0.05$ divided by the number of performed tests (i.e. either $p=0.03$ or $p=0.02$). Frequencies and median with ranges are reported in tables 1, 2, and 3.

Results

The results are presented according to the two divisions of the cohort: CAG repeat length and presence of motor signs.

Cohort divided based on CAG length

Division based on CAG length resulted in 22 reduced penetrance - and 465 full penetrance participants (table 1).

Demographic data

Age at baseline: The reduced penetrance group was significantly older (median age: 55years) than the full penetrance group (median age: 46years) at time of baseline visit ($U=3736$, $z=-2.14$, $p=0.03$). There was no significant age difference between the reduced penetrance group and controls ($U=523$, $z=-1.44$, $p=0.15$).

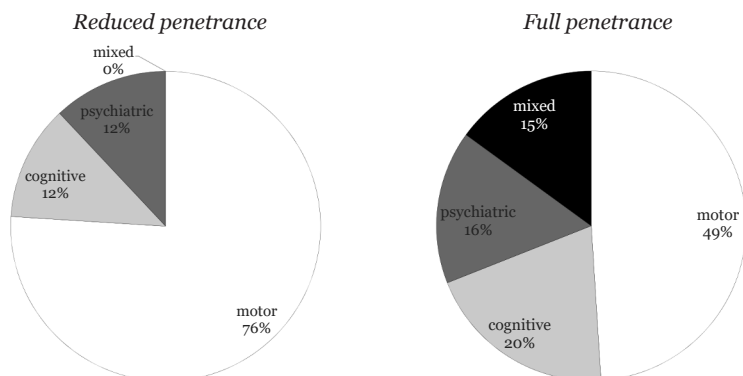
CAG smaller allele: The three groups did not differ significantly in the length of the smaller CAG allele ($H(2)=3.26$, $p=0.2$). Noteworthy is that one participant of the reduced penetrance group had an intermediate CAG length on the smaller allele (28/38). Seventeen participants of the full penetrance group had a smaller allele in the intermediate range, and one participant had a reduced penetrance CAG length on the smaller allele (36/46) and was considered to be homozygote.

Table 1: Division based on expanded CAG repeat length

		Reduced penetrance <i>N</i> =22	Full penetrance <i>N</i> =465	Control <i>N</i> =60	p-value
Full cohort (<i>N</i> =547)	Age in years ^a	55 (27-81)	46 (19-82)	49 (23-88)	$p < 0.05$
	Gender: male/female	11/11	191/274	26/34	$p > 0.05$
	CAG smaller allele ^a	17 (15-28)	17 (9-36)	17 [49] (16-18)	$p > 0.05$
	CAG larger allele ^a	39 (36-39)	43 (40-59)	18 [49] (17-24)	$p < 0.01$
		<i>N</i> =9	<i>N</i> =317	<i>N</i> =0	
Clinically diagnosed cohort (<i>N</i> =335)	Age at diagnosis in years ^a	67 (36-81)	48 (23-82)	NA	$p < 0.05^b$
	Age at symptoms first noted by subject in years ^a	53 (36-74)	45 [4] (20-78)	NA	$p = 0.05^b$
	Age at symptoms first noted by family in years ^a	53 (36-74)	44 [11] (20-75)	NA	$p < 0.05^b$
	Rater's estimate of age at first symptoms in years ^a	53 (36-73)	44 [11] (20-72)	NA	$p < 0.05^b$
	Disease duration before baseline visit in years ^a	3 (0-17)	5 [11] (0-24)	NA	$p > 0.05^b$

Note: ^a median [number of missing data], (range); ^b testing only between reduced penetrance and full penetrance;
NA: Not applicable; N: Number.

Figure 1: First Huntington's disease sign judged by rater, for reduced and full penetrance groups



HD disease onset

In total, 335 participants were already diagnosed with HD at time of REGISTRY baseline visit: 9 reduced penetrance participants (41% of reduced penetrance group) and 317 full penetrance participants (68% of full penetrance group).

Age at diagnosis: The reduced penetrance group was significantly older (median age: 67) than the full penetrance group (median age: 48) at time of clinical HD diagnosis ($U=845$, $z=-2.09$, $p<0.03$).

Age at first HD sign: Within both the reduced penetrance and full penetrance groups, there was relative consensus between participant, family and professional rater about the age at which first HD signs occurred (table 1). Based on the rater's judgment, the reduced penetrance group was significantly older (median age: 53) than the full penetrance group (median age: 44) at time of first HD sign ($U=777.5$, $z=-2.23$, $p=0.03$).

First HD sign: For the reduced penetrance group, the rater judged that disease onset started with motor signs in about 76%, cognitive decline in about 12 % and psychiatric changes in about 12% (see figure 1).

For the full penetrance group, the rater judged that disease onset started with motor signs in about 49%, psychiatric changes in about 20%, cognitive decline in about 16% and mixed in about 15% (see figure 1).

Years between disease onset and baseline visit: There was no difference between the reduced and full penetrance group regarding the years between rater's estimate of disease onset and baseline REGISTRY visit ($U=1045.5$, $z=-1.24$, $p=0.21$).

Table 2: Division based on motor symptoms

	Pre-motormanifest N=170	Motormanifest N=317	Control N=60	p-value
Age in years ^a	38 (19-66)	51 (26-82)	49 (23-88)	p < 0.05
Gender: male / female	58 / 112	144 / 173	26 / 34	p = 0.05
Employment: employed / unemployed	127 / 43	76 / 241	41 / 19	p < 0.05
Marital status: partner / no partner	125 / 44 [1]	217 / 97 [3]	41 / 5 [14]	p < 0.05
Total Functional Capacity ^a	13 (8-13)	9 [1] (0-13)	13 [13] (10-13)	p < 0.05
Functional Assessment score ^a	25 [3] (20-25)	22 [2] (0-25)	25 [14] (24-25)	p < 0.05
Total Cognitive Score ^a	291 [34] (189-407)	178 [123] (45-341)	298 [3] (189-439)	p < 0.05
Total Behavioral Score ^a	0 [31] (0-23)	4 [14] (0-26)	1 [42] (0-15)	p < 0.05
Family history				
Affected parent: Mother/father/both	95 / 72 / 0 [3]	159 / 134 / 1 [25]	8 / 8 / 0 [44]	p > 0.05 ^b
Age at onset mother in years ^a	45 [31] (25-71)	45 [54] (25-72)	50 [2] (44-57) [†]	p > 0.05 ^b
Age at onset father in years ^a	46 [17] (27-75)	48 [51] (20-91)	55 [1] (41-75) [†]	p > 0.05 ^b

Note: ^a median [number of missing data], (range); ^b testing only between pre-motormanifest and motormanifest;
[†] only participants from a confirmed HD family.

Cohort divided based on presence of motor signs

In total, 170 pre-motormanifest (PMHD) - and 317 motormanifest (MHD) participants were included (table 2).

General characteristics

Age at baseline: At time of baseline visit, the PMHD group (median age: 38 years) was significantly younger than the MHD group (median age: 51 years; U=11895.5, z=-10.17, p<0.01) and PMHD was also significantly younger than the control group (median age: 49 years; U=2497.5, z=-5.88, p<0.01).

Gender: There was a significant difference in the distribution of men and women between the three groups ($\chi^2(2)=5.9$, p=0.05). The PMHD had the highest percentage of female participants (about 66% compared to 55% in MHD and 57% in control).

TFC: The TFC score of the PMHD group was significantly higher than that of the MHD group (U=5809.5, z=-13.77, p<0.01), but significantly lower than the control group (U=2694.5, z=-3.56, p<0.01).

Table 3: Huntington's disease history for participants with clinical diagnosis

	Pre-motormanifest with clinical diagnosis N=35	Motormanifest with clinical diagnosis N=291	p-value
Age at diagnosis ^a	40 (28-65)	49 (23-82)	p < 0.05
Age at symptoms first noted by subject ^a	38 (28-63)	46 [4] (20-78)	p < 0.05
Age symptoms first noted by family ^a	38 [2] (28-63)	45 [9] (20-75)	p < 0.05
Rater's estimate of age at first symptoms ^a	38 [1] (28-63)	45 [10] (20-73)	p < 0.05
Disease duration ^{a,b}	3 [1] (0-11)	5 [10] (0-24)	p < 0.05

Note: ^a median in years [number of missing data], (range); ^b age at symptom onset by rater – age at baseline visit

On further classifying the MHD group into disease stages based on the TFC score by Shoulson and Fahn²²: 126 (40%) participants were in stage 1, 94 (29%) in stage 2, 75 (24%) in stage 3, 19 (6%) in stage 4, and two (<1%) in stage 5; the data for one participant's baseline visit were missing.

HD disease onset for participants with clinical diagnosis

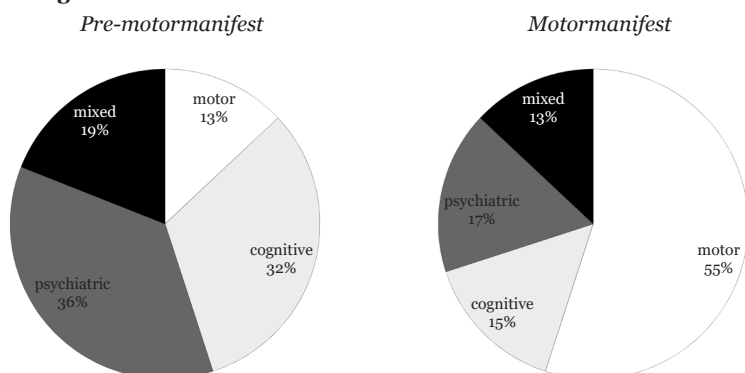
At time of REGISTRY baseline visit, 326 out of the 487 gene carriers were already clinically diagnosed with HD based on either motor, cognitive, psychiatric or mixed symptoms: 35 PMHD (21% of all PMHD participants), and 291 MHD (92% of all MHD participants) (see table 3).

Age at diagnosis: The PMHD group was significantly younger than the MHD group at time of clinical diagnosis ($U=3313$, $z=-3.38$, $p<0.01$).

Age at first HD sign: There was a relative consensus between participants, families and raters regarding the age at which first HD signs were noted within the PMHD group as well as within the MHD group (see table 3). According to the judgment of the rater, the first HD signs occurred significantly earlier in the PMHD group than the MHD group ($U=33337$, $z=-2.87$, $p<0.01$).

First HD sign: Within both the PMHD group and MHD groups, there was consensus between participants, families, and rater regarding the type of first noted HD sign. According to the rater's judgment in the PMHD group, the most frequently noted HD signs were psychiatric problems in 36%, followed by cognitive decline in 32%, motor signs in 13% and mixed first signs in 19%. For the MHD group, the rater judged that the first HD signs to be noted were motor signs in 55%, psychiatric problems in 17%, cognitive decline in 15%, and mixed in the remaining 13%¹ (see figure 2).

Figure 2: First Huntington's disease sign judged by rater, for pre-motormanifest and motormanifest gene carriers



¹ Numbers are approximates

Years between disease onset and baseline visit: After disease onset, as judged by rater, the PMHD group attended their first REGISTRY visit after a median of 3 years, which was significantly lower than the MHD group (median of 5 years; $U=3385$, $z=-2.79$, $p < 0.01$).

Discussion

The present paper presents the descriptive data on demographics, clinical and HD-specific characteristics of the Leiden REGISTRY cohort. This is the largest REGISTRY cohort in Europe with primarily full penetrance participants. At baseline visit, the majority of participants were clinically diagnosed with HD and were in an early or mid-stage of the disease.

In the Leiden REGISTRY cohort, the percentage of participants with an allele in the reduced penetrance range (about 5%) was comparable to the percentage described in the literature^{23, 24}. About 40% of these participants had already been clinically diagnosed with HD. As yet, little is known about disease progression for gene carriers in the reduced penetrance range. There are suggestions that these individuals have late HD onset²⁵⁻²⁷ with chorea as primary disease sign^{27, 28}. This supports the notion that gene carriers with a lower number of CAG repeats express a decreased phenotype variability compared to gene carriers with a high number of CAG repeats²⁹.

The majority of the Leiden REGISTRY participants were already clinically diagnosed with HD prior to the REGISTRY visit with a relatively high functional capacity (e.g. being able to travel to the outpatient clinic). For these participants, the rater judged that disease onset started most frequently with motor abnormalities. Nevertheless, for about one-third, disease onset started with cognitive and/or psychiatric signs as judged by the rater. Previous findings support that cognitive and psychiatric signs can precede motor signs by several years^{10, 30-35}. This is even more stressed by the finding that about 21% of participants without any motor signs were already clinically diagnosed with HD based on psychiatric and/or cognitive problems. This implies that the TMS cut-off score of >5 , as used in research, only distinguished between pre-motormanifest and motormanifest participants and ignores all other HD symptoms.

Unfortunately, no consensus has been achieved on when psychiatric and/or cognitive signs are disease-specific and which instruments should be used for making a distinction between purely premanifest and manifest participants. More studies are, therefore, needed to investigate thoroughly the progression of psychiatric and cognitive problems throughout the disease and to be able to advise which instrument is useful for identifying psychiatric and cognitive problems related to HD. Also the use of the TMS cut-off score of >5 for motor abnormalities is not always unambiguous as

shown in the Leiden cohort. Some participants were even clinically diagnosed with HD based on motor abnormalities without reaching the TMS threshold. This suggests that certain items on the motor UHDRS are more associated with HD signs than others, and a re-evaluation of the UHDRS might be useful. At this point in time, in designing research with purely premanifest HD, we can only advise that the clinical impression of the professional rater about whether any signs related to HD are present, should be taken into consideration. This could be implemented according to the newly proposed clinical diagnostic criteria which include and evaluate all HD signs³⁶.

Interestingly, the clinically diagnosed PMHD participants were enrolled in REGISTRY after a shorter period between estimated disease onset and baseline visit than the MHD group. This supports the findings that cognitive and/or psychiatric problems are more devastating for patients and caregivers^{37, 38} and, therefore, they attend the outpatient clinic earlier. Moreover, patients who attend an outpatient clinic at a younger age and have regular follow-ups have a higher chance that HD signs will be identified by a professional at an early age.

Surprisingly, the occurrence of psychiatric symptoms was relatively low in the Leiden cohort compared to the estimates found in the literature³⁹. One explanation could be that these patients are not recognized, under-diagnosed, referred directly to psychiatrists, or not willing to participate in studies.

In conclusion, the Leiden REGISTRY cohort is characterized by a majority of participants who already experienced symptoms related to HD but who were still relatively functionally independent at time of enrolment. For the majority of clinically diagnosed participants, disease onset was based on motor symptoms followed by psychiatric and/or cognitive symptoms. As this (Leiden) cohort consisted mainly of early HD patients, it is particularly interesting for future clinical trials with the focus on delaying disease onset and/or progression.

