# Huntington's disease: cognition and apathy

Baake, V.

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## Cognition and Apathy

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# Huntington's Disease
## Cognition and Apathy

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Verena Baake
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**Promotor:**
Prof. Dr. R.A.C. Roos

**Promotiecommissie:**
Dr. D. Craufurd, the University of Manchester
Prof. Dr. H.P.H. Kremer, Rijksuniversiteit Groningen
Prof. Dr. R.C. van der Mast
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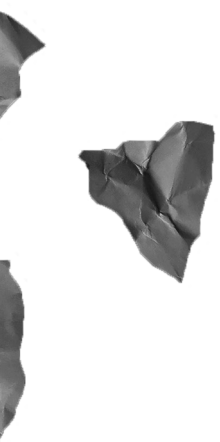


# Chapter 1
## Introduction

Huntington's disease (HD) is an autosomal, dominant inherited neurodegenerative disorder, characterized by a triad of symptoms including motor abnormalities, behavioral symptoms and cognitive decline[1]. The prevalence of HD varies between regions, in western countries approximately 10 per 100.000 individuals are affected by HD[2]. The mean age of disease onset is between 30 and 50 years of age with a disease duration of 17 to 20 years[1].

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 symptoms[3]. Roughly 100 years later, in 1983, the huntingtin gene was mapped to the short arm of chromosome 4 which made linkage analysis possible[4]. 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 risk[5]. 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 symptoms[6]. In general, a longer CAG expansion is associated with early disease onset[7].

## 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 walking[1]. 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 reliability[9]. 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 trials[10].

Cognitive decline is another major HD symptom and was already recognized by George Huntington[3]. 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 tools[11]. 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 present[11-13] whereas tasks of memory and executive functioning appear to become sensitive in the early HD stages[12-14]. Still the exact course of cognitive decline for each domain is still unknown, but finally cognitive deterioration results in dementia in HD[11]. 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 apathy[17]. 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 stage[16]. 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 dysfunction[21]. In HD it has been shown that apathy is associated with cognitive decline[22]. 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 symptoms[23]. The Problem Behavior Assessment – short (PBA-s), a semi-structured psychiatric interview, was develop for HD and is now commonly used to rate the presence and severity of the different behavioral symptoms[24].

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 HD[25]. These studies showed that atrophy of the putamen is correlated to motor symptoms[26,27], atrophy of the caudate is correlated to cognitive deficits[14], and that striatal atrophy already starts before symptoms become apparent[19]. 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 depression[28]. 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 practice[29-31].

## Aims

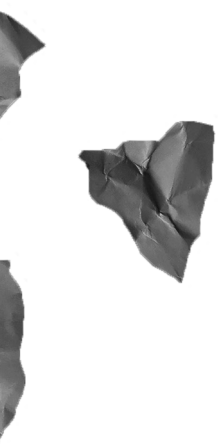
As exact knowledge of the course of cognitive decline and the underlying cause of developing apathy is still lacking in HD, the primary aim of this thesis was to gain further insight into the cognitive profile and apathy in Huntington's disease (HD). This information is incredible useful to advice future 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 study[32]. 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**.

# References


1. Roos RA. Huntington's disease: a clinical review. OrphanetJRareDis 2010;5:40.
2. Morrison PJ. Prevalence estimates of Huntington disease in Caucasian populations are gross underestimates. Mov Disord 2012;27:1707-1708.
3. Huntington G. On Chorea. the Medical and Surgical Reporter 1872;26:317-321.
4. Gusella JF, Wexler NS, Conneally PM, et al. A polymorphic DNA marker genetically linked to Huntington's disease. Nature 1983;306:234-238.
5. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 1993;72:971-983.
6. Novak MJ, Tabrizi SJ. Huntington's disease. Bmj 2010;340:c3109.
7. Sturrock A, Leavitt BR. The clinical and genetic features of Huntington disease. Journal of geriatric psychiatry and neurology 2010;23:243-259.
8. Reilmann R, Leavitt BR, Ross CA. Diagnostic criteria for Huntington's disease based on natural history. Mov Disord 2014;29:1335-1341.
9. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. Mov Disord 1996;11:136-142.
10. Reilmann R, Schubert R. Motor outcome measures in Huntington disease clinical trials. Handb Clin Neurol 2017;144:209-225.
11. Dumas EM, van den Bogaard SJ, Middelkoop HA, Roos RA. A review of cognition in Huntington's disease. Frontiers in bioscience (Scholar edition) 2013;5:1-18.
12. Maroof DA, Gross AL, Brandt J. Modeling longitudinal change in motor and cognitive processing speed in presymptomatic Huntington's disease. JClinExpNeuropsychol 2011;33:901-909.
13. Snowden JS, Craufurd D, Thompson J, Neary D. Psychomotor, executive, and memory function in preclinical Huntington's disease. JClinExpNeuropsychol 2002;24:133-145.
14. Montoya A, Price BH, Menear M, Lepage M. Brain imaging and cognitive dysfunctions in Huntington's disease. JPsychiatry Neurosci 2006;31:21-29.
15. Stout JC, Queller S, Baker KN, et al. HD-CAB: a cognitive assessment battery for clinical trials in Huntington's disease 1,2,3. Mov Disord 2014;29:1281-1288.
16. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. JNeuropsychiatry ClinNeurosci 2012;24:53-60.
17. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. JNeuropsychiatry ClinNeurosci 2007;19:441-448.
18. Martinez-Horta S, Perez-Perez J, van Duijn E, et al. Neuropsychiatric symptoms are very common in premanifest and early stage Huntington's Disease. Parkinsonism Relat Disord 2016;25:58-64.

19. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801.
20. Thompson JC, Snowden JS, Craufurd D, Neary D. Behavior in Huntington's disease: dissociating cognition-based and mood-based changes. JNeuropsychiatry ClinNeurosci 2002;14:37-43.
21. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex 2006;16:916-928.
22. van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. JNeuropsychiatry ClinNeurosci 2010;22:287-294.
23. Mestre TA, van Duijn E, Davis AM, et al. Rating scales for behavioral symptoms in Huntington's disease: Critique and recommendations. Mov Disord 2016;31:1466-1478.
24. Callaghan J, Stopford C, Arran N, et al. Reliability and Factor Structure of the Short Problem Behaviors Assessment for Huntington's Disease (PBA-s) in the TRACK-HD and REGISTRY studies. JNeuropsychiatry ClinNeurosci 2015;27:59-64.
25. Niccolini F, Politis M. Neuroimaging in Huntington's disease. World J Radiol 2014;6:301-312.
26. Aylward EH, Liu D, Nopoulos PC, et al. Striatal volume contributes to the prediction of onset of Huntington disease in incident cases. Biol Psychiatry 2012;71:822-828.
27. Coppen EM, van der Grond J, Roos RAC. Atrophy of the putamen at time of clinical motor onset in Huntington's disease: a 6-year follow-up study. J Clin Mov Disord 2018;5:2.
28. Priller J, Ecker D, Landwehrmeyer B, Craufurd D. A Europe-wide assessment of current medication choices in Huntington's disease. Mov Disord 2008;23:1788.
29. van Duijn E. Treatment of Irritability in Huntington's Disease. Curr Treat Options Neurol 2010;12:424-433.
30. van Duijn E. Medical treatment of behavioral manifestations of Huntington disease. Handb Clin Neurol 2017;144:129-139.
31. Burgunder JM, Guttman M, Perlman S, Goodman N, van Kammen DP, Goodman L. An International Survey-based Algorithm for the Pharmacologic Treatment of Chorea in Huntington's Disease. PLoS Curr 2011;3:RRN1260.
32. Orth M, Handley OJ, Schwenke C, et al. Observing Huntington's disease: the European Huntington's Disease Network's REGISTRY. JNeurolNeurosurgPsychiatry 2011;82:1409-1412.



# Chapter 2
## Participants at the Leiden site of the REGISTRY study:a demographic approach

Verena Baake[1], MSc, Ellen P. Hart[2], PhD, Reineke Bos[1], MSc, and Raymund A.C. Roos[1], MD, PhD

[1]Leiden University Medical Center, department of Neurology, Leiden, The Netherlands

[2]Center for Human Drug Research, Leiden, The Netherlands

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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 deterioration[3]. HD is caused by an unstable trinucleotide repeat expansion which codes for mutant huntingtin on chromosome 4[4]. With the discovery of the expanded gene and its exact location[4] 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 span[5]. Over a course of, on average, 15 years, signs will gradually worsen, severely debilitate the patient, resulting in premature death[6]. 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 REGISTRY[7], COHORT[8], PREDICT-HD[9] and TRACK-HD[10].