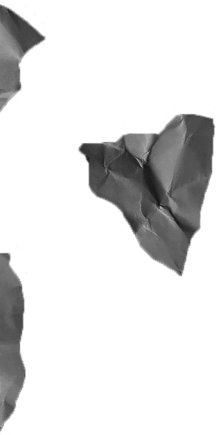
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Chapter 3

Cognitive decline in Huntington's disease expansion gene carriers

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Abstract

Background: In Huntington's disease (HD) cognitive decline can occur before unequivocal motor signs become apparent. As cognitive decline often starts early in the course of the disease and has a progressive nature over time, cognition can be regarded as a key target for symptomatic treatment. The specific progressive profile of cognitive decline over time is unknown.

Objective: The aim of this study is to quantify the progression of cognitive decline across all HD stages, from pre-motormanifest to advanced HD, and to investigate if CAG length mediates cognitive decline.

Methods: In the European REGISTRY study 2,669 HD expansion gene carriers underwent annual cognitive assessment. General linear mixed models were used to model the cognitive decline for each cognitive task across all disease stages. Additionally, a model was developed to evaluate the cognitive decline based on CAG length and age rather than disease stage.

Results: There was significant cognitive decline on all administered tasks throughout pre-motormanifest (close to estimated disease onset) participants and the subsequent motormanifest participants from stage 1 to stage 4. Performance on the Stroop Word and Stroop Color tests additionally declined significantly across the two pre-motormanifest groups: far and close to estimated disease onset.

The evaluation of cognition performance in relation to CAG length and age revealed a more rapid cognitive decline in participants with longer CAG length than participants with shorter CAG length over time.

Conclusion: Cognitive performance already shows decline in pre-motormanifest HD gene expansion carriers and gradually worsens to late stage HD. HD gene expansion carriers with certain CAG length have their own cognitive profile, i.e. longer CAG length is associated with more rapid decline.

Introduction

Huntington's disease (HD) is an autosomal dominant inherited, progressive neurodegenerative disorder caused by a CAG repeat expansion in the huntingtin gene on chromosome 4¹ and is characterized by motor and psychiatric symptoms, and cognitive decline. Typically, a formal clinical diagnosis of HD is based on the appearance of unequivocal motor signs². The importance of psychiatric symptoms and cognitive decline has become more recognized and new guidelines have been proposed, which include these signs for clinical diagnosis³. Still, these signs are insufficiently specified and to date it is arbitrary when these signs are disease specific and should be taken into consideration for a clinical diagnosis³.

In the last decade, there has been a growing interest in the cognitive decline and many studies have focused on this aspect in HD. Nevertheless, there have been relatively few longitudinal studies to date to track the progression of cognitive functioning, and their results have been somewhat conflicting⁴⁻⁹ which can be attributed to the diversity of study designs. The diversity in methodology is reflected in the selection of tasks administered, length of follow-up, sample size and characteristics of participant population. These different studies suggest that certain types of cognitive tasks are sensitive to particular stages of HD to track disease progression: simple psychomotor tasks have been shown to be particularly sensitive in the 5-10 years preceding motor symptoms onset¹⁰⁻¹³ whereas performance on tasks of memory and executive function appear to decline particularly around the time of clinical disease onset^{10, 11, 14, 15}. It has also been demonstrated that simple psychomotor tasks are more sensitive to use in longitudinal studies than more complex tasks of executive function in pre-motor manifest and early HD^{4, 16, 17}. Thus far studies of cognition in HD over time have been limited to the study of pre-motormanifest and/or early HD. To our knowledge no studies have longitudinally examined cognition across all separate disease stages with a large sample size, which is essential to fully understand the natural course of cognitive decline in HD. It is important to know if specific cognitive domains gradually worsen over time or if, and when, floor and ceiling effects occur. This knowledge is particularly useful for future clinical trials targeting cognition, in order to evaluate the effectiveness of potential interventions in stopping or slowing down cognitive decline in HD. In HD it is known that CAG negatively influences disease progression, i.e. earlier disease onset with longer CAG length¹⁸. As cognitive decline is associated with brain atrophy^{15, 19}, which in turn is also negatively influenced by CAG length¹⁸, it is of interest to investigate if CAG length also mediates cognitive deterioration. If indeed CAG influences cognitive decline this could help to explain why HD gene carriers develop cognitive deficits at different ages. From a clinical point of view this could

raise more awareness that certain individuals have a higher risk at developing early cognitive deficits. Additionally, this information can be used to inform the design of future trials, e.g. in defining the study population or to determine whether expensive MRI protocol is necessary or if cognitive tasks would be sufficient.

In 2004 the European Huntington's Disease Network (EHDN) launched the observational REGISTRY study²⁰, in which HD expansion gene carriers undergo annual assessment of motor function, cognition, behavior, and day-to-day functioning. After years of longitudinal data collection, the REGISTRY study provides the opportunity to explore cognitive change across all HD stages. The aim of this study is to evaluate the progression of cognitive decline in HD throughout the disease stages, from pre-motormanifest to advanced HD, and to evaluate if CAG length mediates cognitive decline. The second aim is to assess whether the individual cognitive tasks are efficacious for measuring cognitive decline across all disease stages or if the task sensitivity is disease stage specific.

Methods

Data was acquired from the European, multicenter, longitudinal, observational REGISTRY study which was conducted in 17 countries. All participating sites acquired ethical approval before conducting the study and all participants gave written informed consent. Study assessments were administered by trained professionals and all data was monitored. For a full description of the study, see Orth et al.²⁰.

Participants

By April 2014, a total of 2,815 participants met the criteria for the requested data cut; i.e. all participants with confirmed CAG length expansion of ≥ 36 and cognitive assessment. After receiving the data cut, only participants with CAG length between 38 and 50 (both inclusive) and visits of participants with age between 25 and 80 (both inclusive) at time of assessment were included in the analysis. Resulting in a total of 2,669 participants for analysis with a mean of 3.7 annual visits, ranging from one to 12 visits per participants (table 1).

Participants were defined as pre-motormanifest if their total motor score on the Unified Huntington's Disease Rating Scale (UHDRS) was less than or equal to five, indicating no substantial motor signs. This pre-motormanifest group was further divided into a group which is far from estimated disease onset (preA) and a group which is close to estimated disease onset (preB), split at the median of the estimated disease onset (median: 13.3 years) according to the formula developed by Langbehn

and colleagues²¹⁻²⁴. The manifest participants were divided into the five disease stages as defined by Shoulson et al.²⁵, using the total function capacity scale of the UHDRS.

Assessments

All participants were clinically assessed on an annual basis with a time window of $\pm$ three months. The time window was not strictly enforced and it was possible to assess participants outside their time window or even miss annual visits without exclusion of the study.

The REGISTRY cognitive battery consisted of the UHDRS' cognitive tasks: Phonemic Verbal Fluency (total number correct in three minutes), the three conditions of the Stroop-Color-Word-Interference task: word reading, color naming and interference condition (total number correct within 45 seconds for each condition), and Symbol Digit Modalities task (total number correct in 90 seconds)²⁶. In 2010, the Categorical Fluency task was added to the cognitive battery (total number correct in one minute)²⁷. On each task a higher numerical score indicates higher cognitive performance. These raw cognitive scores at each visit were used for the statistical analysis.

Depression was assessed by means of the behavior assessment of the UHDRS²⁶ or the Problem Behavior Assessment – short version (PBA-s)²⁸.

Medication use was also recorded as part of the REGISTRY study; medications with possible influence on cognitive performance were grouped into the following categories: benzodiazepine, antidepressant, antipsychotic, atypical antipsychotic, anticonvulsant, opioids, antiparkinsonian and others.

Statistical analysis

A linear mixed models analysis was used because it allows for varying time windows, an unequal number of visits and missing values²⁹. Two models were designed to understand the progressive nature of cognitive decline in HD.

First, change over time in performance on the cognitive tasks as a function of disease stage was analyzed, adjusting for depressive mood, sex, years of education, medication use, study site and third order polynomial function of age. The results of this longitudinal model were used to analyze if group differences were present in rate of cognitive decline by disease stage. Per task it was analyzed if there was a significant difference in cognitive performance between one stage and the subsequent stage; e.g. significant difference between disease stage 1 and disease stage 2. It is important to note, as participants came in for testing over several years, it was common that participants progressed from one disease stage to the next. In order to

compare cognitive performance between disease stages participants were allowed to transfer into the next category of disease stage on a subsequent visit dates to maintain homogenous groups.

The second model assessed change over time in performance on the cognitive tasks as a function of CAG length and third order polynomial function of age, adjusting for depression, sex, years of education, medication use, and study site. Per task it was analyzed if there was a significant difference in cognitive performance between different CAG lengths for a certain age. For this between group comparison subsequent CAG lengths are compared to each other by steps of 2 (from CAG length 38 to 48) at certain ages (30, 45, 60). For example, task performance of participants with CAG lengths of 38 and 40 was compared for ages 30, 45, and 60.

For both models multiple testing was performed and therefore a conservative significance level was used: $p = 0.05$ divided by the number of performed tests (i.e. either $p = 0.008$ or 0.01).

Results

The baseline characteristics are presented in table 1. The seven groups differed significantly from each other on the following variables: age ($F(6,2662)=124.86$, $p<0.01$), years of education ($F(6,2524)=23.08$, $p<0.01$), CAG length ($F(6,2662)=37.89$, $p<0.01$), and gender $\chi^2(6)=42.56$, $p<0.01$).

Cognitive task performance based on disease stage

For this section, the data was longitudinally modelled in order to assess group differences (i.e. disease stage) as described in the methods section. Performance on all cognitive tasks declined throughout the different groups (see figure 1). As participants progressed from preA to stage 5 the cognitive performance of the Stroop Word Test declined most rapidly. More precisely, performance on the Stroop Word Test decreased

Table 1: Group characteristics

	PreA	PreB	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Gender (m/f) baseline visit ^a	118 / 219	108 / 143*	423 / 365*	357 / 386	234 / 239	25 / 46	1 / 5
Gender (m/f) last visit ^a	78/162	69/115*	250/238*	352/316	384/399	120/150	13/23
Number of visits ^b	3.8 (1-8)	4.2 (1-12)	3.8 (1-10)	3.6 (1-9)	3.1 (1-9)	2.6 (1-7)	2.0 (1-2)
Age (years) ^c	36 (9)*	42 (10)*	48 (11)*	52 (11)*	54 (11)*	55 (10)	58 (11)
Education (years) ^c	13 (4)	13 (4)*	12 (4)*	11 (4)*	11 (3)*	10 (4)	11 (4)
CAG length ^c	41 (2.0)*	44 (2.6)*	44 (2.8)	44 (2.8)	44 (2.6)	44 (2.7)	43 (3.7)

PreA: pre-motormanifest A; PreB: pre-motormanifest B
^atotal number; significant difference between the groups marked with *
^bParticipants were grouped based on baseline characteristics; mean (range)
^cmean (standard deviation); significant difference between the groups marked with *

on average by 7.5 correct answers from one group to the subsequent group: preA scored significantly higher than the preB group ($b=5.35$, $t(7895.31)=5.52$, $p<0.01$). PreB was able to read on average seven more words than stage 1 ($t(7849.43)=9.85$, $p<0.01$). Stage 1 scored significantly better on the Stroop Word test than stage 2 ($b=8.34$, $t(7524.45)=18.71$, $p<0.01$). Comparing stage 2 with stage 3, the former showed a significantly better performance ($b=9.60$, $t(7366.26)=22.67$, $p<0.01$). Stage 3 was able to read 8 more words within the time frame than stage 4 ($t(7139.92)=11.90$, $p<0.01$). There was a non-significant trend towards better performance on the Stroop Word test in stage 4 than stage 5 ($b=7.50$, $t(6924.37)=3.40$, $p<0.05$).

In contrast to the results of the Stroop Word Test, no pronounced and rapid decline in cognitive performance of the Phonemic Verbal Fluency Test was found. Task performance on the Phonemic Verbal Fluency Test was similar for the preA and preB groups ($b=1.66$, $t(8340.90)=3.03$, $p>0.05$) as well as for stage 4 and stage 5 ($b=0.39$, $t(6871.93)=0.28$, $p>0.05$). Throughout preB to stage 4 there was a decline by on average three correct responses. This decline was statistically significant (see table 2), but the slope of the decline was relatively flat (see figure 1), i.e. the Phonemic Verbal Fluency Test showed no pronounced discrimination between the disease stages.

The results of the other administered tasks were somewhere in between the results of the Stroop Word Test and the Phonemic Verbal Fluency test: there was a significant difference in cognitive performance between all disease stages on the Stroop Color Test (table 2) but the slope for decline was less steep for the Stroop Color Test than for the Stroop Word Test (figure 1). Significant difference on performance on the Stroop Interference Test and the Symbol Digit Modalities Test was found between all disease stages except between stage 4 and stage 5 (table 2); i.e., the slope flattens at the end. The same result was found for the Categorical Verbal Fluency Test, but overall the decline was less pronounced than for the Stroop Interference and the Symbol Digit Modalities test.