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-HD[11], Riluzole[12], HD-project[13], PEP-HD[14], Track-HD[10], PADDINGTON[15], and local studies by the Department of Psychiatry[16]. 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 15$^{th}$, 1998 (retrospective data) and last baseline visit on June 12$^{th}$, 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 phenotype[17-19]. 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 $\geq 40$ as full penetrance[20].

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).

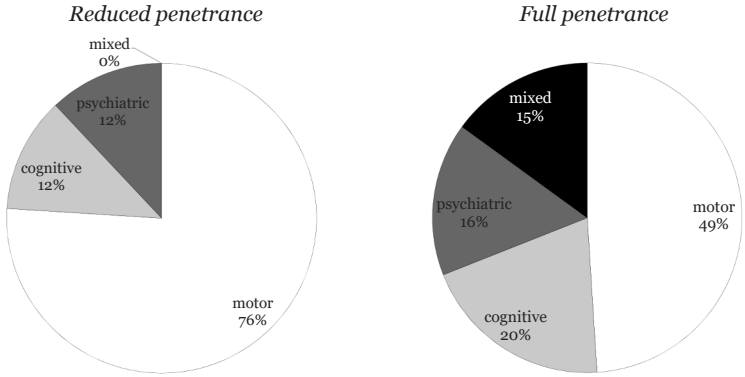
*CAG smaller allele:* The three groups did not differ significantly in the length of the smaller CAG allele (H(2)=3.26, p=0.2). Noteworthy is that one participant of the reduced penetrance group had an intermediate CAG length on the smaller allele (28/38). Seventeen participants of the full penetrance 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 *N=22* | Full penetrance *N=465* | Control *N=60* | p-value |
|---|---|---|---|---|---|
| Full cohort *(N=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) | $p < 0.01$ |
| | | *N=9* | *N=317* | *N=0* | |
| Clinically diagnosed cohort *(N=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 Fahn[22]: 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*

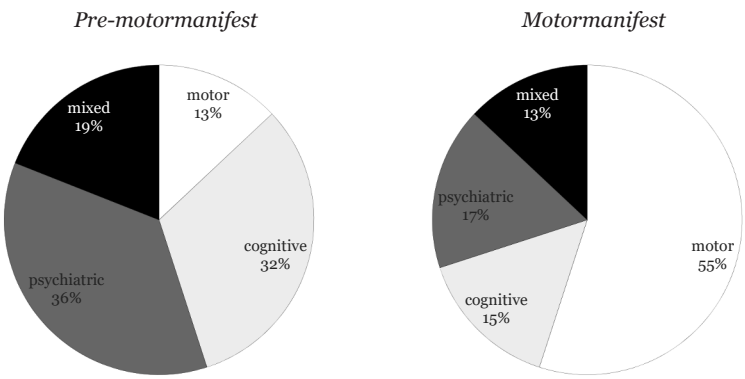
At time of REGISTRY baseline visit, 326 out of the 487 gene carriers were already clinically diagnosed with HD based on either motor, cognitive, psychiatric or mixed symptoms: 35 PMHD (21% of all PMHD participants), and 291 MHD (92% of all MHD participants) (see table 3).

*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 onset[25-27] 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 repeats[29].

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 signs[36].

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 literature[39]. One explanation could be that these patients are not recognized, under-diagnosed, referred directly to psychiatrists, or not willing to participate in studies.

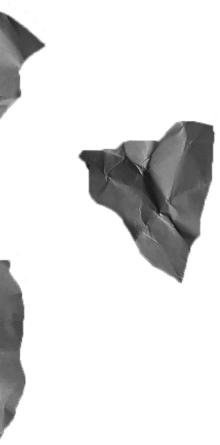
In conclusion, the Leiden REGISTRY cohort is characterized by a majority of participants who already experienced symptoms related to HD but who were still relatively functionally independent at time of enrolment. For the majority of clinically diagnosed participants, disease onset was based on motor 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.

# References


1. Fisher ER, Hayden MR. Multisource ascertainment of Huntington disease in Canada: prevalence and population at risk. Mov Disord 2014;29:105-114.
2. Morrison PJ. Prevalence estimates of Huntington disease in Caucasian populations are gross underestimates. Mov Disord 2012;27:1707-1708.
3. Novak MJ, Tabrizi SJ. Huntington's disease: clinical presentation and treatment. International review of neurobiology 2011;98:297-323.
4. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 1993;72:971-983.
5. Novak MJ, Tabrizi SJ. Huntington's disease. Bmj 2010;340:c3109.
6. Sturrock A, Leavitt BR. The clinical and genetic features of Huntington disease. Journal of geriatric psychiatry and neurology 2010;23:243-259.
7. Orth M, Handley OJ, Schwenke C, et al. Observing Huntington's disease: the European Huntington's Disease Network's REGISTRY. JNeurolNeurosurgPsychiatry 2011;82:1409-1412.
8. Dorsey ER, Beck CA, Darwin K, et al. Natural history of Huntington disease. JAMA neurology 2013;70:1520-1530.
9. Paulsen JS, Langbehn DR, Stout JC, et al. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. JNeurolNeurosurgPsychiatry 2008;79:874-880.
10. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801.
11. Quinn N, Brown R, Craufurd D, et al. Core Assessment Program for Intracerebral Transplantation in Huntington's Disease (CAPIT-HD). Mov Disord 1996;11:143-150.
12. Landwehrmeyer GB, Dubois B, de Yebenes JG, et al. Riluzole in Huntington's disease: a 3-year, randomized controlled study. AnnNeurol 2007;62:262-272.
13. Witjes-Ane MN, Vegter-van der Vlis M, van Vugt JP, et al. Cognitive and motor functioning in gene carriers for Huntington's disease: a baseline study. JNeuropsychiatry ClinNeurosci 2003;15:7-16.
14. A'Campo LE, Spliethoff-Kamminga NG, Roos RA. The Patient Education Program for Huntington's Disease (PEP-HD). JHuntingtonsDis 2012;1:47-56.
15. Hobbs NZ, Cole JH, Farmer RE, et al. Evaluation of multi-modal, multi-site neuroimaging measures in Huntington's disease: Baseline results from the PADDINGTON study. NeuroimageClin 2012;2:204-211.
16. van Duijn E, Kingma EM, Timman R, et al. Cross-sectional study on prevalences of psychiatric disorders in mutation carriers of Huntington's disease compared with mutation-negative first-degree relatives. JClinPsychiatry 2008;69:1804-1810.

17. Groen JL, de Bie RM, Foncke EM, Roos RA, Leenders KL, Tijssen MA. Late-onset Huntington disease with intermediate CAG repeats: true or false? JNeurolNeurosurgPsychiatry 2010;81:228-230.
18. Killoran A, Biglan KM, Jankovic J, et al. Characterization of the Huntington intermediate CAG repeat expansion phenotype in PHAROS. Neurology 2013;80:2022-2027.
19. Semaka A, Hayden MR. Evidence-based genetic counselling implications for Huntington disease intermediate allele predictive test results. ClinGenet 2014;85:303-311.
20. Bean L, Bayrak-Toydemir P. American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories, 2014 edition: technical standards and guidelines for Huntington disease. GenetMed 2014;16:e2.
21. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. Mov Disord 1996;11:136-142.
22. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1-3.
23. Dorsey E. Characterization of a large group of individuals with huntington disease and their relatives enrolled in the COHORT study. PLoSOne 2012;7:e29522.
24. Sequeiros J, Ramos EM, Cerqueira J, et al. Large normal and reduced penetrance alleles in Huntington disease: instability in families and frequency at the laboratory, at the clinic and in the population. ClinGenet 2010;78:381-387.
25. Quarrell OW, Rigby AS, Barron L, et al. Reduced penetrance alleles for Huntington's disease: a multi-centre direct observational study. JMedGenet 2007;44:e68.
26. Roos RA. Huntington's disease: a clinical review. OrphanetJRareDis 2010;5:40.
27. Rubinsztein DC, Leggo J, Coles R, et al. Phenotypic characterization of individuals with 30-40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36-39 repeats. AmJHumGenet 1996;59:16-22.
28. Britton JW, Uitti RJ, Ahlskog JE, Robinson RG, Kremer B, Hayden MR. Hereditary late-onset chorea without significant dementia: genetic evidence for substantial phenotypic variation in Huntington's disease. Neurology 1995;45:443-447.
29. Hadzi TC, Hendricks AE, Latourelle JC, et al. Assessment of cortical and striatal involvement in 523 Huntington disease brains. Neurology 2012;79:1708-1715.
30. Maroof DA, Gross AL, Brandt J. Modeling longitudinal change in motor and cognitive processing speed in presymptomatic Huntington's disease. JClinExpNeuropsychol 2011;33:901-909.
31. Montoya A, Price BH, Menear M, Lepage M. Brain imaging and cognitive dysfunctions in Huntington's disease. JPsychiatry Neurosci 2006;31:21-29.
32. Snowden JS, Craufurd D, Thompson J, Neary D. Psychomotor, executive, and memory function in preclinical Huntington's disease. JClinExpNeuropsychol 2002;24:133-145.
33. Solomon AC, Stout JC, Weaver M, et al. Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. Mov Disord 2008;23:1830-1836.