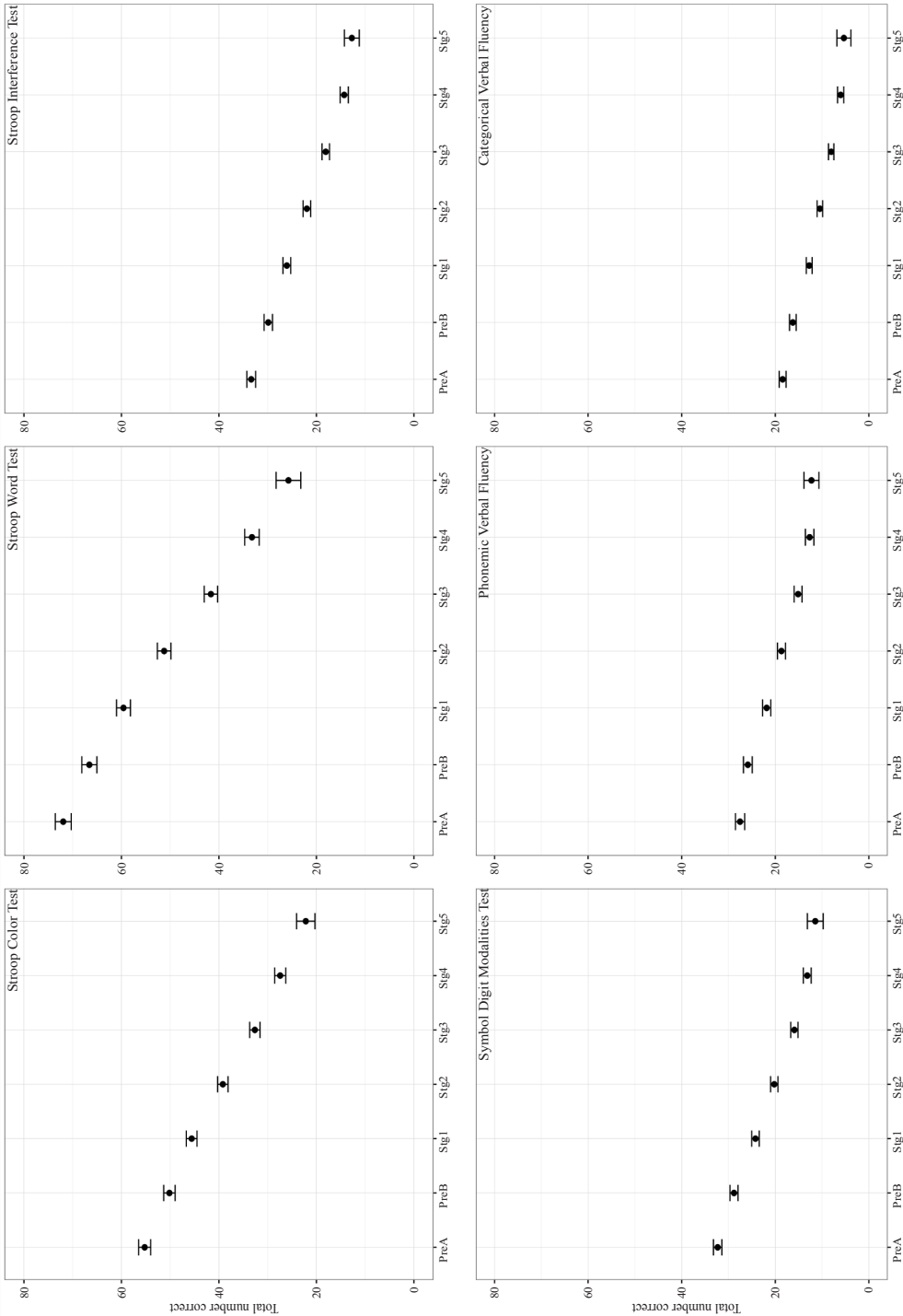
Table 2: Results of the linear mixed effects models; comparing subsequent disease stages per cognitive task

	N	PreA – PreB	PreB – Stg1	Stg1 – Stg2	Stg2 – Stg3	Stg3 – Stg4	Stg4 – Stg5
Phonemic verbal fluency ^a	2548	1.66 (0.55)	4.03 (0.40)*	3.16 (0.26)*	3.56 (0.25)*	2.46 (0.42)*	0.39 (1.40)
Stroop Color ^a	2554	5.08 (0.70)*	4.56 (0.51)*	6.40 (0.33)*	6.56 (0.32)*	5.20 (0.53)*	5.25 (1.62)
Stroop Word ^a	2526	5.35 (0.97)*	7.00 (0.71)*	8.34 (0.45)*	9.60 (0.42)*	8.41 (0.71)*	7.49 (2.21)
Stroop Interference ^a	2540	3.50 (0.52)*	3.81 (0.39)*	4.10 (0.25)*	3.90 (0.24)*	3.78 (0.42)*	1.57 (1.37)
Symbol Digit Modalities Test ^a	2521	3.49 (0.49)*	4.59 (0.36)*	4.02 (0.23)*	4.29 (0.22)*	2.76 (0.40)*	1.71 (1.53)
Categorical Fluency ^a	1410	2.18 (0.51)*	3.50 (0.42)*	2.27 (0.27)*	2.42 (0.25)*	2.02 (0.42)*	0.69 (1.44)

PreA: pre-motormanifest A; PreB: pre-motormanifest B; Stg1: disease stage 1; Stg2: disease stage 2; Stg3: disease stage 3; Stg4: disease stage 4; Stg5: disease stage 5

^a Estimate (SE); * sig < 0.008.

Figure 1: Performance on all cognitive tasks per disease stage



PreA: pre-motormanifest A; PreB: pre-motormanifest B; Sig1: disease stage 1; Sig2: disease stage 2; Sig3: disease stage 3; Sig4: disease stage 4; Sig5: disease stage 5; Note: Group comparison of longitudinal data is presented. Participants were allowed to switch stages as disease progressed

Cognitive task performance based on CAG length and age

For this section, the data was longitudinally modelled according to the second described model in the methods section, and these results were used to compare cognitive performance between different CAG length for certain ages. Here we only display the comparison on Stroop Word test performance between CAG length of 42 and CAG length of 44 at three different ages. Due to the chosen model with interaction between CAG lengths and a third order polynomial function of age the group comparison of the other CAG lengths for this test revealed the same results at these ages; i.e. if the distance between two CAG lengths is the same then the distance between the cognitive performance is the same as well.

Task performance on the Stroop Word Test was mediated by CAG length and age; i.e. participants with a higher CAG length showed a more rapid decline than participants with a lower CAG length over time, see figure 2. Differences on task performance between CAG length 42 and 44 increased as a function of age. More precisely, performance on the Stroop Word Test was significantly higher for participants with a CAG length of 42 than for participants with CAG length of 44 at age 30 ($b=5.09$, $t(3831.8)=10.25$, $p<0.01$). The score on the Stroop Word Test was 12 points higher for participants with CAG length of 42 compared to participants with CAG length of 44 at age 45 ($t(3674.51)=32.57$, $p<0.01$). At age 60 participants with a CAG length of 42 scored significantly higher than participants with CAG length of 44 ($b=16.03$, $t(3870.75)=26.9$, $p<0.01$).

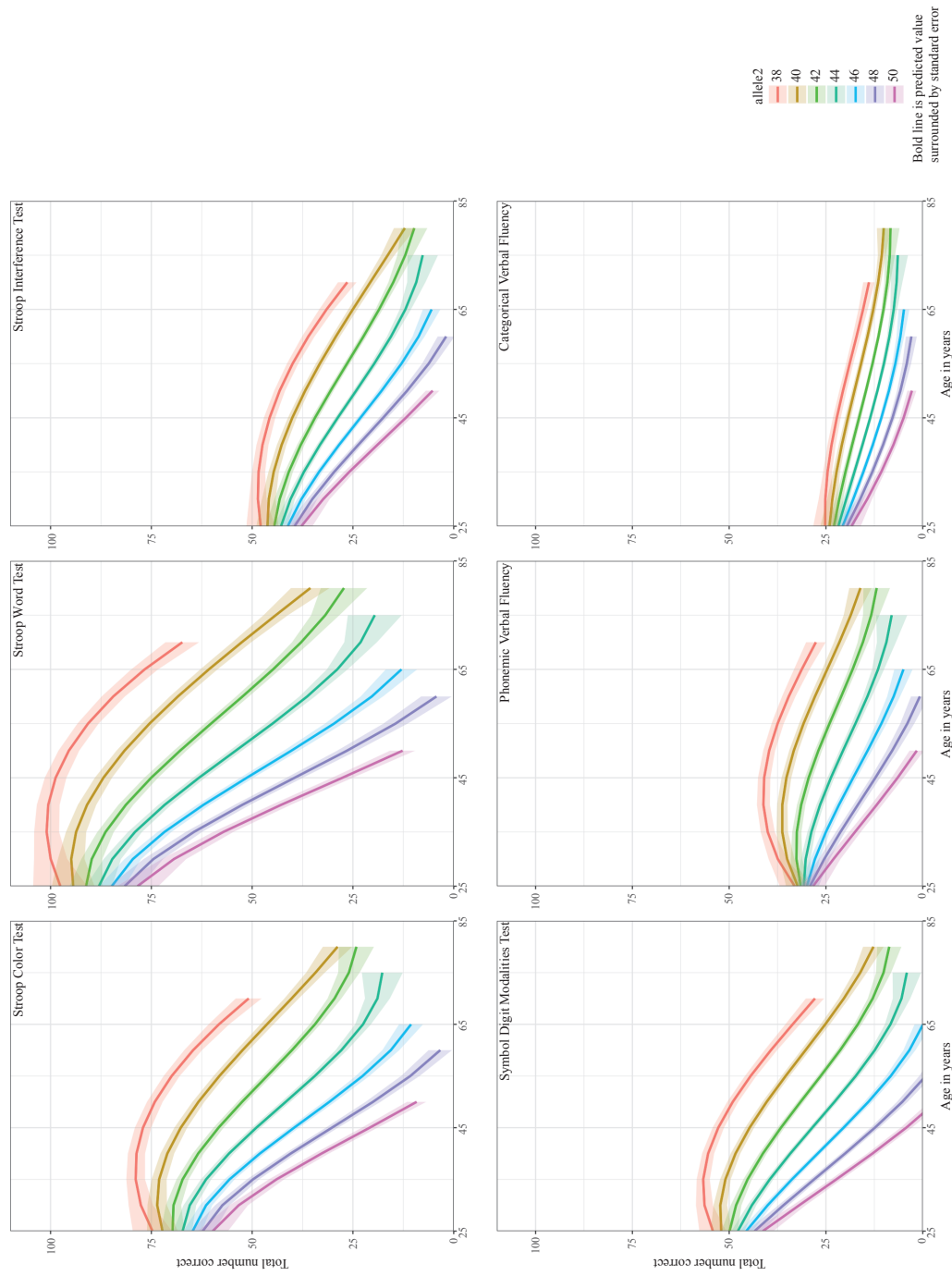
In contrast to the Stroop Word Test the Categorical Verbal Fluency Test did not discriminate well between the different CAG lengths. As participants aged the performance worsened but the different lines stay close to each other (see figure 2). For the Stroop Color Test, Strop Interference Test, Symbol Digit Modalities Test and Phonemic Verbal Fluency test significant different was found for all CAG comparisons at age 30, 45, 60. Figure 2 shows that for these tasks the separate lines stayed closer

Table 3: Comparing CAG length 42 with 44 on cognitive task performance based on longitudinal model

	N	For age 30	For age 45	For age 60
Phenomic verbal fluency ^a	2548	2.39 (0.29)*	5.75 (0.22)*	6.77 (0.36)*
Stroop Color ^a	2554	4.05 (0.37)*	9.37 (0.28)*	12.26 (0.46)*
Stroop Word ^a	2526	5.09 (0.50)*	11.90 (0.36)*	16.03 (0.60)*
Stroop Interference ^a	2540	2.70 (0.27)*	5.63 (0.20)*	6.84 (0.34)*
Symbol Digit Modalities Test ^a	2521	4.08 (0.27)*	8.09 (0.21)*	8.95 (0.34)*
Categorical Fluency ^a	1410	1.80 (0.22)*	2.88 (0.15)*	2.83 (0.23)*

^a Estimate (SE); * sig < 0.01.

Figure 2: Cognitive performance plotted against age and CAG length



together than for the Stroop Word Test. The results for all cognitive tasks are presented in table 3 and figure 2.

Discussion

This current study evaluates the progression of cognitive decline in HD, from pre-motormanifest to late stage. Performance on the REGISTRY cognitive battery significantly worsened as HD progressed from preA to disease stage 4 with the exception of the Phonemic Verbal Fluency Test in the pre-motormanifest phase (i.e. no significant difference between preA and preB). The early decline of the other five cognitive tasks supports the notion that cognitive decline starts early in the disease process and even proceeds overt motor signs^{8, 10-12}. By direct comparison of the cognitive tasks, taking into consideration the clinical relevance of decline, we demonstrated that the Stroop Word and Stroop Color Test are the most sensitive of the REGISTRY battery in discriminating between the different disease stages. These findings are supported by previous observations that the Stroop Word and Stroop Color Test are sensitive in pre-motormanifest⁸ and early HD³⁰. We have now demonstrated that this remains so over the disease course and that these tasks remain sensitive in later stages of HD. These results are in line with suggestions of previous studies that simple psychomotor tasks are the most appropriate to use in longitudinal research in HD^{4,16,17}. This information is particularly useful for clinical trials as cognition is seen as a key target for symptomatic treatment.

It has been argued that because the Stroop Word test and Stroop Color test have high linguistic demands they should not be included in test batteries for HD as clinical trials rely heavily on multicenter research across several countries³¹. Nevertheless, the REGISTRY study was conducted in several countries with different languages and with correcting for study site we conclude that these tasks are sensitive in tracking psychomotor speed across multilingual HD populations. Additionally, these tasks are relatively easy to administer, efficient, and do not require fine motor skills. Therefore, we would strongly recommend to include the Stroop Word and Stroop Color test in HD clinical trials. All cognitive tasks showed a floor effect from disease stage 4 to disease stage 5; i.e. none of the tasks discriminated between these two stages. This illustrates that it is difficult to identify cognitive tasks in advanced HD, because of the severe cognitive deterioration in this stage. To our knowledge no study has identified a suitable cognitive task for late stage HD. It is a challenge to administer cognitive tasks in this patient group because many patients are not able to write or speak anymore.

A challenge when analyzing data with the most commonly examined disease stages is that no one continuous variable is used for defining all groups but rather different variables are used for defining pre-motormanifest groups and motormanifest groups. For the later the total functional capacity score (TFC) is used, however, the inter rater reliability of this scale is unknown, which could be challenging for multi-center studies. Therefore, we chose to also evaluate the data in a different way. It is known that CAG length influences disease progression; longer CAG length indicates earlier disease onset and faster disease progression³². Therefore, we plotted cognitive performance in relation to CAG length and age. These patient characteristics are objective and therefore more suitable variables than disease stage to investigate the natural course of cognitive decline in HD. This approach revealed that participants with a certain CAG length follow their own cognitive performance curve: Individuals with a longer CAG length show a more rapid cognitive decline as individuals with a shorter CAG length. This is in line with the findings from Paulsen et al.⁸ in the pre-motormanifest group. The results in general support that CAG length highly influences disease progression³², including cognitive decline. More precisely, the relationship between CAG length and cognitive decline over time was most pronounced for tasks of psychomotor function, i.e. Stroop Color and Stroop Word Test, rather than tasks relying on executive function, i.e. Stroop Interference and Phonemic Verbal Fluency Test. A possible explanation for the greater sensitivity of psychomotor tasks is that the role of the striatum is reflected in execution of these more automated tasks^{17, 33}. As the striatum starts to degenerate early in the course of HD³⁴ it seems logical that functions relying on the involvement of the nucleus caudate decline early on and are progressive in HD, such as psychomotor speed.

A limitation of this study was that REGISTRY was not designed to thoroughly capture cognitive decline in HD but rather to map disease progression of several domains in HD including cognition. As the REGISTRY study was designed to include also moderate to advanced HD patients the cognitive battery was rather short. We acknowledge that other studies purely focusing on cognition in HD have utilized a wider range of cognitive tasks³¹. However, given the large sample size available, representing all stages of disease across multiple sites and countries, our results provide a valuable contribute to the understanding of cognitive decline in HD.

Another limitation is that no control group with annual cognitive testing was available in the REGISTRY database. Thus, we were not able to compare the cognitive decline in HD to a control group population. Another challenge of the REGISTRY database was that a large number of participants were included and small differences between groups can result in statistical significant differences with large sample size. Therefore, we also evaluated if the cognitive decline was clinical relevant: for example

we have found a statistical significant decline for the phonemic verbal fluency test but evaluated a decline of on average three points as not clinically relevant and concluded that this task does not discriminate sufficiently between the different groups.

In conclusion, cognitive performance is negatively influenced by longer CAG length and worsens with age. The Stroop Word and Stroop color test are sensitive in tracking psychomotor speed in HD in all stages and we recommend inclusion of these tasks in cognitive batteries for clinical trials.

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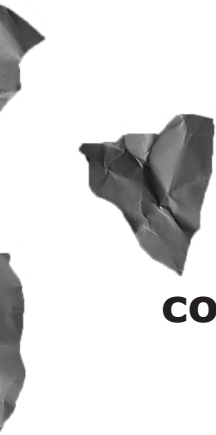
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Chapter 4

Influence of medication use on cognitive performance in Huntington's disease

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Submitted

Abstract

Background: In Huntington's disease (HD), cognitive decline starts early and continues as the disease progresses. As cognition is recognized as a potential clinical trial endpoint, it is essential to identify factors which can influence cognitive performance in HD. Medication treating non-cognitive neuropsychiatric disturbances and tetrabenazine, which are generally known to have a negative influence on cognition, are often prescribed in HD patients.

Objective: This study evaluates whether cognitive performance differs between users and non-users of these drugs at HD clinics throughout Europe.

Methods: In total, 2,289 participants of the REGISTRY study fulfilled the criteria for cognitive assessment and recorded medication use at their baseline visit. Participants were grouped according to disease stage and medication use: i.e. benzodiazepines, selective serotonin reuptake inhibitor (SSRI) antidepressants, antipsychotics, atypical antipsychotics and tetrabenazine. Univariate general linear model analysis was conducted.

Results: Medication use was common in the REGISTRY cohort. In total 42% of the participants used any of the predefined drugs whereas percentage of medication used increased from 12% in the pre-motormanifest stage to 81% in the advanced motormanifest stages. A significant effect of antipsychotic use on the Stroop Word Test was found in the early HD stages.

Conclusions: No effect of benzodiazepines, SSRIs, atypical antipsychotics and tetrabenazine on cognitive performance was found. Only the use of antipsychotics had a negative effect on cognitive performance in the early stages and should be considered when designing clinical trials with cognition as clinical endpoint.

Introduction

Huntington's disease (HD) is an autosomal dominant inherited, progressive neurodegenerative disease caused by a CAG repeat expansion in the huntingtin gene on chromosome 4¹. HD is characterized by a triad of symptoms: motor abnormalities, behavioral signs and cognitive deterioration². As the exact location of the expanded gene is known, individuals at risk can be tested for the expanded HD gene before any symptoms or signs appear.

Motor abnormalities are the most characteristic signs of HD, but gene-expansion carriers and caregivers perceive cognitive decline and behavioral signs to be the most burdensome^{3, 4}. These can precede motor signs by several years⁵⁻¹³. As cognitive decline starts early and continues as the disease progresses, cognition is recognized as a potential endpoint in clinical trials. Nowadays, a broad range of cognitive domains is evaluated in almost all clinical trials¹⁴, including psychomotor speed which starts to slow down early on and continues to worsen throughout the later HD stages^{15, 16}. It is essential to know which factors could possibly influence cognitive performance in HD in order to evaluate whether potential interventions could stop or slow down cognitive decline in HD.

As there is no cure for HD, medication is prescribed to manage HD symptoms. Many HD gene expansion carriers take psychotropic medication for behavioral and depressive signs; i.e. medication targeting non-cognitive neuropsychiatric signs^{2, 17}. For instance, one study showed that in a European HD population 84% of HD patients received symptomatic treatment¹⁸. Unfortunately, there is only low level of evidence on the effect and side effects of using certain medication in HD, most prescriptions are based on clinical experience^{19, 20}. Depression is common in HD and is often treated with antidepressants with a first choice of selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). There is some evidence that some SSRIs might have a positive effect on cognition in the prodromal phase of HD, i.e. before any definite HD symptoms are present²¹. Behavioral symptoms, e.g. anxiety, are often treated with benzodiazepines²⁰. However, the effect of benzodiazepine on cognitive performance in HD is not well documented. We do know from other studies that the higher the intake of benzodiazepines the greater risk of cognitive impairment and in the elderly population it is related to a higher risk of dementia^{22, 23}. In a French study it was shown that also the use of antipsychotics is common in HD and some have a negative effect on cognition²⁴. In another study it was found that HD patients using antipsychotic medication (classical and atypical) or tetrabenazine had a faster disease progression²⁵. By taking these reports together, there is some indication that the use of these types of medication have an impact on cognitive performance on HD.

Some of these studies only evaluated whether using one or few drugs has an effect on cognitive performance, but not the entire medication group was evaluated. But for many clinical trials individuals are not allowed to take any of these drugs because it might influence the outcome measures.

Therefore, the aim of this observational, explorative study is to investigate whether there is a difference in cognitive performance between HD gene-expansion carriers using medication targeting non-cognitive neuropsychiatric signs or tetrabenazine compared to non-users in a clinical HD population. We expect that the SSRI group has the same cognitive performance as non-users. For all other medication groups, we expect that users display a more impaired cognitive performance. This is evaluated in a large HD population seen at several specialized HD clinics throughout Europe, no medication use was adapted for this study.

Methods

Participants

REGISTRY is a European, multicenter, longitudinal, observation study, facilitated by the European Huntington's Disease Network (EHDN). A total of 2,289 confirmed HD gene expansion carriers with a CAG > 39 of the REGISTRY study were included; all completed the cognitive assessment at baseline. Participants without any motor signs, as defined by a total motor score (TMS) of ≤ 5 on the Unified Huntington's Disease Rating Scale (UHDRS)¹⁴, were considered pre-motormanifest. These participants were further divided into 'far from estimated disease onset' (pre-A) and 'close to estimated disease onset' (pre-B), calculated by the Langbehn formula²⁶⁻²⁹ and split at the median of 13.3 years. Participants with unequivocal motor symptoms, TMS > 5, were further divided into disease stages based on total functional capacity scale³⁰. The last two disease stages were merged into one due to the small number of participants in these two groups, stages 4 and 5. Ethical approval was obtained for all sites and all participants gave written informed consent. The study was conducted by trained professionals and all data were monitored. For a full description of the study, see Orth et al.³¹.

Assessments

HD gene expansion carriers were assessed for day-to-day functioning, motor, behavior and cognition. The cognitive battery of the Unified Huntington Disease Rating Scale (UHDRS)¹⁴ was used to evaluate cognitive performance: letter verbal

fluency test (total number correct in one minute for three letters; as the study was administered in different countries, the letters also differed by country), Stroop Color-Word-Interference Test: word-reading, color-naming and interference condition (total number correct for each condition in 45 seconds; here the colors are red, blue and green), and the Symbol Digit Modalities Test (total number correct in 90 seconds).

All medications used were recorded in the REGISTRY study. For analysis purposes, participants were grouped as follows: taking benzodiazepines, selective serotonin reuptake inhibitor (SSRI) antidepressants, antipsychotics, atypical antipsychotics or tetrabenazine. For more information on the exact medication taken, see supplementary appendix 1. Participants were allowed to take other medication prescribed for other conditions such as hypertension.

Statistical analysis

To assess whether there were group characteristic differences an ANOVA or, when appropriate, a chi-square test was used.

Univariate general linear model was applied to evaluate whether medication users performed differently on the cognitive tasks than non-medication users during the baseline visit. In this model, medication group and disease stage are added as fixed factors, gender, age, CAG length and years of education as covariates; interaction effect of disease stage and medication use was also added to the model. For the multiple comparison analysis, a conservative significant level was used: $p = 0.05$ divided by the number of tests performed (i.e. $p = 0.002$).

Table 1: Group characteristics

	PreA N=283	PreB N=239	Stage 1 N=712	Stage 2 N=619	Stage 3 N=378	Stage 4+5 N=58
Age ^a	34 (8)	42 (10)	47 (11)	51 (12)	53 (11)	54 (11)
CAG repeat length ^a	42 (2)	44 (3)	44 (3)	44 (3)	44 (3)	45 (4)
Years of education ^a	13 (3)	13 (7)	12 (5)	11 (4)	11 (6)	10 (3)
Sex (Male/Female) ^b	96/187	104/135	384/328	304/315	189/189	20/38

PreA: pre-motormanifest A; PreB: pre-motormanifest B

^aMean (standard deviation)

^bTotal number

Results

The six disease stage groups differed significantly from each other based on: age ($F(5,2283)=139.44$, $p<0.01$), years of education ($F(5,2152)=12.26$, $p<0.01$), CAG repeat length ($F(5,2283)=22.83$, $p<0.01$) and gender ($\chi^2(5) =39.59$; $p<0.01$), see table 1.

In total 58% of the participants did not use any medication. If disease stage was considered, the percentage of participants not taking medication gradually declined from pre-A (88%) to stages 4 and 5 (19%), see table 2. In addition, polypharmacy increased from pre-A (3%) to stages 4 and 5 (48%). About 85% of the medication users were already on medication for at least 2 months with stable doses.

The use of antipsychotics had a significant effect on the results of the Stroop Word Test ($F(1, 1993)=14.9$, $p=0.0001$), suggesting that participants using antipsychotics scored worse on the Stroop Word Test than non-users, see figure 1. Antipsychotics users in group stage 2 and stage 3 scored on average lower than then non-users (mean difference: 13 and 10, respectively). However, this effect disappeared with the interaction effect of all disease stages ($F(4, 1993)=0.47$, $p=0.76$). The use of benzodiazepines, SSRI antidepressants, atypical antipsychotics or tetrabenazine had no effect on cognitive performance on any of the administered tasks.

Discussion

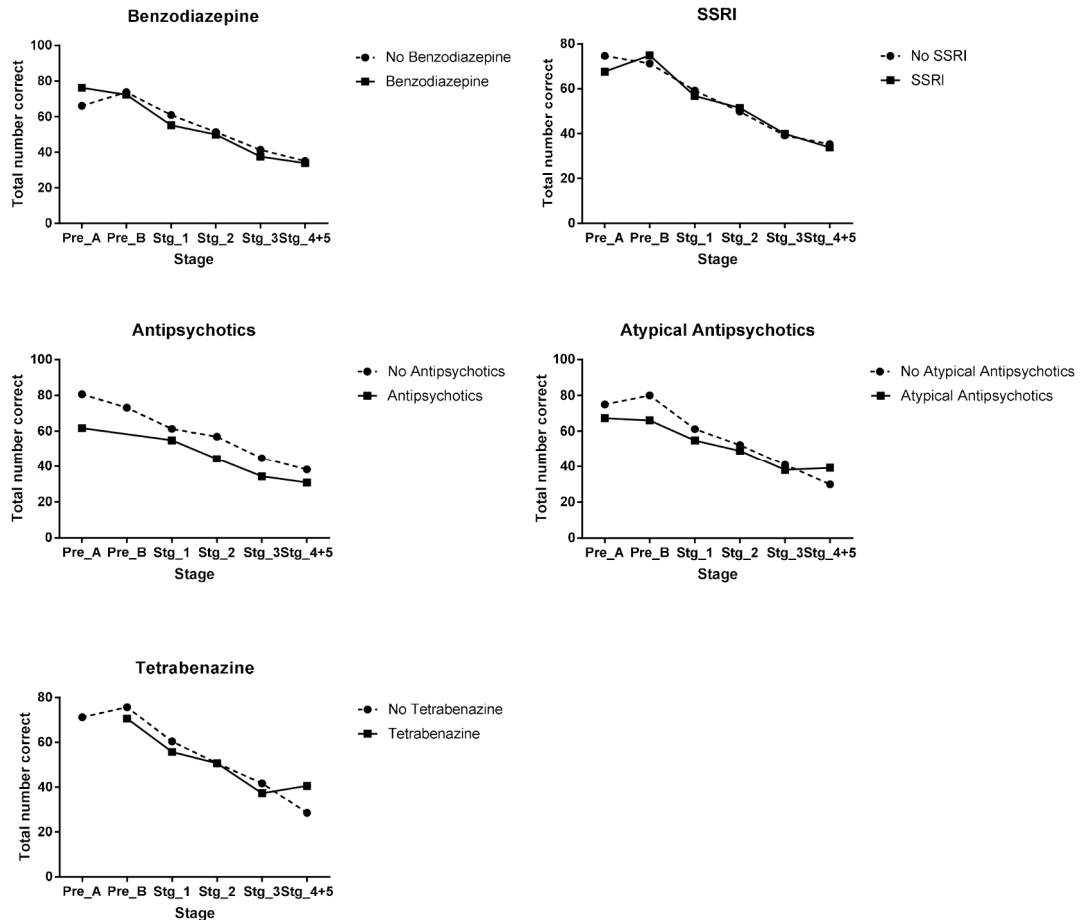
This study shows that about half of the HD-REGISTRY population used medication targeting non-cognitive neuropsychiatric disturbances and/or tetrabenazine. The percentage of HD gene carriers taking these medications increased from pre-motormanifest to the advanced HD. The most logical explanation for this increase throughout the disease stages is that advanced HD individuals have severe symptoms

Table 2: Total number of participants taking medications

	PreA N=283	PreB N=239	Stage 1 N=712	Stage 2 N=619	Stage 3 N=378	Stage 4+5 N=58
No medication ^a	251 (88%)	202 (85%)	463 (65%)	283 (46%)	113 (30%)	11 (19%)
Benzodiazepines ^a	6 (2%)	5 (2%)	23 (3%)	29 (4%)	9 (2%)	2 (3%)
SSRI ^a	16 (6%)	24 (10%)	84 (12%)	78 (13%)	43 (12%)	3 (5%)
Antipsychotics ^a	1 (<1%)	—	8 (1)	10 (2%)	14 (4%)	—
Atypical antipsychotics ^a	1 (<1%)	—	62 (9%)	86 (14%)	66 (17%)	13 (23%)
Tetrabenazine ^a	—	1 (1%)	6 (1%)	13 (2%)	9 (2%)	1 (2%)
Mix ^a	8 (3%)	7 (2%)	66 (9%)	120 (19%)	124 (33%)	28 (48%)

PreA: pre-motormanifest A; PreB: pre-motormanifest B
^aTotal number (%)

Figure 1: Performance on the Stroop Word Test per disease stage and medication group



which need to be managed with medication. In addition, the pre-motormanifest individuals might still benefit from non-pharmacological interventions which should first be explored in treating symptoms²⁰. Throughout disease progression symptoms become more severe, global functioning decreases and medication treatment becomes useful, supported by adjunctive therapies, to manage all symptoms³². Polypharmacy is common in HD due to the complexity of the disease and several symptoms which need to be addressed²⁰ which is supported by our results that about 40% of all medication users used a mix of the pre-defined medication groups.