34. Kingma EM, van DE, Timman R, van der Mast RC, Roos RA. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. GenHospPsychiatry 2008;30:155-161.
35. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. JNeuropsychiatry ClinNeurosci 2012;24:53-60.
36. Reilmann R, Leavitt BR, Ross CA. Diagnostic criteria for Huntington's disease based on natural history. Mov Disord 2014;29:1335-1341.
37. Hamilton JM, Salmon DP, Corey-Bloom J, et al. Behavioural abnormalities contribute to functional decline in Huntington's disease. JNeurolNeurosurgPsychiatry 2003;74:120-122.
38. Peavy GM, Jacobson MW, Goldstein JL, et al. Cognitive and functional decline in Huntington's disease: dementia criteria revisited. Mov Disord 2010;25:1163-1169.
39. van Duijn E, Craufurd D, Hubers AA, et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). JNeurolNeurosurgPsychiatry 2014.



# Chapter 3
## Cognitive decline in Huntington's disease expansion gene carriers

Verena Baake[1,2], Robert H.A.M. Reijntjes[1], Eve M. Dumas[1,3], Jennifer C. Thompson[4,5] , REGISTRY Investigators of the European Huntington's Disease Network[6] and Raymund A.C. Roos[1]

[1]Leiden University Medical Center, department of Neurology, Leiden, The Netherlands

[2] Topaz, Leiden, The Netherlands

[3] Tjongerschans Hospital, Heerenveen, the Netherlands

[4] Manchester Academic Health Sciences Centre, Cerebral Function Unit, Greater Manchester Neuroscience Centre, Salford Royal NHS Foundation Trust, Salford, United Kingdom

[5] Faculty of Biology, Medicine and Health, Division of Neuroscience and Experimental Psychology, University of Manchester, Manchester, United Kingdom

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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 4[1] 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 signs[2]. The importance of psychiatric symptoms and cognitive decline has become more recognized and new guidelines have been proposed, which include these signs for clinical diagnosis[3]. 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 diagnosis[3].

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 conflicting[4-9] 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 onset[10-13] 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 length[18]. As cognitive decline is associated with brain atrophy[15, 19], which in turn is also negatively influenced by CAG length[18], 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 study[20], 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 colleagues[21-24]. 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 ±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 UHDRS[26] 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 values[29]. 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
[a]total number; significant difference between the groups marked with *
[b]Participants were grouped based on baseline characteristics; mean (range)
[c]mean (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.

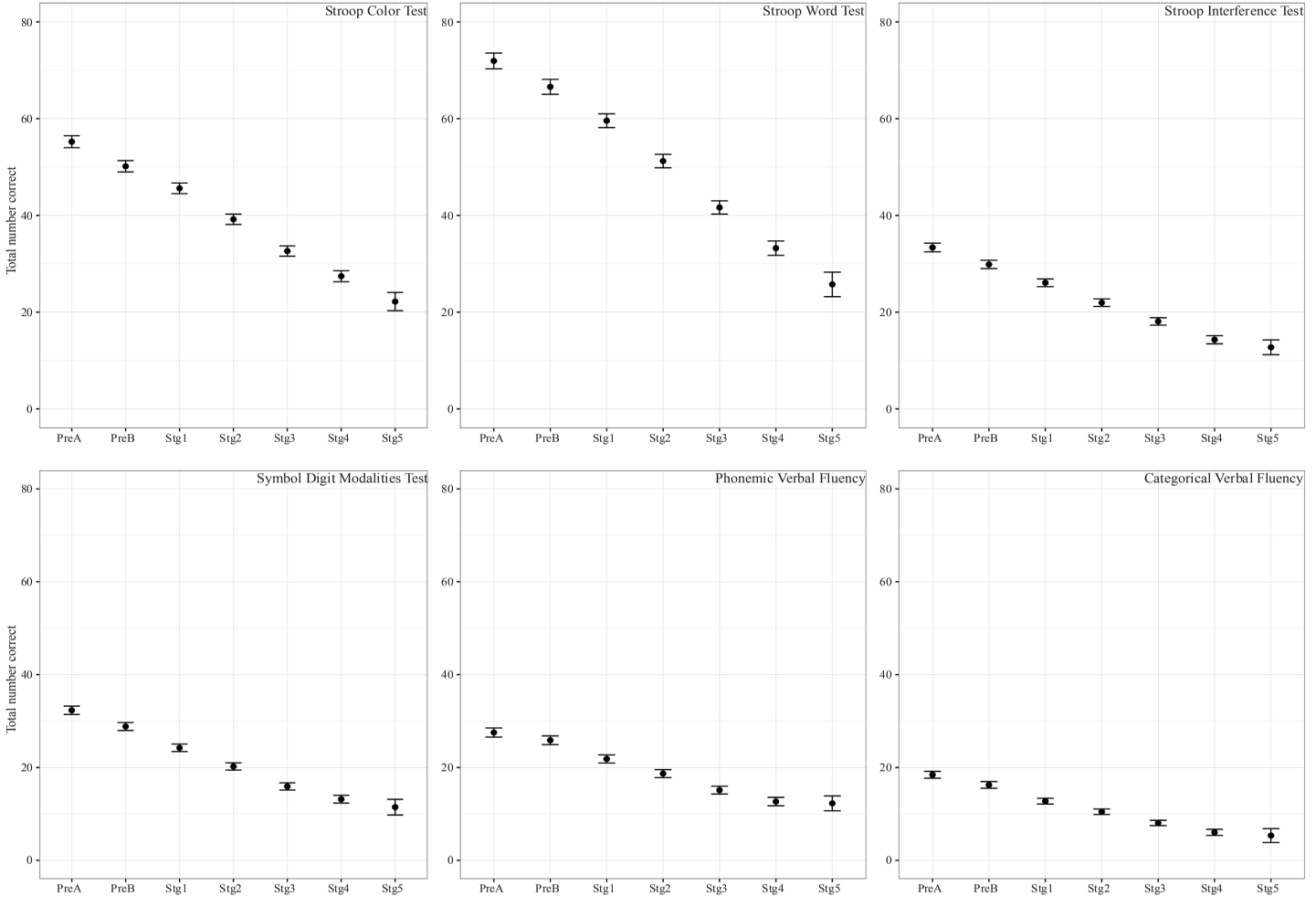
**Table 2: Results of the linear mixed effects models; comparing subsequent disease stages per cognitive task**

| | 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-motormanifst 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; Stg1: disease stage 1; Stg2: disease stage 2; Stg3: disease stage 3; Stg4: disease stage 4; Stg5: disease stage 5;
Note: Group comparrison 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 ($b=16.03$, $t(3870.75)=26.9$, $p<0.01$).