By evaluating the effect of medication use on cognitive performance, we only found a negative effect of antipsychotic medication on a task measuring psychomotor speed, that is the Stroop Word Test, in the early HD phase. This is an important finding for future clinical trials, especially because the effect was found in the early stages. Future clinical trials will most likely focus on pre-motormanifest and/or early HD gene carriers to evaluate whether treatment influences disease progression in an early

stage of the disease to ensure the highest quality of life for the HD gene carriers. With our findings we would recommend to be cautious to include HD gene carriers using antipsychotic medication if cognition is an important outcome measure of a clinical trial.

Secondly, our study showed that the use of benzodiazepine, SSRI antidepressant, atypical antipsychotic or tetrabenazine has no effect on performance of the UHDRS cognitive battery in the clinical setting. Our finding that tetrabenazine has no effect on cognition is in line with the 80 week open label study of tetrabenazine in HD in which cognitive decline resembled the natural deterioration in HD³³. Regarding future clinical trials targeting cognition in HD, we advise that the use of benzodiazepine, SSRI antidepressant, atypical antipsychotic or tetrabenazine should be allowed if participants are on a stable dose and if there is no suggestion that these medications could have an adverse effect in combination with the investigational drug. This should make it easier to recruit participants for clinical trials as many HD gene carriers use these medications. It also allows to test an investigational drug in a cohort which more closely represents the population seen in clinics, rather than in a strictly pre-defined population and improves the chance to have a successful phase III study.

One of the limitations of this study is that we grouped together the most commonly used medications; i.e. treating slightly different acting agents in the same way. It is possible that one particular drug might have a relatively stronger effect on cognitive performance, but that this effect is masked by grouping several medications together. In addition, we chose to group the medication based on relatively broad categorization as used by the Dutch regulatory agency. These categorization is based on broad pharmacogenetics, we did not create more subgroups based on the mechanic profile of the acting agent. The reason for this is that most studies are based on animal or cell studies but we do not know how all the different acting agents work in the human brain or even in the diseased human brain. It might be of interest for future studies to explore this more extensively. Furthermore, we only looked at whether participants used medication, not at the exact doses taken, although we do know that the majority was on a stable dose. In addition, participants were allowed to take co-medications, such as antihypertensive drugs, combinations which could affect cognitive performance. On a positive note, the REGISTRY database provides an opportunity to look at real-life medication use and its effect on cognitive performance seen at the clinics.

To conclude, antipsychotics have a negative effect on cognitive performance in the early HD stages, whereas benzodiazepines, SSRIs, atypical antipsychotics and tetrabenazine seem to have no effect on cognitive performance in HD.

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Supplementary Appendix

Medications included in the different groups

Benzodiazepines: Alprazolam, Bromazepam, Brotizolam, Chlordiazepoxide, Clobazam, Clorazepate, Diazepam, Estazolam, Etizolam, Flurazepam, Loprazolam, Lorazepam, Lormetazepam, Midazolam, Nitrazepam, Oxazepam, Prazepam, Temazepam, Zolpidem, Zopiclone

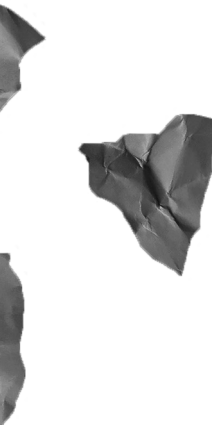
SSRI Antidepressants: Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline

Antipsychotics: Amisulpride, Chlorprothixene, Fluphenazine, Flupentixol, Fluspirilene, Haloperidol, Perphenazine, Pimozide, Pipamperone, Sulpiride, Thioridazine, Tiapride, Zuclopenthixol

Atypical antipsychotics: Aripiprazole, Clozapine, Melperone, Olanzapine, Quetiapine, Risperidone

Tetrabenazine





Chapter 5

Apathy and atrophy of subcortical brain structures in Huntington's disease: a two-year follow-up study

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Abstract

Background: Huntington's disease (HD) is characterized by motor and behavioral symptoms, and cognitive decline. HD gene carriers and their caregivers report the behavioral and cognitive symptoms as the most burdensome. Apathy is the most common behavioral symptom of HD and is related to clinical measures of disease progression, like functional capacity. However, it is unknown whether apathy is directly related to the neurodegenerative processes in HD.

Objective: The aim is to investigate whether an association between atrophy of subcortical structures and apathy is present in HD, at baseline and after 2 years follow-up.

Method: Volumes of 7 subcortical structures were measured using structural T1 MRI in 171 HD gene carriers of the TRACK-HD study and apathy was assessed with the Problem Behaviors Assessment-Short, at baseline and follow-up visit. At baseline, logistic regression was used to evaluate whether volumes of subcortical brain structures were associated with the presence of apathy. Linear regression was used to assess whether subcortical atrophy was associated with the degree of apathy at baseline and with an increase in severity of apathy over time.

Results: At baseline, smaller volume of the thalamus showed a higher probability of the presence of apathy in HD gene carriers, but none of the subcortical structures was associated with the degree of apathy. Over time, no association between atrophy of any subcortical structures and change in degree of apathy was found.

Conclusion: The presence of apathy is associated with atrophy of the thalamus in HD, suggesting that apathy has an underlying neural cause and might explain the high incidence of apathy in HD. However, no association was found between atrophy of these subcortical structures and increase in severity of apathy over a 2-year time period.

Introduction

Huntington's disease (HD) is an autosomal dominant inherited, progressive neurodegenerative disorder, characterized by motor and behavioral symptoms, and cognitive decline¹. Despite motor symptoms being the most specific to HD, the highest burden reported by HD gene carriers and caregivers are the cognitive and behavioral symptoms². Behavioral symptoms are diverse and the degree of severity fluctuates for the majority of symptoms throughout disease progression^{3, 4}. The most common behavioral symptoms are depressive mood, irritability, and apathy with a prevalence varying between 33% to 76% for each symptom dependent on definition, measurement tools used, and disease stage⁴. Of these symptoms, apathy is the only behavioral symptom that worsens as the disease progresses^{3, 5, 6}. In general, apathy has clinically been defined as “a disorder of diminished motivation, as manifested by reduced goal oriented behavior, emotions, and cognitions”⁷ and has a strong influence on psychosocial functioning, including relationships with partners and caregivers, e.g. apathetic individuals need to be prompted into starting daily tasks such as getting dressed^{8, 9}.

In HD, apathy can develop early in the course of the disease^{3, 10} and can even be mildly present in pre-motormanifest gene carriers^{5, 11}. Over the course of the disease, apathy worsens and eventually apathy is severely present in almost all late stage gene carriers³. In addition, apathy itself is negatively related to functional capacity, cognitive performance and motor impairment in HD¹². To better understand this behavioral symptom it is of interest to investigate the presence, severity and course of apathy in relation to the structural neurodegenerative processes that occur in HD.

Previous research has shown that apathy is caused by an interruption of the prefrontal cortex – basal ganglia circuit¹³, specifically the anterior cingulate circuit in the brain^{14, 15}. This circuit functionally connects the anterior cingulate cortex, nucleus accumbens, olfactory tubercle, and the ventromedial parts of the caudate nucleus and ventral putamen¹⁵. In subcortical neurodegenerative diseases, such as Parkinson's disease and progressive supranuclear palsy, there is evidence that atrophy of the basal ganglia results in apathy^{14, 16}. One study showed that the nucleus accumbens, an important subcortical structure of the reward circuit¹⁷, is associated with apathy in Parkinson's disease¹⁸. In HD, it is not clear whether the same or other structures are related to apathy. Since degeneration of the basal ganglia is a key feature of HD, it is likely that these structures are associated with the occurrence of apathy in HD.

Dependent on disease stage, grey matter atrophy can be found in almost all grey matter structures in HD^{6, 19, 20}. The caudate nucleus is known to already show atrophy in pre-motor manifest HD gene carriers, far from estimated disease onset^{19, 21-23} and

also shows the highest rate of degeneration as the disease progresses^{15, 24-26}, followed by the putamen^{11, 27-29}. Volume loss of the nucleus accumbens is already present in the late pre-motormanifest stage³⁰. It is expected that volume loss of subcortical structures of the anterior cingulate circuit will be related to the development of apathy in HD patients.

Given the progressive nature of apathy and its close relationship with measures of disease progression such as a decrease of cognitive function³¹, and general functioning³, it is possible that apathy is related to a neurodegenerative progress of subcortical gray matter in HD. Therefore, the aim of this study is to investigate the relationship between volume loss of subcortical structures and apathy in HD and whether there are changes over time.

Methods

Participants

TRACK-HD was a multicenter, longitudinal, observational study conducted at 4 different sites in the following cities: Vancouver (Canada), Paris (France), London (United Kingdom), and Leiden (the Netherlands). Of the 222 TRACK-HD participants, a total of 171 HD gene carriers (91 pre-motormanifest HD gene carriers and 80 motormanifest HD gene carriers) completed the baseline and follow-up visit after 24 months and were included in this study. HD gene carriers had a confirmed genetic testing, i.e. CAG $\geq$ 39. HD gene carriers with no substantial motor signs at baseline, as indicated with a total motor score (TMS) of $\leq$ 5 on the Unified Huntington's Disease Rating Scale (UHDRS), were defined as pre-motormanifest gene carriers. This pre-motormanifest group was further divided into 'far from estimated disease onset' (PreHD-A: more than 10.8 years) and 'close to estimated disease onset' (PreHD-B: less than 10.8 years), as calculated by the Langbehn formula³². The group consisting of motormanifest HD gene carriers, as defined by a TMS of $>$ 5, was further divided into disease stage 1 and disease stage 2 based on the Total Functional Capacity (TFC) score³³. All participating sites acquired ethical approval and all participants gave written informed consent prior study procedures. The study was conducted by trained professionals and all data was monitored, for a full description of the study, see Tabrizi et al.¹¹.

Clinical measures

In addition to the collection of general sociodemographic and clinical characteristics, the short version of the Problem Behaviors Assessment (PBA-s) was administered. This is a semi-structured psychiatric interview designed for HD. The PBA-s consists of 11 items, each item measuring a different behavioral symptom such as apathy, depression and irritability. The PBA-s rates each behavioral symptom for both severity and frequency on a 5-point scale³⁴. Severity score ranges from absent (score 0) to severe (score 4) and frequency score ranges from absent (score 0) to every day/all day (score 4). In this study, both the product score of severity and frequency of the apathy item, and only the severity score of the apathy item were used.

In this study two concepts were evaluated: the degree of apathy and the presence of apathy (i.e. apathy is or is not present). To indicate the degree of apathy the product score of the apathy item is used. To indicate whether apathy is present a cut-off of ≥ 2 on only the severity apathy item was used.

MRI acquisition and processing

All participants underwent 3T MRI scanning at baseline and after 24 months follow-up on a Siemens or Philips whole body scanner depending on study site. 3D-T1-weighted image volumes were acquired with the following imaging parameters, as reported in the supplementary appendix in Tabrizi et al.¹¹: TR=2200ms (Siemens)/7.7ms (Philips), TE=2.2ms (Siemens)/3.5ms (Philips), FA=10° (Siemens)/8° (Philips), FOV=28cm (Siemens)/24cm (Philips), matrix size 256×256 (Siemens)/224×224 (Philips), 208 (Siemens)/164 (Philips), sagittal slices to cover the entire brain with a slice thickness of 1.0mm with no gap between slices.

Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL)³⁵ was used for analyzing the structural T1-weighted images. Combined left and right volumes of the following seven subcortical brain regions were measured: nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, and thalamus, using FMRIB's Integrated Registration Segmentation Tool (FIRST)³⁶. All non-brain tissue was first removed from the T1-weighted image using a semi-automated brain extraction tool (BET), implemented in FSL³⁷. All images were registered to the Montreal Neurological Institute (MNI) 152-space standard image, using linear registration with 12 degrees of freedom³⁸. Then, segmentation of the seven subcortical regions was carried out and volumes for each region were calculated. Visual inspection was performed during the registration and segmentation steps. The volumes of these brain regions were corrected for estimated brain tissue volume, normalized for individual head size using SIENAX in FSL³⁹.

Statistics

To assess whether there were differences in the group characteristics at baseline an ANOVA or, when appropriate, a chi-square test was used.

The following groups of medication were identified to have a possible effect on the apathy scores: SSRIs, SNRIs, anti-psychotics, tricyclic antidepressants, bupropion, benzodiazepines, anti-epileptic, and tetrabenazine. One binary variable was created to indicate whether any of these medications were taken during the visit. We acknowledge that several different acting agents were treated as if they would have the same effect on apathy. Therefore, each model was run with and without the variable medication to identify the impact of medication on apathy.

A linear regression model between each subcortical brain structure and apathy product score was developed to investigate a possible association between volume of these structures and degree of apathy. As a next step a binary logistic regression between each subcortical brain structure and presence of apathy (i.e. apathetic versus not apathetic) was developed. Both regression models accounted for gender, medication use, group, age, study site and CAG length. As a last step depressive mood (severity*frequency) was added as additional covariate.

To explore the relationship between apathy and volume loss over time, delta scores for apathy product score and delta scores for each brain structure were calculated to indicate change over time. For each subcortical brain structure, a linear regression model was designed to examine an association between delta score of apathy and delta score of the subcortical brain structures. Again, the model accounted for gender, medication use at baseline and follow-up, group, age, study site and CAG length. This model was run once for all participants and once only for participants with an increase in the degree of apathy over time.

IBM SPSS version 23 was used for the group characteristics analysis the significance threshold was set to 0.05. Baseline and follow-up models were corrected for multiple comparisons; i.e. $p < 0.007$ (significant threshold of 0.05 divided by the number of executed tests).

Results

Group characteristics are described in table 1. The four groups differed significantly in age, CAG length, medication use, and apathy scores. On average, all participants were seen 23 months (SD: 1 month) after baseline visit.

Baseline visit

Throughout the consecutive disease stages the percentage of participants with apathy steadily increased: at baseline 12% in the PreHD-A groups to 50% in the stage 2 HD group, see table 1.

The linear regression model did not reveal any association between volume of the separate subcortical brain structures and the apathy product score. The results did not change by adding the covariate depressive mood or by excluding the covariate medication use in the original model.

The logistic model showed that only a smaller volume of the thalamus (OR=0.57; 95% CI:0.38–0.84; p=0.004) was associated with the presence of apathy; i.e. smaller thalamus indicates a higher probability of presence of apathy, see figure 1. No other associations were found, and the results did not change when the covariate depressive mood was added. If medication use was excluded as a covariate in our original model, again, only the thalamus was associated with the presence of apathy (OR=0.56; 95% CI:0.38-0.82; p=0.003). Volumes of the nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum and putamen were not associated with the apathy product score.

Table 1: Group characteristics

	PreA N=52	PreB N=39	HD1 N=50	HD2 N=30	p-value
Gender: m/f ^a	25/27	18/21	19/31	17/13	p = 0.43
Age in years (SD) at baseline ^b	46 (9)	46 (9)	51 (10)	56 (8)	p < 0.001
CAG length ^b	42 (2)	44 (2)	44 (4)	43 (2)	p = 0.001
Medication use at baseline (%) ^a	9 (17%)	9 (23%)	18 (36%)	26 (87%)	p < 0.001
Medication use at baseline and FU (%) ^a	8 (15%)	9 (23%)	18 (36%)	25 (83%)	p < 0.001
Apathy at baseline (%) ^a	6 (12%)	6 (15%)	12 (24%)	15 (50%)	p = 0.001
Apathy at FU (%) ^a	5 (9%)	10 (25%)	18 (36%)	21 (70%)	P < 0.001
Months between visits ^b	23 (1)	23 (1)	24 (1)	24 (1)	p = 0.33

Subgroups are created on baseline characteristics: PreA: pre-motormanifest A; PreB: pre-motormanifest B;

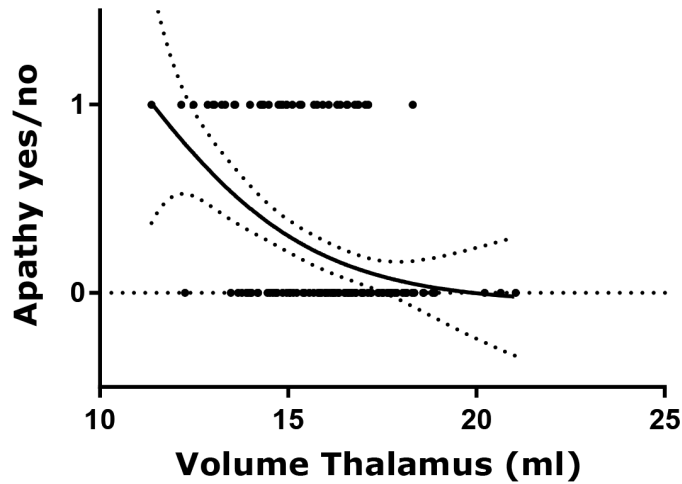
HD1: motormanifest stage 1; HD2: motormanifest stage 2; FU: follow-up visit;

p-value for main comparison, no post-hoc results are displayed

^atotal number

^bmean (standard deviation)

Figure 1: Probability of being apathetic based on volume of the thalamus



Follow-up

Overall, the percentage of apathetic participants increased over a time period of 2 years, see table 1. When comparing the apathy product score at baseline with the apathy product score at follow-up for 16% of the participants apathy product score decreased by at least one point. Of 53% of the participants the apathy severity score stayed exactly the same and for 31% of the participants the apathy severity score increased by at least one point.

For the linear regression model over time no significant associations were found. None of the volumes of the subcortical brain structures were associated with change in the apathy product score between the two assessments; removing the covariate medication use did not make any difference. Additional analysis with only participants with increase of the apathy product score included in the analysis did not show other results, data not shown.

Discussion

This study investigated the relationship between atrophy of subcortical brain structures and apathy in HD gene carriers at baseline and after 2 years follow-up. Cross-sectional analyses at baseline revealed that only atrophy of the thalamus was associated with the presence of apathy in HD, but no association between atrophy of the subcortical brain structures and the degree of apathy at baseline or over time were found. The former finding supports the notion that the prefrontal cortex – basal ganglia circuit is involved in occurrence of apathy in HD, i.e. disruption of the circuit at the level of the thalamus is related to apathy. However, solely association with the thalamus is not specific to any of the circuits as the thalamus connects the subcortical brain structures and the cortex in all prefrontal cortex – basal ganglia circuits. Since disruption of the anterior cingulate circuit was associated with apathy in other neurodegenerative diseases^{13, 14, 16, 40}, it is most likely that this circuit is also involved in the occurrence of apathy in HD. However, with only one structure being associated with apathy in our study, there is no conclusive evidence that the presence of apathy is associated with this specific circuit in HD. We only evaluated possible associations between apathy and atrophy of subcortical structures in HD. This is in accordance with findings that subcortical structures are associated with apathy in other neurodegenerative disease^{14, 16, 18} and that degeneration of subcortical structures is prominently present in HD^{19, 22, 30, 41}. However, we have neglected a possible association with parts of the prefrontal cortex which might also differentiate between the prefrontal cortex – basal ganglia circuits. It is known that HD is a whole brain disease and the cortex degenerates in the early HD stages^{11, 42}. In these early stages apathy also drastically increases³ which is also supported by our results. This leads us to speculate that the underlying neural cause of apathy might not only be ascribed to atrophy of subcortical brain structures, but might also be associated with atrophy of the cortex. For future research, we suggest to evaluate a possible association between the cortex and apathy in HD. In addition, it might be useful to explore other measurement tools for neural dysfunction, such as structural integrity or dopamine binding rather than volume reduction, to assess the relationship between apathy and neurodegenerative process in HD.

In the cross-sectional analysis we only found an association between the presence of apathy and volume reduction of the thalamus but not between the degree of apathy and volume reduction of any subcortical brain structure. To measure the degree of apathy in HD, we used the product score of severity and frequency of the apathy PBA-s item, as was done previously¹¹. However, the product score bares some degree of uncertainty in what exactly is measured, it is unknown whether a high product score is a result of a

high severity score, a high frequency score or a mix of both. This means that different clinical presentations may have the same product score, e.g. someone with chronically mild apathy may have the same score as someone with occasionally severe apathy. In our opinion, these cases are not equal; hypothesis is that it is more likely that severity – rather than frequency – of apathy is related to the neurodegenerative process in HD. McNally et al.⁴³ have also pointed out in their re-evaluation of the PBA-s that using the product score might statistically not be appropriate as it is not a ratio scale. For future research, it would be of interest to further evaluate the use of the different PBA-s scores.

Over a time period of 2 years follow-up, we did not find any association between atrophy of the subcortical brain structures and change in the severity of apathy. In our cohort, apathy was already present in the early stages and the number of apathetic HD gene carriers increased. Over a time period of 2 years, in 31% of the HD gene carriers apathy scores worsened, while in 16% of the HD gene carriers apathy scores improved. The last finding was rather unexpected, as previous studies have shown that apathy worsens over time in HD^{2, 3}, to our knowledge only one other study found that over a time period of 2 years some apathetic individuals improved⁴⁴. A possible explanation might be that apathy itself is related to depression and the use of psychotropic medication; successful treatment of depression and/or use of other medication can affect apathy⁴⁵. As medication use has such an influence on apathy, our statistical model was adjusted for medication use. We acknowledge that by creating a binary variable (i.e. use or no use of certain medication), the different acting agents were treated as if they all have the same effect on apathy. However, more research is needed to investigate whether medication itself triggers apathy or whether apathetic HD gene carriers are more likely to use certain medication, which is important for the prescription of effective individualized medication in HD. From our longitudinal results, we can only conclude that the severity in apathy does not drastically increase over a time period of 2 years in the pre-motormanifest and early stage of the disease, for the majority of individuals the apathy score stayed the same. The time period of 2 years might be too short to find a significant increase in apathy in a pre-motor manifest and early HD population considering that disease duration is 17-20 years¹. This is supported by Thompson et al.'s study³ in which more increase in apathy was found over a longer time period of on average 5 years and more advanced HD gene carriers.

In conclusion, apathy is present in early stages of HD and is associated with atrophy of the thalamus in HD gene carriers, suggesting that occurrence of apathy has an underlying neural cause. Further research is necessary to evaluate apathy over a

longer time period in more advanced stages and to evaluate the possible association between apathy and cortical atrophy in HD.

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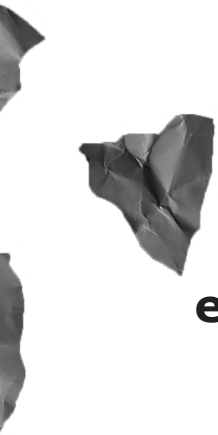
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Chapter 6

Huntington's disease gene expansion carriers are aware of their degree of apathy

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Abstract

Huntington's disease (HD) is characterized by motor and behavioral symptoms, and cognitive decline. Apathy is a common behavioral symptom and its severity is related to disease progression. It has been suggested that HD gene expansion carriers are unaware of signs and symptoms of the disease, which might also account for their awareness of their own level of apathy. Therefore, the aim is to investigate the level of agreement on the degree of apathy severity between HD gene expansion carriers and their proxies using a self-report questionnaire. In total 109 REGISTRY participants (31 pre-motormanifest, 49 early motormanifest, and 29 late motormanifest) and their proxies completed the Apathy Evaluation Scale (AES). The Wilcoxon signed-rank test was used to assess whether HD gene expansion carriers and their proxies agreed on apathy severity. The AES score significantly increased from the early motormanifest to late motormanifest stage. Pre-motormanifest HD gene expansion carriers scored themselves significantly higher on the AES than their proxies, whereas no differences were found between all motormanifest HD gene expansion carriers and their proxies. Apathy severity increases in the motormanifest stages of HD. HD gene expansion carriers can adequately assess their level of apathy on a self-report questionnaire. Our results even suggest that slight changes in the degree of apathy in pre-motormanifest HD gene expansion carriers remain unnoticed by their proxies.

Introduction

Huntington's disease (HD) is an autosomal dominant inherited, progressive neurodegenerative disorder caused by an expanded trinucleotide expansion which codes for mutant huntingtin on chromosome 4¹. HD is clinically characterized by a triad of symptoms: motor abnormalities, behavioural symptoms, and cognitive deterioration². The formal clinical diagnosis of HD is typically based on the appearance of unequivocal motor signs even though behavioural signs and cognitive decline often occur before motor signs are present^{2,3}, but with the identification of the exact location of the huntingtin gene, individuals at risk can be tested for the expanded HD gene before any signs and symptoms become apparent. New guidelines have agreed that clinical diagnosis can be made solely on behavioural and/or cognitive signs⁴.

The behavioural symptoms in HD are diverse^{5,6}; the most common behavioural symptoms are depressed mood, irritability, and apathy with a prevalence varying from 33% to 76% dependent on definition, measurement tools used, and disease stage⁶. Of all behavioural symptoms, apathy - defined as 'lack of motivation resulting in diminished goal directed behaviour, cognition, and emotion'⁷ - is the only behavioural symptom which is closely related to disease progression in HD⁵. Therefore, it is suggested that apathy is caused by the neurodegenerative process in HD and could be seen as a marker of disease progression⁸. In HD, apathy is also associated with cognitive dysfunction and the use of psychotropic medication⁹. In their review of rating scales for behavioural symptoms in HD, Mestre et al.¹⁰ discuss three scales for assessing apathy in HD. Several studies¹¹⁻¹³ have used the Apathy Scale (AS), which is based on the Apathy Evaluation Scale (AES)¹⁴, however the AS was suggested for screening only. The AES was suggested for assessing severity of apathy in HD. The reviewers mention a possible lack of insight by HD patients and they therefore favour the clinician version of the AES.

Previous studies have shown that HD patients can be unaware of the signs and symptoms of the disease, including behavioural symptoms^{15,16}. The degree of impaired awareness of their own disability (anosognosia) varies dependent on symptom and its severity, cognitive function, and disease stage¹⁶. In clinical trials, a proxy is often asked to rate behavioural symptoms to avoid the risk of unawareness in HD gene expansion carriers (HDGECs). However, since it is not always possible to include HDGECs together with a reliable proxy only, it is of great relevance to evaluate whether HDGECs themselves are capable to adequately rate the severity of apathy using a self-report questionnaire.

So far, only two studies have been conducted to investigate the level of agreement between HDGECs and their proxies in rating severity of apathy using a self-report

questionnaire. However, the results of these studies are conflicting: one study found a difference in the severity of apathy between clinically diagnosed HDGECs and their proxies¹¹, but the second study did not find a difference in the total apathy score between pre-manifest and manifest HDGECs and their proxies¹⁷. These different results could be ascribed to different methodology of the studies: the former used the AS and included clinically diagnosed HDGECs only, whereas the latter used the AES and included both pre-manifest and manifest HDGECs. The AS is an abridged version of the AES¹⁸, and on face value, the two questionnaires are comparable, although there is lack of psychometric data for the assessment of apathy with the AS in HD¹⁰. Because of the aforementioned conflicting results and the discussed unawareness of apathy in HDGECs, we have conducted an additional study to evaluate whether HDGECs are less aware of their apathy severity than their proxies.

Methods

Participants

The REGISTRY study¹⁹ is a European, multicentre, longitudinal, observational study conducted in 17 countries. The Leiden University Medical Center (LUMC) is the largest REGISTRY site. All REGISTRY participants at the LUMC seen between January 2013 and August 2014 and their proxies were asked to fill out the AES. The LUMC acquired ethical approval for this study and all participants gave written informed consent. In total 109 (31 pre-motormanifest, 49 early motormanifest, and 29 late motormanifest) HDGECs and their proxies completed the Registry battery and additional questionnaire. All HDGECs were genetically confirmed with a CAG >39. HDGECs with a total motor score (TMS) of ≤ 5 on the Unified Huntington's Disease Rating Scale (UHDRS)²⁰, indicating no substantial motor signs, were defined as pre-motormanifest. The group with a TMS of >5 was considered to be motormanifest with obvious HD motor signs. This motormanifest group was further divided into early motormanifest and late motormanifest according to disease stage based on the Total Functional Capacity (TFC) score²¹. TFC stage 1 and 2 were considered early motormanifest and stage 3 and 4 were considered late motormanifest. No participants of stage 5 participated in this study.

Clinical measures

The Apathy Evaluation Scale (AES) was used to quantify the level of apathy. The AES has three versions available: one for the patient, one for the proxy, and one for the care professional/investigator; in this study the patient and proxy version were used. The AES was developed to provide a global measure of apathy on an 18-item questionnaire, rated on a 4-point Likert scale with a maximum score of 72¹⁴. The HDGECs and proxies were independently of each other asked to rate to which degree they agree with a specific statement, for instance '*S/he gets things done during the day*'¹⁴.

Statistical analysis

To assess group differences in the demographic and clinical characteristics ANOVA or the non-parametric counterpart was used. As the use of certain medications can affect apathy⁹, the following groups of medication were identified to have a possible effect on the level of apathy: SSRI, SNRI, antipsychotics (atypical and typical), tricyclic antidepressants, bupropion, benzodiazepines, and tetrabenazine. A binary variable was created to indicate whether the HDGEC used any of this medication. To evaluate whether there was a difference between the three groups (pre-motormanifest, early, and late motormanifest) on the severity of apathy, an analysis of covariance was carried out with medication use and age entered as a covariate. The Wilcoxon signed-rank test was used to assess whether gene carriers and their proxies rated apathy severity differently.

IBM SPSS version 23 was used for all analysis. A significance threshold was set to 0.05 and if multiple comparison was carried out Bonferroni correction was applied.

Results

The group characteristics are described in table 1. The three groups differed significantly in age ($F(2,106)=33$, $p<0.01$), TMS ($H(2)=79$, $p<0.01$) and medication use ($\chi^2(2)=12$, $p<0.01$); i.e. medication use increased from 23% in pre-motormanifest group to 65% in the late motormanifest group. The groups did not differ in CAG length and gender.