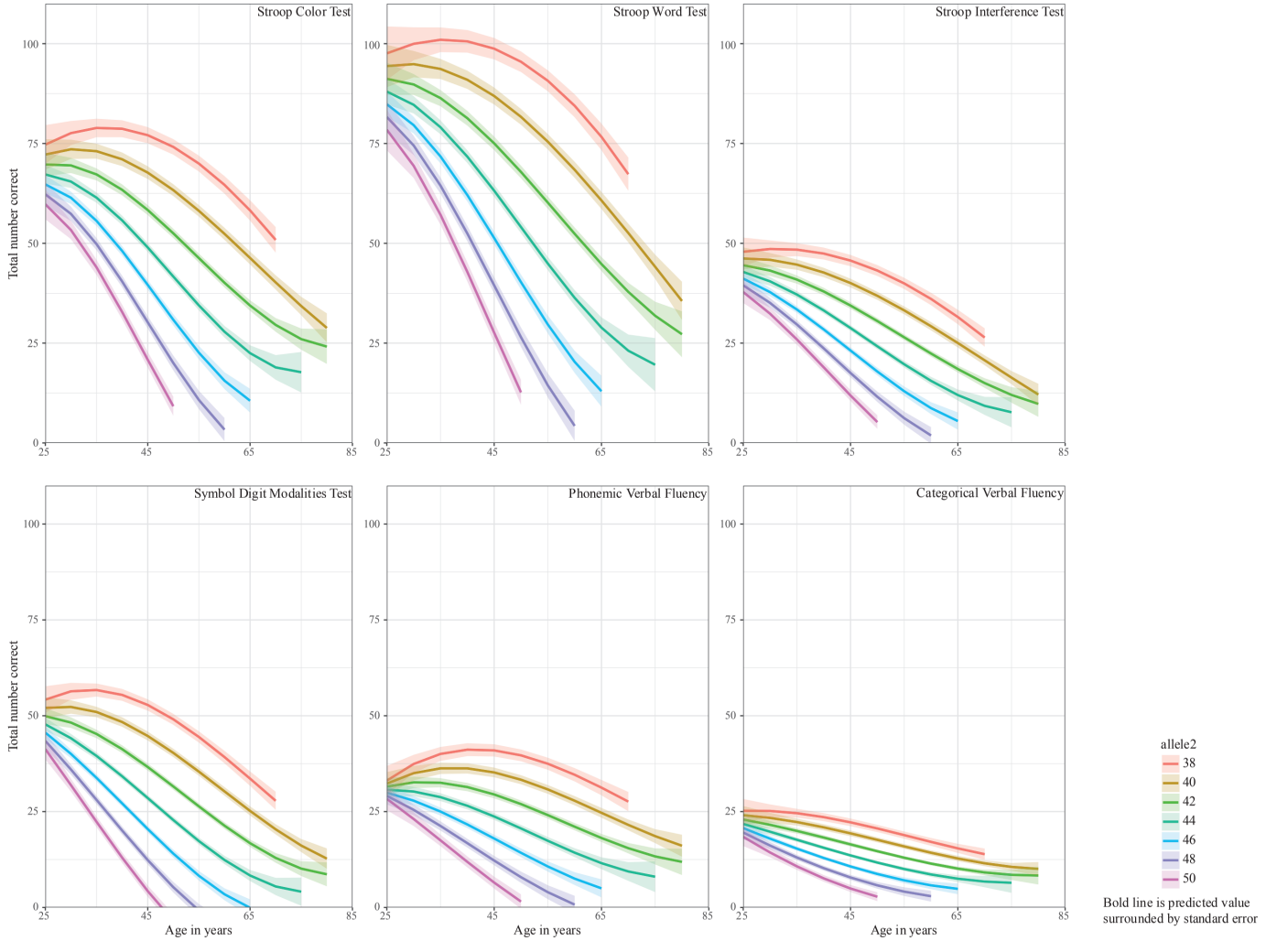
In contrast to the Stroop Word Test the Categorical Verbal Fluency Test did not discriminate well between the different CAG lengths. As participants aged the performance worsened but the different lines stay close to each other (see figure 2). For the Stroop Color Test, Strop Interference Test, Symbol 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-motormanifest[8] and early HD[30]. 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 countries[31]. 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 progression[32]. 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 progression[32], 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 HD[34] 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 tasks[31]. 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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**Language coordinators:** Verena Baake (formerly Rödig), Katrin Barth, Monica Bascuñana Garde, Tomáš Bernard, Sabrina Betz, Reineke Bos, Adrien Come, Leonor Correia Guedes, Jenny Callaghan, Selene Capodarca, Sébastien Charpentier Wildson, Vieira da Silva, Martina Di Renzo, Daniel Ecker, Ana Maria Finisterra,, Ruth Fullam, Camille Genoves, Mette Gilling, Olivia J Handley, Carina Hvalstedt, Christine Held, Kerstin Koppers, Claudia Lamanna, Matilde Laurà, Asunción Martínez Descals, Saul Martinez-Horta, Tiago Mestre, Sara Minster, Daniela Monza, Kristina Münkel, Lisanne Mütze, Martin Oehmen, Helene Padieu, Laurent Paterski, Nadia Peppa, Susana Pro Koivisto, Beate Rindal, Dawn Rogers, Niini Røren (formerly Heinonen), Ana Salgueiro, Pavla Šašinková, Catherine Taylor, Erika Timewell, Jenny Townhill, Patricia Trigo Cubillo, Marleen R van Walsem, Marie-Noelle Witjes-Ané, Grzegorz Witkowski, Abigail Wright, Daniel Zielonka, Eugeniusz Zielonka, Paola Zinzi

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**Prague (Extrapyramidové centrum, Neurologická klinika, 1. LF UK a VFN):** Jiří Klempíř, Veronika Majerová, Jan Roth

## *FINLAND*

**Kuopio:** Paivi Hartikainen, Mari Ollokainen

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*GERMANY*

**Aachen (Universitätsklinikum Aachen, Neurologische Klinik):** Christoph Michael Kosinski, Eva Milkereit, Daniela Probst, Kathrin Reetz, Christian Sass, Johannes Schiefer, Christiane Schlangen, Cornelius J. Werner

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*POLAND*

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*PORTUGAL*

**Coimbra – (Hospital Universitário de Coimbra):** Cristina Januário, Filipa Júlio

**Lisbon-HSM (Hospital de Santa Maria, Clinical Pharmacology Unit, Instituto de Medicina Molecular):** Leonor Correia Guedes, Miguel Coelho, Joaquim J Ferreira, Tiago Mestre, Tiago Mendes, Anabela Valadas

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*SPAIN*

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**Burgos (Servicio de Neurología Hospital General Yagüe):** Esther Cubo, Cecilia Gil Polo, Natividad Mariscal

**Canarias (Hospital Insular de Gran Canaria):** Sandra Gutierrez Romero, José Matías Arbelo, Rocío Malo de Molina, Idaira Martín, Juan Manuel Periañez, Beatriz Udaeta

**Fuenlabrada (Hospital Universitario):** Fernando Alonso-Frech, María del Valle Loarte

**Granada (Hospital Universitario San Cecilio, Neurología):** Francisco Barrero, Blas Morales

**Madrid-BTCIEN (Fundación CIEN):** Belén Frades, Marina Ávila Villanueva, Maria Ascension Zea Sevilla

**Madrid-Clinico (Hospital Clínico Universitario San Carlos):** Fernando Alonso Frech, María del Mar Fenollar, Rocío García-Ramos García, Clara Villanueva

**Madrid RYC (Hospital Ramón y Cajal, Neurología):** Mónica Bascuñana, Marta Fatás Ventura, Juan García Caldentey, Guillermo García Ribas, Justo García de Yébenes, José Luis López–Sendón Moreno, Verónica Mañanes Barral, Patricia Trigo Cubillo

**Madrid FJD (Madrid-Fundación Jiménez Díaz):** Cici Feliz Feliz, Pedro José García Ruíz, Ana García, Juan García Caldentey, Rosa Guerrero López, Antonio Herranz Bárcenas, Asunción Martínez-Descals, Veronica Puertas Martin, Noelia Rodríguez Martínez, María José Sainz Artiga, Vicenta Sánchez, Angel Martínez Pueyo, Javier del Val Fernandez

**Murcia (Hospital Universitario Virgen de la Arrixaca):** Moreau María Dolores Alarcón, Carmen Antúnez Almagro, Esther Diéguez, Lorenza Fortuna, Salvadora Manzanares, Juan Marín Muñoz, María Martirio Antequera Torres, Fuensanta Noguera Perea, Laura Vivancos

**Oviedo (Hospital Central de Asturias):** Sonia González, Luis Menéndez Guisasola, Marta Para Prieto, René Ribacoba, Carlos Salvador, Pablo Sánchez Lozano

**Palma de Mallorca (Hospital Universitario Son Espases):** Juan García Caldentey, Aránzazu Gorospe, Inés Legarda Ramirez, Penelope Navas Arques, Monica Rodriguez Lopera, Barbara Vives Pastor

**Pamplona (Complejo Hospitalario de Navarra):** Itziar Gaston, Fermin Garcia-Amigot, Maria Dolores Martinez-Jaurrieta, Maria Antonia Ramos-Arroyo

**Sevilla (Hospital Virgen Macarena):** Fátima Damas Hermoso, José Manuel García Moreno, Carolina Mendez Lucena, Eva María Pacheco Cortegana, José Chacón Peña, Luis Redondo, Violeta Sánchez Sánchez