The analysis of covariance of the AES patient version revealed that the three groups differed significantly in apathy score ($F(2,102)=5$, $p<0.01$). Post-hoc analysis showed that the pre-motormanifest group scored on average 10 points lower on the AES ($p<0.01$) than the late manifest group. The early motormanifest group scored

significantly lower on the AES than the late motormanifest group (mean difference 6 points, $p=0.03$). No significant difference was found between the pre-motormanifest and the early motormanifest groups, see figure 1.

The Wilcoxon signed Rank test showed that there was no difference in apathy score when the total group of HDGECs was compared with the rating of their proxies ($Z= -0.65$, $p=0.52$). However, when the three HDGEC groups were analysed separately, the pre-motormanifest HDGECs rated themselves as being more apathetic than their proxies ($Z= -2.6$, $p<0.01$), figure 1. The pre-manifest HDGECs rated themselves one point higher (worse) on 8 of the 18 questions than their proxies, figure 2. In the early and late motormanifest groups no significant difference was found between total AES score of the HDGECs and their proxies. Notable, the proxies of the early motormanifest HDGECs group rated apathy on 3 items one point higher than the HDGECs themselves, but this did not result in a significant different total AES score.

Table 1: Group characteristics

Characteristics	Pre-motormanifest (N=31)		Early motormanifest (N=49)		Late motormanifest (N=29)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Age in years ^b	38	9	54	11	57	11	$p<0.01^{a,b}$
	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	
CAG larger length	43	3	43	3	43	2	$p=0.33$
Total motor score	1	2	22	23	52	22	$p<0.01^{a,b,c}$

SD: Standard deviation
^asignificant difference between pre-motormanifest and early motormanifest
^bsignificant difference between pre-motormanifest and late motormanifest
^csignificant difference between early motormanifest and late motormanifest

Figure 1: Patient and proxy Apathy Evaluation Scale (AES) score

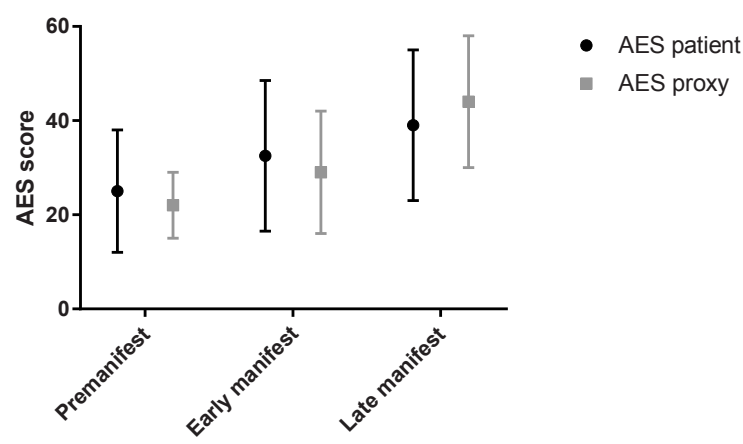
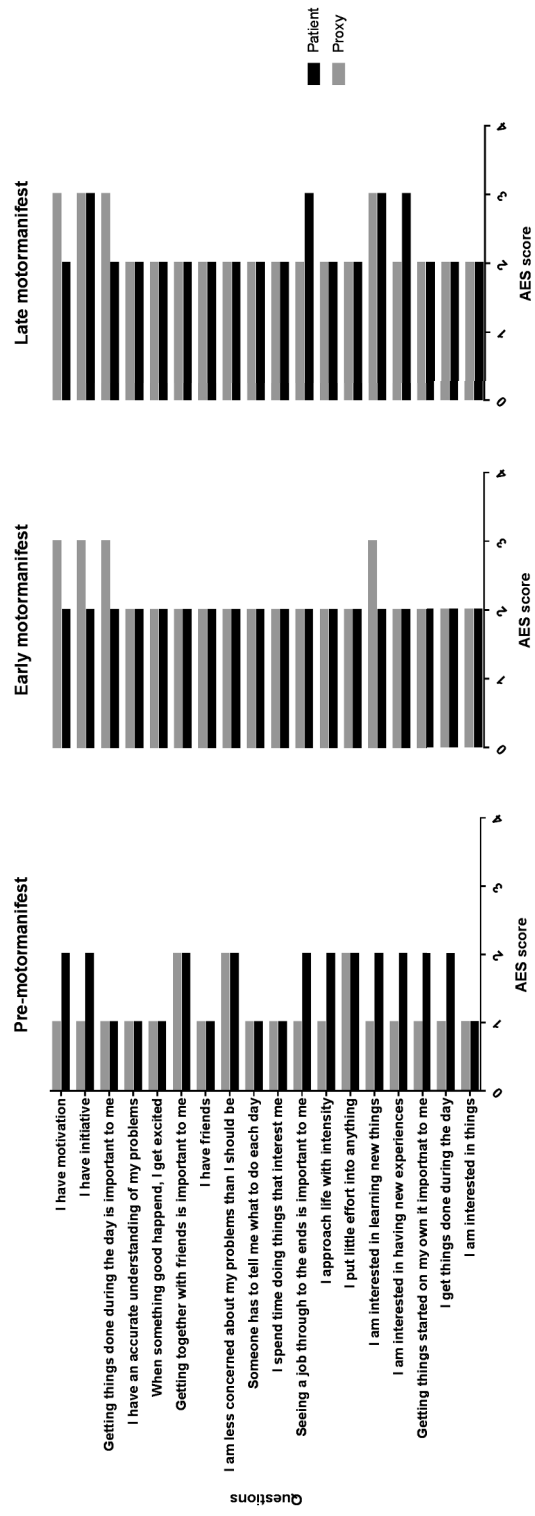


Figure 2: Average score on each question per participant group



Reference: Marin R.S., Biedrzycki RC, & Firinciogullari S. 1991. Reliability and validation of the Apathy Evaluation Scale. Psychiatry Res. 38 (2): 143-62.

Discussion

In our cohort, apathy severity increased overall as the disease progressed throughout the clinically manifest stages. More precisely, the pre-motormanifest and early motormanifest group scored about the same on the AES, but there was a significant increase in AES score from the early motormanifest group to the late motormanifest group. This is in line with previous findings that apathy increases throughout disease progression and that apathy is a common behavioural symptom in the advanced disease stage⁵. We did not find a difference in apathy rating when the score of the entire HDGEC cohort was compared with the score of their proxies, indicating an agreement on the severity of apathy between HDGECs and their proxies. However, by evaluating the different disease stages separately, in our study pre-motormanifest HDGECs rated themselves higher on the AES than their proxies; indicating that pre-motormanifest HDGECs experienced a higher level of apathy than was noticed by their proxies. These findings are in line with Mason's et al.¹⁷ study that the apathy score of the entire HDGEC group did not differ from their proxies' score, and that pre-motormanifest HDGECs tend to rate themselves as being more apathetic than their companions. However, differences with our study appear when evaluating the motormanifest groups: Mason et al. reported that early disease patients also tend to rate themselves as more apathetic, whereas in late stage disease the proxies scored higher than the HDGECs, which we did not find. This may be explained by the use of a different definition of the motormanifest groups in our study.

The other study that compared the self-reported with the caregiver assessment found that the proxies rated apathy as more severe than the HDGECs.¹¹ However, in this study only clinically diagnosed HDGECs were included and the AS was used. Their study population was divided according to their cognitive ability: the agreement between HDGECs with good cognitive abilities and their proxies was high and this agreement dropped as cognitive abilities declined. Since HDGEC with better cognitive function is related to early disease stage, this group is comparable to the early motormanifest HDGEC group in our study, in which we have also found that HDGECs and proxies agreed on the degree of apathy. However, we did not find that this agreement weakens in the late motormanifest group with assumed declined cognitive abilities.

By taking the results of these three studies together, it seems that HDGECs in the early stage of the disease and the proxies have equal awareness of apathy severity. However, the pre-motormanifest HDGEC experience more apathy than is noticed by their proxies. One explanation for this difference may be the hyper-alertness of pre-motormanifest HDGECs for the development of signs of the disease; the knowledge of being a HDGEC could lead to a higher report of possible symptoms. This effect may

disappear when HDGECs are clinically diagnosed – as in the early motormanifest stage. Another possible explanation for this difference is, these apathy symptoms are very subtle^{3, 22} and it might be a more internal feeling of which the proxies are not aware. This is supported by that most discrepancies are on questions relating to internal drive, such as: ‘I am interested in having new experiences’. The results of the three studies for the late motormanifest HDGECs diverted, although apathetic patients in advanced stages with cognitive impairments may be less aware of their symptoms.

One limitation of our study is that we might have a selection bias. We asked all REGISTRY participants during a specific time period to participate in this study. It is possible that more severe apathetic or cognitively impaired participants declined to participate in this study. In addition, we assumed that the proxy is the most reliable individual to indicate the severity of apathy of the HDGECs. However, the proxy is personally involved and might not be able to objectively judge the degree of apathy.

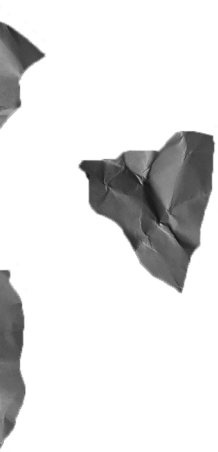
Concluding, this study replicates prior findings that apathy is more severe in the advanced disease stage, and it provides further evidence that the HDGECs were capable of assessing the level of apathy on a self-report questionnaire in the early stage of the disease. More precisely, in our study the pre-motormanifest individuals were aware of subtle changes which were unnoticed by their proxies. Taken together with the previous findings, this implies that the absence of a proxy is not a legitimate reason for exclusion in clinical trials for the assessment of apathy in the pre-motormanifest and early manifest disease stages.

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Chapter 7

Discussion and concluding remarks

The general aim of this thesis was to gain further insight into the cognitive profile and apathy in Huntington's disease (HD). This information is particularly useful to optimize clinical care and to aid the design of future clinical trials.

Cognitive profile

For research purposes it is common that HDGECs are grouped according to absence (i.e. pre-motormanifest) or presence (i.e. motormanifest) of motor symptoms. First, we evaluated whether this commonly used participant classification makes a useful distinction between HDGECs and whether these groups are homogeneous, especially in light of cognition. An overview of the participants' characteristics of the largest REGISTRY center was given by using different classifications (**chapter 2**). When dividing our cohort of 487 HDGECs according to absence and presence of motor symptoms, about 20% of the pre-motormanifest individuals were already clinically diagnosed based on cognitive and/or psychiatric symptoms. This leads to the conclusion that cognitive decline starts before motor symptoms are present and that these symptoms are clinically severe enough to diagnose individuals with HD without any motor symptoms. This is in line with previous research¹⁻⁴. These results emphasize that the recently published guidelines, which state that HD diagnosis can be given purely on cognitive and/or psychiatric symptoms⁵, fulfill a real need. In order to understand how this early cognitive decline further develops throughout disease progression, we used the entire REGISTRY cohort with the aim of mapping the cognitive profile throughout all disease stages (**chapter 3**). We found that significant cognitive decline is present even in the pre-motormanifest stages, which again leads to the conclusion that cognitive decline is often present before motor symptoms are apparent. In our study, tasks measuring psychomotor speed with low motor component, i.e. Stroop Word and Color test, were sensitive in detecting early cognitive decline, as well as tracking this decline throughout the later stages of the disease. Thus, psychomotor tasks are suitable for tracking cognitive abilities over time in HD.

We do not know why cognitive decline starts early in the course of their disease for some individuals and also, we do not understand the different rates of decline. Why do some patients progress much faster than others? In general, we do know that CAG length influences disease progression as has been shown for motor function, total functional capacity and atrophy in the brain^{6,7}. Therefore, we evaluated whether cognitive decline is also mediated by CAG length (**chapter 3**). Indeed, our results show that individuals with longer CAG lengths have a more rapid cognitive decline. This is not surprising as cognitive deficits are associated with changes in the brain and

this neurodegenerative process in the brain itself is mediated by CAG length. Thus, it seems logical that CAG mediates cognitive performance. CAG length is a disease specific factor which influences cognitive decline but there might be other factors influencing cognitive performance. As there is no cure for HD, many HDGECs take symptomatic medication. Therefore, we explored whether there is a difference in cognitive performance between HDGECs taking medication targeting non-cognitive neuropsychiatric signs and/or tetrabenazine and non-users (**chapter 4**). First, we have shown that symptom management is common in HD: about 42% of all REGISTRY participants used one or more of the predefined drugs; benzodiazepines, selective serotonin reuptake inhibitor (SSRI) antidepressants, antipsychotics, atypical antipsychotics or tetrabenazine. Medication use gradually increased from pre-motormanifest participants (12%) to late stage manifest participants (81%) and polypharmacy also increased from 3% to 48%. However, the only effect found in our study was a negative effect of using antipsychotic on cognitive performance in the early HD stages. We did not find any effects of using benzodiazepine, SSRIs, atypical antipsychotics and tetrabenazine on cognitive performance in the real-life medication use at the clinics. A major limitation of this study is that we used relatively broad medication categorization and that this could mask effects of any one particular drug. But at least, this study shows the groups effect of real-life medication use on cognitive performance. Concluding, group analysis did not show medication to have a significant effect on cognitive performance, except for antipsychotics.

Apathy

The behavioral symptoms in HD are diverse⁸. Apathy is common, is the only behavioral symptom closely related to disease progression⁹⁻¹¹ and is present in almost all late stage HDGECs¹¹. Apathy is defined as 'lack of motivation resulting in diminished goal-directed behavior, cognition, and emotion'¹² and, in general, is associated with a disruption of the prefrontal cortex - basal ganglia circuit¹³. Therefore, we aimed to find a relationship between apathy and the neurodegenerative process in HD (**chapter 5**). Our results are in line with previous studies that apathy is common and can already be present in the pre-motormanifest stage. In addition, we have shown that that atrophy of the thalamus is associated with apathy leading us to conclude that also in HD apathy is associated with a disruption of the prefrontal cortex – basal ganglia circuit. However, no other subcortical structure was found to be associated with apathy. Very recently one study found that the prefrontal cortex is associated with apathy in HD¹⁴, the prefrontal cortex – basal ganglia circuit is indeed disrupted in HD but the

prefrontal cortex is associated with developing apathy in HD rather than subcortical structures.

Some studies have shown that HDGECs are unaware of their symptoms, including their behavioral symptoms^{15, 16}. Therefore, we evaluated whether HDGECs and their proxies agree on the degree of apathy by using a self-report questionnaire (**chapter 6**). As mentioned, apathy can already be present in pre-motormanifest individuals, the incident and severity rate drastically increase from the early HD stage to the late motormanifest stages. Overall, proxies and HDGECs agree on the degree of apathy. In the pre-motormanifest stage HDGECs even report more apathy than their proxies, although the overall degree of apathy is generally low in this stage. However, it could be the case that pre-motormanifest HDGECs are more aware of internal changes than their proxies.

Concluding remarks

Over the recent years a unique situation has arisen for HDGECs, as several clinical trials were set up to evaluate medication for symptomatic treatment¹⁷. Very recently, one trial has been launched which aims to lower the huntingtin level in the brain to stop or delay the neurogenerative process¹⁸. Many trials have been set up and there are some promising studies, but nothing has been proven yet. And even more studies are at the horizon. With the results of our work we can advise to include executive function (especially psychomotor speed) in the battery when cognition is being studied. At the moment, no threshold is known at which to conclude that cognitive impairment (due to HD) has started. When it comes to evaluating cognition, we would favor to group participants according to age and CAG length rather than on presence and absence of motor symptoms. In addition, we have shown that medication targeting non-cognitive neuropsychiatric disturbances and tetrabenazine might not have such an enormous influence on cognitive outcome as previously assumed, when groups are analyzed. We think that exclusion criteria based on medication use should be carefully evaluated, as in group analysis the individual usage of certain medication might not make much difference. Of course, on individual basis these medications can have side effects which should be carefully evaluated and if necessary be replaced by other medication.

Considering that executive dysfunction and apathy seem to be closely related, we would advise to also evaluate apathy in a standardized way when cognition is measured in a clinical trial. If an agent under investigation is supposed to have effect on the prefrontal cortex, it might also positively affect apathy.

The HD community hopes that an intervention which slows or stops the disease progression will be found soon. And our results help to at least shape those studies to be able to evaluate a possible effect.

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Nederlandse Samenvatting

Het hoofddoel van dit proefschrift was om meer kennis over het beloop van cognitie en apathie bij de ziekte van Huntington (ZvH) te krijgen. Deze informatie is belangrijk om de zorg te kunnen optimaliseren en om te kunnen adviseren hoe een klinische studie opgezet moet worden.

Cognitie

In de wetenschap is het gebruikelijke dat ZvH gendragers ingedeeld worden op basis van afwezigheid (pre-motormanifest) en aanwezigheid (motormanifest) van motorische symptomen. Daarom hebben we eerst uitgezocht of deze gebruikelijke deelnemersclassificatie een onderscheid tussen de ZvH gendragers maakt en of deze groepen homogeen zijn. Met behulp van twee verschillende classificaties (CAG-lengte en af/aanwezigheid van motor symptomen) wordt een overzicht van de deelnemerskarakteristieken aan het grootste Europese REGISTRY-onderzoekscentrum (Leids Universitair Medisch Centrum) gegeven (**hoofdstuk 2**). Het Leidse REGISTRY-cohort van 487 ZvH gendragers werd verdeeld op basis van af- of aanwezigheid van motorische symptomen, waarbij ongeveer 20% van de pre-motormanifeste individuen al klinisch met HD gediagnosticeerd waren op grond van evidente cognitieve en/of psychiatrische symptomen. Dit leidt tot de conclusie dat cognitieve achteruitgang begint voordat motorische symptomen aanwezig zijn en dat deze symptomen klinisch ernstig genoeg waren om de ZvH diagnose te stellen zonder enige motorische symptomen, wat in lijn is met eerder onderzoek. Deze resultaten bevestigen de behoefte aan de onlangs gepubliceerde richtlijn waarin is vastgelegd dat de ZvH diagnose op grond van alleen cognitieve en/of psychiatrische symptomen gesteld kan en mag worden. Om te begrijpen hoe deze vroege cognitieve achteruitgang zich gedurende het ziekteproces verder ontwikkelt, hebben we het volledige REGISTRY-cohort gebruikt met als doel het cognitieve profiel in alle ziektestadia in kaart te brengen (**hoofdstuk 3**). We vonden dat in de pre-motormanifeste stadia er significante cognitieve achteruitgang meetbaar is. Dit versterkt de eerdere conclusie dat cognitieve achteruitgang vaak al voor de motorische symptomen aanwezig is. In onze studie bleken taken die de psychomotorische snelheid meten met een lage motorcomponent (Stroop Word en Stroop Kleuren test) gevoelig te zijn voor het detecteren van vroege cognitieve achteruitgang en deze cognitieve achteruitgang ook in de late stadia te kunnen blijven volgen. Psychomotorische taken zijn uitermate geschikt om de cognitieve vaardigheden in de loop van de tijd te volgen bij de ZvH.

We kunnen niet verklaren waarom bij sommige ZvH gendragers de cognitieve achteruitgang sneller verloopt dan bij anderen. Over het algemeen weten we dat de CAG-lengte de progressie van de ziekte beïnvloedt, zoals is aangetoond bij motorische symptomen, totale functionele capaciteiten en atrofie van de hersenen. Daarom evalueerden we of cognitieve achteruitgang ook wordt beïnvloed door de CAG-lengte (**hoofdstuk 3**). Onze resultaten laten zien dat personen met een langere CAG-lengte een snellere cognitieve achteruitgang laten zien. Dit is niet verrassend omdat cognitieve tekorten worden geassocieerd met veranderingen in de hersenen en dit neurodegeneratief proces in de hersenen zelf al wordt beïnvloed door de CAG-lengte. Het lijkt dus logisch dat CAG direct de cognitieve achteruitgang beïnvloedt. CAG-lengte is een ziekte specifieke factor die de cognitieve achteruitgang beïnvloedt maar er kunnen ook andere factoren, zoals medicatiegebruik, zijn die de cognitieve prestaties beïnvloeden. Omdat geen genezing voor de ZvH beschikbaar is, gebruiken veel ZvH gendragers medicatie om de symptomen te bestrijden. Daarom hebben we onderzocht of er verschil bestaat in cognitieve prestaties tussen ZvH gendragers die medicatie gericht op niet-cognitieve neuropsychiatrische symptomen en/of tetrabenazine gebruiken en niet-gebruikers (**hoofdstuk 4**). Ten eerste hebben we aangetoond dat symptoombehandeling gebruikelijk is bij de ZvH: ongeveer 42% van alle REGISTRY-deelnemers gebruikte één van de volgende medicijnen: benzodiazepine, selectieve serotonineheropnameremmer (SSRI) antidepressiva, antipsychotica, atypische antipsychotica of tetrabenazine. Het medicatiegebruik steeg geleidelijk van pre-motormanifeste deelnemers (12%) naar laatstadium manifest deelnemers (81%); ook het tegelijkertijd gebruik van meerdere medicijnen, polyfarmacie, steeg van 3% naar 48%. We vonden slechts één negatief effect van het gebruik van antipsychotica op cognitieve prestaties in de vroege ZvH stadia; dat willen zeggen dat deelnemers die antipsychotica gebruikten slechter presteerden op de cognitieve taken. We hebben geen effect van benzodiazepine, SSRI's, atypische antipsychotica en tetrabenazine op de cognitieve prestaties gevonden, het betreft hierbij het gebruik van medicatie zoals we dat in de dagelijkse praktijk zien, niet aangepast voor deze studie. Een belangrijke beperking van dit onderzoek is dat we een relatief brede medicatie classificatie hebben gebruikt, waardoor effecten van bepaalde medicijnen mogelijk gemaskeerd kunnen worden. Het voordeel is echter wel dat naar het groepseffect van het werkelijke medicatie gebruik is gekeken. Concluderend, in groepsanalyse lijkt medicatie geen groot effect te hebben op de cognitieve prestaties, met uitzondering van antipsychotica in de vroege ZvH stadia.

Apathie

Bij de ZvH zijn gedragssymptomen zeer divers. Apathie komt veel voor bij de ZvH en is het enige gedragssymptoom dat nauw verband houdt met ziekteprogressie en aanwezig is bij bijna alle ZvH gendragers in de late stadia. Apathie wordt gedefinieerd als “gebrek aan motivatie resulterend in verminderd doelgericht gedrag, cognitie en emotie” en wordt in het algemeen geassocieerd met een verstoring van het prefrontale cortex – basal ganglia circuit. Daarom hebben we onderzocht of er een verband tussen apathie en het neurodegeneratieve proces bestaat bij de ZvH (**hoofdstuk 5**). Onze resultaten zijn in overeenstemming met eerdere studies: apathie komt veel voor en kan al aanwezig zijn in de pre-motormanifeste stadia. Bovendien hebben we aangetoond dat atrofie van de thalamus geassocieerd wordt met apathie, hetgeen aangeeft dat apathie bij de ZvH ook geassocieerd wordt met een verstoring van het prefrontale cortex – basal ganglia circuit. Echter, geen andere subcorticale hersenstructuur was geassocieerd met apathie. Zeer recent werd in één studie een associatie tussen apathie en de prefrontale cortex bij de ZvH gevonden. Dit pleit er wederom voor dat het prefrontale cortex - basal ganglia circuit betrokken is, maar dan vooral de prefrontale cortex en niet de subcorticale structuren.

Sommige studies hebben aangetoond dat ZvH gendragers zich niet bewust zijn van hun symptomen, inclusief hun eigen gedrag. Daarom evalueerden we of ZvH gendragers en hun partners het eens zijn over de mate van apathie bij de ZvH gendrager door een zelfrapportagevragenlijst te gebruiken (**hoofdstuk 6**). Zoals eerder vermeld kan apathie reeds aanwezig zijn in een laag aantal pre-motormanifest individuen, maar neemt de frequentie en mate van apathie drastisch toe van de vroege motormanifest fase naar de late motormanifest stadia. Over het algemeen zijn partners en ZvH gendragers het eens over de mate van apathie. In het pre-motormanifeste stadium melden ZvH gendragers zelfs meer apathie dan hun partners/mantelzorgers, hoewel de mate van apathie over het algemeen laag is in deze fase. Dit doet vermoeden dat pre-motormanifeste ZvH gendragers zich meer bewust zijn van interne veranderingen dan hun mantelzorgers.

Slotopmerkingen

De afgelopen jaren is er een unieke situatie voor ZvH gendragers ontstaan omdat er verschillende klinische studies opgezet zijn om het effect van symptomatische behandeling te evalueren. In 2019 zal een studie starten met als doel het huntingtine niveau in de hersenen te verlagen en op deze manier te bezien of het neurodegeneratieve proces te vertragen of te stoppen is. Er zijn inmiddels veel studies opgezet, maar helaas heeft tot nu toe nog geen enkele studie het gewenste effect laten

zien. Met de resultaten van onze studies pleiten wij ervoor dat executieve functies in het onderzoeksprotocol opgenomen moeten worden als de cognitie getest wordt, met nadruk op psychomotorische snelheid. Toch is er nog geen drempelwaarde bekend waarbij geconcludeerd mag worden dat er cognitieve stoornissen veroorzaakt door de ZvH aanwezig zijn. Als het gaat om het evalueren van cognitie geven we de voorkeur aan het classificeren van deelnemers op basis van leeftijd en CAG-lengte in plaats van de huidige classificatie op basis van af- en aanwezigheid van motorische symptomen. Bovendien hebben we aangetoond dat medicatie gericht op niet-cognitieve neuropsychiatrische stoornissen en tetrabenazine mogelijk niet een zo grote invloed heeft op de cognitieve uitkomst op groepsniveaus als eerder werd aangenomen. We denken dat exclusiecriteria op basis van medicatiegebruik zorgvuldig moeten worden geëvalueerd, omdat het aannemelijk is dat er in de groepsanalyse weinig invloed is van medicatie gebruik. Uiteraard kunnen deze medicijnen wel op individuele basis effecten hebben welke zorgvuldig bekeken moeten worden.

Gezien het feit dat executieve dysfunctie en apathie nauw samengaan, adviseren we om apathie op een gestandaardiseerde manier te evalueren in alle gevallen dat er cognitie wordt gemeten in een klinische studie. Zeker wanneer verwacht wordt dat een medicijn effect heeft op de prefrontale cortex, omdat hierdoor apathie ook beïnvloed kan worden.

De ZvH gemeenschap hoopt dat een interventie die het ziekteproces vertraagt of stopt snel zal worden gevonden. Onze resultaten dragen bij om deze klinische studies beter vorm te geven zodat mogelijk effecten goed geëvalueerd kunnen worden.

List of publications

1. **Baake V**, Coppen EM, van Duijn E, et al. Apathy and atrophy of subcortical brain structures in Huntington's disease: A two-year follow-up study. *Neuroimage Clin* 2018;19:66-70.
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Curriculum Vitae

Verena Baake (meisjesnaam Rödiger) werd op 1 oktober 1985 geboren te Saarlouis, Duitsland. Het schooljaar 2002-2003 heeft ze gevolgd als uitwisselingsstudent in Fisher, Illinois, Verenigde Staten. Vervolgens heeft ze in 2005 haar 'Abitur' (Duits vwo-diploma) aan het Gertrud-Bäumer-Gymnasium behaald. In 2005 heeft ze een spoedcursus Nederlands gevolgd en ze heeft deze afgerond met het behalen van het Staatsexamen Nederlands als tweede taal (NT2). Nu kon ze haar studie psychologie aan de Universiteit Twente beginnen. Gedurende haar studieperiode aan de Universiteit Twente heeft ze zich ingezet voor toneelvereniging NEST als gewoon lid op het podium en later ook als penningmeester en voorzitter van de vereniging. De studieperiode aan de Universiteit Twente ronde Verena af in 2009 met het behalen van haar bachelor diploma psychologie. Haar master klinische neuropsychologie volgde zij aan de Universiteit Leiden. De klinische stage volgde Verena bij de afdeling neuropsychologie van het Universitair Medisch Centrum Utrecht. Haar wetenschappelijke stage liep ze op de afdeling neurologie van het Leids Universitair Medisch Centrum (LUMC). In het kader van haar wetenschappelijk stage kwam ze voor het eerst in aanraking met de ziekte van Huntington en heeft ze 9 maanden als stagiaire meegedraaid bij het internationale TRACK-HD onderzoek.

In 2011, na het behalen van haar master klinische neuropsychologie, begon ze als onderzoeksassistent bij de afdeling Neurologie van het LUMC en was betrokken bij de internationale studies TRACK-HD en PADDINGTON. In 2012 werd ze coördinator van het European Huntington's Disease Network (EHDN) in Nederland en Vlaanderen. Op deze manier zette ze zich veel in voor wetenschappelijk onderzoek naar de ziekte van Huntington. In het kader hiervan was ze bij veel wetenschappelijk studies en werkgroepen rondom de ziekte van Huntington betrokken. Gelijk met haar coördinatorfunctie startte ze ook in 2012 met haar promotietraject aan het LUMC. In 2016, heeft ze naast deze twee functies ook de rol projectmanager 'slaapproblematiek bij Huntington cliënten in het verpleeghuis' op zich genomen bij Topaz, Overduin.

In 2018 is ze begonnen als psychologe bij stichting Wijdezorg en werkt ze voornamelijk op de gesloten psychogeriatrische afdelingen. Sinds 2017 is Verena ook vrijwilliger bij de Vereniging van Couveuseouders (VOC) waarbij ze vanuit de vereniging de contactpersoon naar het Amsterdam Universitair Medisch Centrum is.