Valencia (Hospital la Fe): Maria Bosca, Juan Andres Burguera, Francisco Castera Brugada Carmen Peiró Vilaplana, Pilar Solís, Begoña Jeweinat Figuerola, Paloma Millan Palanca

*SWEDEN*

**Göteborg (Sahlgrenska University Hospital**): Maria Berglund, Peter Berglund, Radu Constantinescu, Gunnel Fredlund, Ulrika Høsterey-Ugander, Kajsa Lewin, Petra Linnsand, Liselotte Neleborn-Lingefjärd, Jan Wahlström+

**Lunds University Hospital:** Åsa Petersén, Jan Reimer, Håkan Widner

**Umeå (Umeå University Hospital):** Måns Berglund, Ghada Loutfi, Carina Olofsson, Eva-Lena Stattin, Laila Westman, Birgitta Wikström

**Uppsala University Hospital:** Camilla Ekwall, Marie-Lousie Göller, Valter Niemelä, Jimmy Sundblom

*SWITZERLAND*

**Bern:** Jean-Marc Burgunder, Yanik Stebler (Swiss HD Zentrum), Alain Kaelin, Irene Romero, Michael Schüpbach, Sabine Weber Zaugg (Zentrum für Bewegungsstörungen, Neurologische Klinik und Poliklinik, Universität Bern)

**Zürich (University Hospital and University of Zurich):** Hans H. Jung, Jens A. Petersen, Maria Ligon-Auer, Violeta Mihaylova

*U.K.*

**Aberdeen (NHS Grampian Clinical Genetics Centre & University of Aberdeen):** Lorna Downie, Roisin Jack, Kirsty Matheson, Zosia Miedzybrodzka, Daniela Rae, Sheila A Simpson, Fiona Summers, Alexandra Ure, Vivien Vaughan

**Birmingham (The Barberry Centre, Dept of Psychiatry):** Shahbana Akhtar, Jenny Crooks, Adrienne Curtis, Jenny de Souza (Keylock), John Piedad, Hugh Rickards, Jan Wright

**Bristol (North Bristol NHs Trust, Southmead hospital):** Elizabeth Coulthard, Louise Gethin, Beverley Hayward, Kasia Sieradzan, Abigail Wright

**Cambridge (Cambridge Centre for Brain Repair, Forvie Site**): Roger A. Barker, Deidre O'Keefe, Anna Gerrtiz (nee Di Pietro), Kate Fisher, Anna Goodman, Susan Hill, Sarah Mason, Rachel Swain, Natalie Valle Guzman

**Cardiff (Schools of Medicine and Biosciences, Cardiff University):** Monica Busse, Cynthia Butcher, Stephen Dunnett, Catherine Clenaghan, Ruth Fullam, Sarah Hunt, Lesley Jones, Una Jones, Hanan Khalil, Sara Minster, Michael Owen, Kathleen Price, Jenny Townhill, Anne Rosser

**Dundee (Scottish Huntington's Association, Ninewells Hospital):** David Goudie, Lindsay Buchanan, Paula McFadyen, Alison Tonner, Anne-Marie Taylor

**Edinburgh (SE Scotland Genetic Service, Western General Hospital):** Maureen Edwards, Carrie Ho (Scottish Huntington´s Association), Marie McGill, Mary Porteous, Pauline Pearson

**Exeter (Department of Neurology Royal Devon and Exeter Foundation Trust Hospital):** Timothy Harrower, Sarah Irvine

**Fife (Scottish Huntington's Association Whyteman's Brae Hospital):** Peter Brockie, Jillian Foster, Nicola Johns, Sue McKenzie, Jean Rothery, Gareth Thomas, Shona Yates

**Glasgow (Glasgow HD Management Clinic, Southern General Hospital)**: Catherine Deith, Jane Ireland, Stuart Ritchie

**Gloucester (Department of Neurology Gloucestershire Royal Hospital):** Pauline Brown, Liz Burrows, Amy Fletcher, Alison Harding, Fiona Laver, Mark Silva, Aileen Thomson

**Hull (Castle Hill Hospital):** Carol Chu, Carole Evans, Deena Gallentree, Stephanie Hamer, Alison Kraus, Ivana Markova, Ashok Raman

**Leeds (Chapel Allerton Hospital, Department of Clinical Genetics):** Jeremy Cosgrove, Deena Gallantree, Stephanie Hamer, Emma Hobson, Stuart Jamieson , Alison Kraus, Mandy Longthorpe, Ivana Markova, Hannah Musgrave, Caroline Peacy, Ashok Raman, Liz Rowett, Jean Toscano, Sue Wild, Pam Yardumian

**Leicester (Leicestershire Partnership Trust, Mill Lodge):** Carole Clayton, Heather Dipple, Dawn Freire-Patino, Caroline Hallam, Julia Middleton

**London (St. Georges-Hospital):** Uruj Anjum, Jan Coebergh, Charlotte Eddy, Nayana Lahiri, Meriel McEntagart, Michael Patton, Maria Peterson, Sarah Rose

**London (Guy's Hospital):** Thomasin Andrews, Andrew Dougherty, Charlotte Golding, Fred Kavalier, Hana Laing, Alison Lashwood, Dene Robertson, Deborah Ruddy, Alastair Santhouse, Anna Whaite

**London (The National Hospital for Neurology and Neurosurgery):** Thomasin Andrews, Stefanie Brown, Stefania Bruno, Elvina Chu, Karen Doherty, Charlotte Golding, Salman Haider, Davina Hensman, Nayana Lahiri, Monica Lewis, Marianne Novak, Aakta Patel, Nicola Robertson, Elisabeth Rosser, Sarah Tabrizi, Rachel Taylor, Thomas Warner, Edward Wild

**Manchester (Genetic Medicine, University of Manchester, Manchester Academic Health Sciences Centre and Central Manchester University Hospitals NHS Foundation Trust):** Natalie Arran, Judith Bek, Jenny Callaghan, David Craufurd, Ruth Fullam, Marianne Hare, Liz Howard, Susan Huson, Liz Johnson, Mary Jones, Ashok Krishnamoorthy, Helen Murphy, Emma Oughton, Lucy Partington-Jones, Dawn Rogers, Andrea Sollom, Julie Snowden, Cheryl Stopford, Jennifer Thompson, Iris Trender-Gerhard, Nichola Verstraelen (formerly Ritchie), Leann Westmoreland

**Newcastle-upon-Tyne (Centre for Life, Institute of Medical Genetics):** Ginette Cass, Lynn Davidson, Jill Davison, Neil Fullerton, Katrina Holmes, Suresh Komati, Sharon McDonnell, Zeid Mohammed, Karen Morgan, Lois Savage, Baldev Singh, Josh Wood

**Northampton (St Andrew's Healthcare):** Elvina Chu, Caroline Knight, Mari O'Neill, Debasish Das Purkayastha

**Oxford (Oxford University Hospitals NHS Trust, Dept. of Neurosciences, University of Oxford):** Andrea H Nemeth, Gill Siuda, Ruth Valentine, Kathryn Dixon, Richard Armstrong

**Plymouth (Plymouth Huntington Disease Service, Mount Gould Hospital):** David Harrison, Max Hughes, Sandra Large, John O Donovan, Amy Palmer, Andrew Parkinson, Beverley Soltysiak, Leanne Timings, Josh Williams

**Preston (Neurology Department, Preston Royal Hospital):** Marianne Hare, Tahir Majeed, Nicola Verstraelen (Ritchie)

**Sheffield (The Royal Hallamshire Hospital– Sheffield Children's Hospital):** Oliver Bandmann, Alyson Bradbury, Helen Fairtlough, Kay Fillingham, Isabella Foustanos, Paul Gill, Mbombe Kazoka, Kirsty O'Donovan, Louise Nevitt, Nadia Peppa, Oliver Quarrell, Cat Taylor, Katherine Tidswell, Kirsty O'Donovan

**Swindon (Victoria Centre, Great Western Hospital):** Lesley Gowers, Kingsley Powell, Pamela Bethwaite, Rachel Edwards, Kathleen Fuller, Michelle Phillips

EHDN's associate site in Singapore:

**National Neuroscience Institute Singapore:** Louis Tan, Jean-Marc Burgunder, Puay Ngoh Lau, Emmanuel Pica

# References


1. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 1993;72:971-983.
2. Roos RA. Huntington's disease: a clinical review. OrphanetJRareDis 2010;5:40.
3. Reilmann R, Leavitt BR, Ross CA. Diagnostic criteria for Huntington's disease based on natural history. Mov Disord 2014;29:1335-1341.
4. Ho AK, Sahakian BJ, Brown RG, et al. Profile of cognitive progression in early Huntington's disease. Neurology 2003;61:1702-1706.
5. Lemiere J, Decruyenaere M, Evers-Kiebooms G, Vandenbussche E, Dom R. Cognitive changes in patients with Huntington's disease (HD) and asymptomatic carriers of the HD mutation--a longitudinal follow-up study. JNeurol 2004;251:935-942.
6. Stout JC, Jones R, Labuschagne I, et al. Evaluation of longitudinal 12 and 24 month cognitive outcomes in premanifest and early Huntington's disease. JNeurolNeurosurgPsychiatry 2012;83:687-694.
7. Witjes-Ane MN, Vegter-van der Vlis M, van Vugt JP, et al. Cognitive and motor functioning in gene carriers for Huntington's disease: a baseline study. JNeuropsychiatry ClinNeurosci 2003;15:7-16.
8. Paulsen JS, Smith MM, Long JD, investigators PH, Coordinators of the Huntington Study G. Cognitive decline in prodromal Huntington Disease: implications for clinical trials. J Neurol Neurosurg Psychiatry 2013;84:1233-1239.
9. Hart E, Middelkoop H, Jurgens CK, Witjes-Ane MN, Roos RA. Seven-year clinical follow-up of premanifest carriers of Huntington's disease. PLoSCurr 2011;3:RRN1288.
10. Maroof DA, Gross AL, Brandt J. Modeling longitudinal change in motor and cognitive processing speed in presymptomatic Huntington's disease. JClinExpNeuropsychol 2011;33:901-909.
11. Snowden JS, Craufurd D, Thompson J, Neary D. Psychomotor, executive, and memory function in preclinical Huntington's disease. JClinExpNeuropsychol 2002;24:133-145.
12. Solomon AC, Stout JC, Weaver M, et al. Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. Mov Disord 2008;23:1830-1836.
13. Dumas EM, van den Bogaard SJ, Middelkoop HA, Roos RA. A review of cognition in Huntington's disease. Frontiers in bioscience (Scholar edition) 2013;5:1-18.
14. Solomon AC, Stout JC, Johnson SA, et al. Verbal episodic memory declines prior to diagnosis in Huntington's disease. Neuropsychologia 2007;45:1767-1776.
15. Montoya A, Price BH, Menear M, Lepage M. Brain imaging and cognitive dysfunctions in Huntington's disease. JPsychiatry Neurosci 2006;31:21-29.
16. Bachoud-Levi AC, Maison P, Bartolomeo P, et al. Retest effects and cognitive decline in longitudinal follow-up of patients with early HD. Neurology 2001;56:1052-1058.

17. Snowden J, Craufurd D, Griffiths H, Thompson J, Neary D. Longitudinal evaluation of cognitive disorder in Huntington's disease. JIntNeuropsycholSoc 2001;7:33-44.
18. Penney JB, Jr., Vonsattel JP, MacDonald ME, Gusella JF, Myers RH. CAG repeat number governs the development rate of pathology in Huntington's disease. Ann Neurol 1997;41:689-692.
19. Bohanna I, Georgiou-Karistianis N, Hannan AJ, Egan GF. Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for Huntington's disease. Brain ResRev 2008;58:209-225.
20. Orth M, Handley OJ, Schwenke C, et al. Observing Huntington's disease: the European Huntington's Disease Network's REGISTRY. JNeurolNeurosurgPsychiatry 2011;82:1409-1412.
21. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. ClinGenet 2004;65:267-277.
22. Langbehn DR, Hayden MR, Paulsen JS, Group P-HIotHS. CAG-repeat length and the age of onset in Huntington disease (HD): a review and validation study of statistical approaches. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 2010;153B:397-408.
23. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801.
24. Wild EJ. Huntington's disease conditional onset probability calculator [online]. Available at: http://edwild.com/205-huntingtons-disease-conditional-onset-probability-calculator/.
25. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1-3.
26. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. Mov Disord 1996;11:136-142.
27. Ho AK, Sahakian BJ, Robbins TW, Barker RA, Rosser AE, Hodges JR. Verbal fluency in Huntington's disease: a longitudinal analysis of phonemic and semantic clustering and switching. Neuropsychologia 2002;40:1277-1284.
28. Callaghan J, Stopford C, Arran N, et al. Reliability and Factor Structure of the Short Problem Behaviors Assessment for Huntington's Disease (PBA-s) in the TRACK-HD and REGISTRY studies. JNeuropsychiatry ClinNeurosci 2015;27:59-64.
29. Gibbons RD, Hedeker D, DuToit S. Advances in analysis of longitudinal data. AnnuRevClinPsychol 2010;6:79-107.
30. Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol 2013;12:637-649.
31. Stout JC, Queller S, Baker KN, et al. HD-CAB: a cognitive assessment battery for clinical trials in Huntington's disease 1,2,3. Mov Disord 2014;29:1281-1288.

32. Andrew SE, Goldberg YP, Kremer B, et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nat Genet 1993;4:398-403.
33. Thompson JC, Poliakoff E, Sollom AC, Howard E, Craufurd D, Snowden JS. Automaticity and attention in Huntington's disease: when two hands are not better than one. Neuropsychologia 2010;48:171-178.
34. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP, Jr. Neuropathological classification of Huntington's disease. JNeuropatholExpNeurol 1985;44:559-577.

# Chapter 4
## Influence of medication use on cognitive performance in Huntington's disease

Verena Baake[1,2], REGISTRY Investigators of the European Huntington's Disease Network[3] and Raymund A.C. Roos[1]

[1]Leiden University Medical Center, Department of Neurology, Leiden, The Netherlands

[2] Huntington Center Topaz Overduin, Katwijk, The Netherlands

[3] Membership of the REGISTRY Investigators of the European Huntington's Disease Network is provided in the acknowledgments

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 4[1]. HD is characterized by a triad of symptoms: motor abnormalities, behavioral signs and cognitive deterioration[2]. 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 years[5-13]. 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 trials[14], 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 treatment[18]. 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 present[21]. Behavioral symptoms, e.g. anxiety, are often treated with benzodiazepines[20]. 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 cognition[24]. In another study it was found that HD patients using antipsychotic medication (classical and atypical) or tetrabenazine had a faster disease progression[25]. 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 formula[26-29] 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 scale[30]. 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
[a]Mean (standard deviation)
[b]Total 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

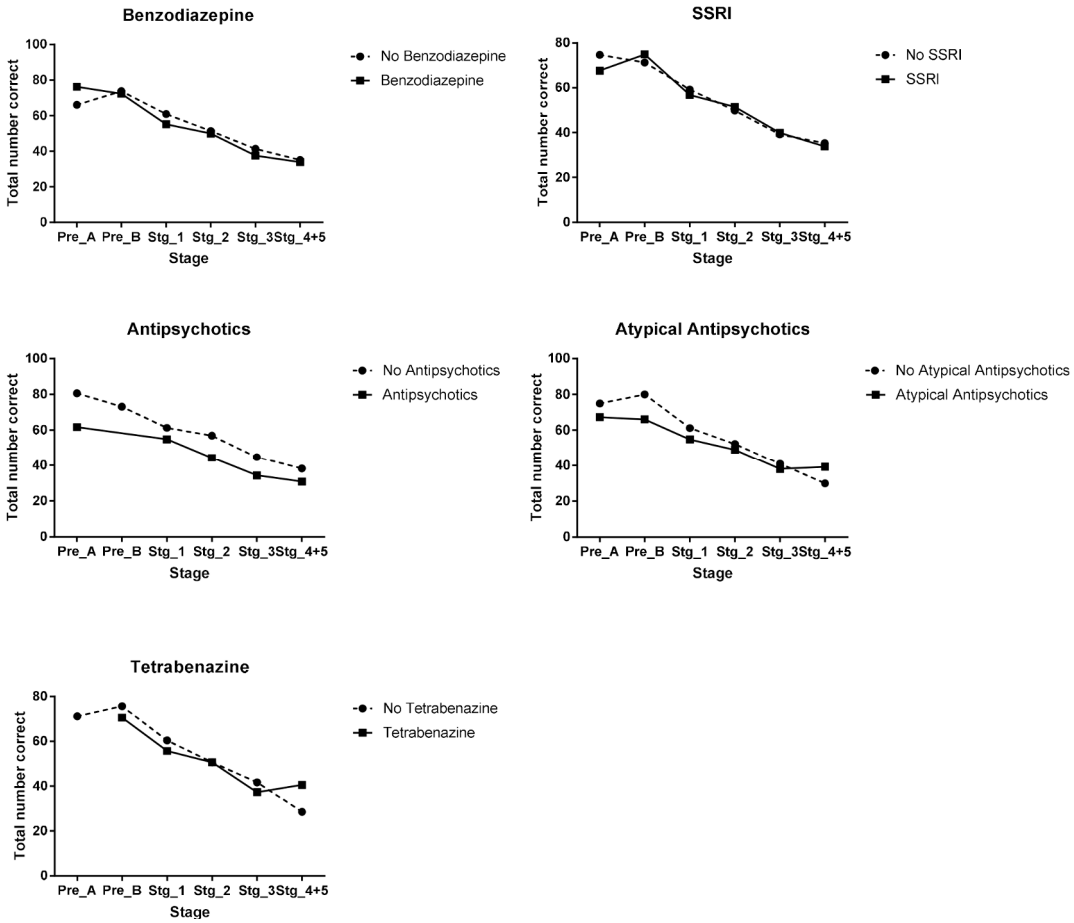
This study shows that about half of the HD-REGISTRY population used medication targeting non-cognitive neuropsychiatric disturbances and/or tetrabenazine. The percentage of HD gene carriers taking these medications increased from pre-motormanifest to the advanced HD. The most logical explanation for 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
[a]Total 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 symptoms[20]. Throughout disease progression symptoms become more severe, global functioning decreases and medication treatment becomes useful, supported by adjunctive therapies, to manage all symptoms[32]. Polypharmacy is common in HD due to the complexity of the disease and several symptoms which need to be addressed[20] 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 HD[33]. 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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**Language coordinators:** Verena Baake (formerly Rödig), Katrin Barth, Monica Bascuñana Garde, Tomáš Bernard, Sabrina Betz, Reineke Bos, Adrien Come, Leonor Correia Guedes, Jenny Callaghan, Selene Capodarca, Sébastien Charpentier Wildson, Vieira da Silva, Martina Di Renzo, Daniel Ecker, Ana Maria Finisterra,, Ruth Fullam, Camille Genoves, Mette Gilling, Olivia J Handley, Carina Hvalstedt, Christine Held, Kerstin Koppers, Claudia Lamanna, Matilde Laurà, Asunción Martínez Descals, Saul Martinez-Horta, Tiago Mestre, Sara Minster, Daniela Monza, Kristina Münkel, Lisanne Mütze, Martin Oehmen, Helene Padieu, Laurent Paterski, Nadia Peppa, Susana Pro Koivisto, Beate Rindal, Dawn Rogers, Niini Røren (formerly Heinonen), Ana Salgueiro, Pavla Šašinková, Catherine Taylor, Erika Timewell, Jenny Townhill, Patricia Trigo Cubillo, Marleen R van Walsem, Marie-Noelle Witjes-Ané, Grzegorz Witkowski, Abigail Wright, Daniel Zielonka, Eugeniusz Zielonka, Paola Zinzi

## *AUSTRIA*

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**Kuopio:** Paivi Hartikainen, Mari Ollokainen

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### *NETHERLANDS*

**Enschede (Medisch Spectrum Twente):** Monique S.E. van Hout, Jeroen P.P. van Vugt, A. Marit de Weert, Marloes Verhoeven

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**Maastricht:** Annelien Duits, Mayke Oosterloo, Mirella Waber

### *NORWAY*

**Bergen (Haukeland University Hospital, Dept of Medical Genetics and Olaviken Psychiatric Hospital):** Ellen Økland Blinkenberg. (NKS Olaviken`s HD clinic): Erik Hauge, Hilde Tyvoll

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**Trondheim (St. Olavs Hospital):** Inga Bjørnevoll, Sigrid Botne Sando, Marte Gjøl Haug, Hanna Haugan Størseth, Vibeke Arntsen

*POLAND*

**Gdansk (St. Adalbert Hospital, Gdansk, Medical University of Gdansk, Neurological and Psychiatric Nursing Dpt.):** Artur Dziadkiewicz, Agnieszka Konkel, Ewa Narożańska, Malgorzata Nowak, Piotr Robowski, Emilia Sitek, Jaroslaw Slawek, Witold Soltan, Michal Szinwelski

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**Poznan (Poznan University of Medical Sciences, Poland):** Jacek Anioła Anna Bryl, Anna Ciesielska, Aneta Klimberg, Jerzy Marcinkowski, Husam Samara, Justyna Sempołowicz, Bartłomiej Wiśniewski, Daniel Zielonka

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*PORTUGAL*

**Coimbra – (Hospital Universitário de Coimbra):** Cristina Januário, Filipa Júlio

**Lisbon-HSM (Hospital de Santa Maria, Clinical Pharmacology Unit, Instituto de Medicina Molecular):** Leonor Correia Guedes, Miguel Coelho, Joaquim J Ferreira, Tiago Mestre, Tiago Mendes, Anabela Valadas

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*SPAIN*

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**Glasgow (Glasgow HD Management Clinic, Southern General Hospital)**: Catherine Deith, Jane Ireland, Stuart Ritchie

**Gloucester (Department of Neurology Gloucestershire Royal Hospital):** Pauline Brown, Liz Burrows, Amy Fletcher, Alison Harding, Fiona Laver, Mark Silva, Aileen Thomson

**Hull (Castle Hill Hospital):** Carol Chu, Carole Evans, Deena Gallentree, Stephanie Hamer, Alison Kraus, Ivana Markova, Ashok Raman

**Leeds (Chapel Allerton Hospital, Department of Clinical Genetics):** Jeremy Cosgrove, Deena Gallantree, Stephanie Hamer, Emma Hobson, Stuart Jamieson , Alison Kraus, Mandy Longthorpe, Ivana Markova, Hannah Musgrave, Caroline Peacy, Ashok Raman, Liz Rowett, Jean Toscano, Sue Wild, Pam Yardumian

**Leicester (Leicestershire Partnership Trust, Mill Lodge):** Carole Clayton, Heather Dipple, Dawn Freire-Patino, Caroline Hallam, Julia Middleton

**London (St. Georges-Hospital):** Uruj Anjum, Jan Coebergh, Charlotte Eddy, Nayana Lahiri, Meriel McEntagart, Michael Patton, Maria Peterson, Sarah Rose

**London (Guy's Hospital):** Thomasin Andrews, Andrew Dougherty, Charlotte Golding, Fred Kavalier, Hana Laing, Alison Lashwood, Dene Robertson, Deborah Ruddy, Alastair Santhouse, Anna Whaite

**London (The National Hospital for Neurology and Neurosurgery):** Thomasin Andrews, Stefanie Brown, Stefania Bruno, Elvina Chu, Karen Doherty, Charlotte Golding, Salman Haider, Davina Hensman, Nayana Lahiri, Monica Lewis, Marianne Novak, Aakta Patel, Nicola Robertson, Elisabeth Rosser, Sarah Tabrizi, Rachel Taylor, Thomas Warner, Edward Wild

**Manchester (Genetic Medicine, University of Manchester, Manchester Academic Health Sciences Centre and Central Manchester University Hospitals NHS Foundation Trust):** Natalie Arran, Judith Bek, Jenny Callaghan, David Craufurd, Ruth Fullam, Marianne Hare, Liz Howard, Susan Huson, Liz Johnson, Mary Jones, Ashok Krishnamoorthy, Helen Murphy, Emma Oughton, Lucy Partington-Jones, Dawn Rogers, Andrea Sollom, Julie Snowden, Cheryl Stopford, Jennifer Thompson, Iris Trender-Gerhard, Nichola Verstraelen (formerly Ritchie), Leann Westmoreland

**Newcastle-upon-Tyne (Centre for Life, Institute of Medical Genetics):** Ginette Cass, Lynn Davidson, Jill Davison, Neil Fullerton, Katrina Holmes, Suresh Komati, Sharon McDonnell, Zeid Mohammed, Karen Morgan, Lois Savage, Baldev Singh, Josh Wood

**Northampton (St Andrew's Healthcare):** Elvina Chu, Caroline Knight, Mari O'Neill, Debasish Das Purkayastha

**Oxford (Oxford University Hospitals NHS Trust, Dept. of Neurosciences, University of Oxford):** Andrea H Nemeth, Gill Siuda, Ruth Valentine, Kathryn Dixon, Richard Armstrong

**Plymouth (Plymouth Huntington Disease Service, Mount Gould Hospital):** David Harrison, Max Hughes, Sandra Large, John O Donovan, Amy Palmer, Andrew Parkinson, Beverley Soltysiak, Leanne Timings, Josh Williams

**Preston (Neurology Department, Preston Royal Hospital):** Marianne Hare, Tahir Majeed, Nicola Verstraelen (Ritchie)

**Sheffield (The Royal Hallamshire Hospital– Sheffield Children's Hospital):** Oliver Bandmann, Alyson Bradbury, Helen Fairtlough, Kay Fillingham, Isabella Foustanos, Paul Gill, Mbombe Kazoka, Kirsty O'Donovan, Louise Nevitt, Nadia Peppa, Oliver Quarrell, Cat Taylor, Katherine Tidswell, Kirsty O'Donovan

**Swindon (Victoria Centre, Great Western Hospital):** Lesley Gowers, Kingsley Powell, Pamela Bethwaite, Rachel Edwards, Kathleen Fuller, Michelle Phillips

EHDN's associate site in Singapore:

**National Neuroscience Institute Singapore:** Louis Tan, Jean-Marc Burgunder, Puay Ngoh Lau, Emmanuel Pica

# References


1. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 1993;72:971-983.
2. Roos RA. Huntington's disease: a clinical review. OrphanetJRareDis 2010;5:40.
3. Nehl C, Paulsen JS, Huntington Study G. Cognitive and psychiatric aspects of Huntington disease contribute to functional capacity. J Nerv Ment Dis 2004;192:72-74.
4. Ready RE, Mathews M, Leserman A, Paulsen JS. Patient and caregiver quality of life in Huntington's disease. Movement disorders : official journal of the Movement Disorder Society 2008;23:721-726.
5. Duff K, Paulsen J, Mills J, et al. Mild cognitive impairment in prediagnosed Huntington disease. Neurology 2010;75:500-507.
6. Kirkwood SC, Siemers E, Hodes ME, Conneally PM, Christian JC, Foroud T. Subtle changes among presymptomatic carriers of the Huntington's disease gene. JNeurolNeurosurgPsychiatry 2000;69:773-779.
7. Lemiere J, Decruyenaere M, Evers-Kiebooms G, Vandenbussche E, Dom R. Longitudinal study evaluating neuropsychological changes in so-called asymptomatic carriers of the Huntington's disease mutation after 1 year. Acta NeurolScand 2002;106:131-141.
8. Paulsen JS, Smith MM, Long JD, investigators PH, Coordinators of the Huntington Study G. Cognitive decline in prodromal Huntington Disease: implications for clinical trials. J Neurol Neurosurg Psychiatry 2013;84:1233-1239.
9. Stout JC, Jones R, Labuschagne I, et al. Evaluation of longitudinal 12 and 24 month cognitive outcomes in premanifest and early Huntington's disease. JNeurolNeurosurgPsychiatry 2012;83:687-694.
10. Dumas EM, van den Bogaard SJ, Middelkoop HA, Roos RA. A review of cognition in Huntington's disease. Frontiers in bioscience (Scholar edition) 2013;5:1-18.
11. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. JNeuropsychiatry ClinNeurosci 2012;24:53-60.
12. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. JNeuropsychiatry ClinNeurosci 2007;19:441-448.
13. Baake V, Reijntjes R, Dumas EM, Thompson JC, Network RIotEHsD, Roos RAC. Cognitive decline in Huntington's disease expansion gene carriers. Cortex 2017;95:51-62.
14. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. Mov Disord 1996;11:136-142.
15. Paulsen JS. Cognitive impairment in Huntington disease: diagnosis and treatment. Current neurology and neuroscience reports 2011;11:474-483.

16. Solomon AC, Stout JC, Weaver M, et al. Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. Mov Disord 2008;23:1830-1836.
17. Killoran A, Biglan KM. Current therapeutic options for Huntington's disease: good clinical practice versus evidence-based approaches? Movement disorders : official journal of the Movement Disorder Society 2014;29:1404-1413.
18. Priller J, Ecker D, Landwehrmeyer B, Craufurd D. A Europe-wide assessment of current medication choices in Huntington's disease. Mov Disord 2008;23:1788.
19. van Duijn E. Treatment of Irritability in Huntington's Disease. Curr Treat Options Neurol 2010;12:424-433.
20. van Duijn E. Medical treatment of behavioral manifestations of Huntington disease. Handb Clin Neurol 2017;144:129-139.
21. Como PG, Rubin AJ, O'Brien CF, et al. A controlled trial of fluoxetine in nondepressed patients with Huntington's disease. Mov Disord 1997;12:397-401.
22. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs 2004;18:37-48.
23. Islam MM, Iqbal U, Walther B, et al. Benzodiazepine Use and Risk of Dementia in the Elderly Population: A Systematic Review and Meta-Analysis. Neuroepidemiology 2016;47:181-191.
24. Desamericq G, Dolbeau G, Verny C, et al. Effectiveness of anti-psychotics and related drugs in the Huntington French-speaking group cohort. PLoS One 2014;9:e85430.
25. Tedroff J, Waters S, Barker RA, Roos R, Squitieri F, Group ERS. Antidopaminergic Medication is Associated with More Rapidly Progressive Huntington's Disease. J Huntingtons Dis 2015;4:131-140.
26. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. ClinGenet 2004;65:267-277.
27. Langbehn DR, Hayden MR, Paulsen JS, Group P-HIotHS. CAG-repeat length and the age of onset in Huntington disease (HD): a review and validation study of statistical approaches. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 2010;153B:397-408.
28. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801.
29. Wild EJ. Huntington's disease conditional onset probability calculator [online]. Available at: http://edwild.com/205-huntingtons-disease-conditional-onset-probability-calculator/.
30. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1-3.
31. Orth M, Handley OJ, Schwenke C, et al. Observing Huntington's disease: the European Huntington's Disease Network's REGISTRY. JNeurolNeurosurgPsychiatry 2011;82:1409-1412.

32. Burgunder JM, Guttman M, Perlman S, Goodman N, van Kammen DP, Goodman L. An International Survey-based Algorithm for the Pharmacologic Treatment of Chorea in Huntington's Disease. PLoS Curr 2011;3:RRN1260.

33. Frank S. Tetrabenazine as anti-chorea therapy in Huntington disease: an open-label continuation study. Huntington Study Group/TETRA-HD Investigators. BMC Neurol 2009;9:62.

## 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

Verena Baake[1,2], Emma M. Coppen[1], Erik van Duijn[3,4], Eve M. Dumas[1,5], Simon J.A. van den Bogaard[1,5], Rachael I. Scahill[6], Hans Johnson[7], Blair Leavitt[8], Alexandra Durr[9], Sarah J. Tabrizi[6], David Craufurd[10,11], Raymund A.C. Roos[1] and the Track-HD investigators

[1]Leiden University Medical Center, department of Neurology, Leiden, The Netherlands

[2] Huntington Center Topaz Overduin, Katwijk, The Netherlands

[3]Leiden University Medical Center, Department of Psychiatry, Leiden, The Netherlands

[4]Mental Health Care of Center Delfland, Delft, The Netherlands

[5]Tongerschans General Hospital, Heerenveen, The Netherlands

[6]Huntington's Disease Centre, UCL Institute of Neurology, University College London, UK

[7]Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa, IA, USA

[8]Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada

[9] ICM - Institut du Cerveau et de la Moelle Epinière, Sorbonne Universités – UPMC Université Paris, Genetic department, Pitié-Salpêtrière University Hospital, Paris, France

[10] Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

[11]Manchester Centre for Genomic Medicine, St. Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

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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 decline[1]. Despite motor symptoms being the most specific to HD, the highest burden reported by HD gene carriers and caregivers are the cognitive and behavioral symptoms[2]. 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 stage[4]. 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 carriers[3]. In addition, apathy itself is negatively related to functional capacity, cognitive performance and motor impairment in HD[12]. 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 circuit[13], 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 putamen[15]. 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 circuit[17], is associated with apathy in Parkinson's disease[18]. 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 stage[30]. 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 function[31], and general functioning[3], 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 ≥39. HD gene carriers with no substantial motor signs at baseline, as indicated with a total motor score (TMS) of ≤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 formula[32]. 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) score[33]. 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 scale[34]. 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 FSL[37]. All images were registered to the Montreal Neurological Institute (MNI) 152-space standard image, using linear registration with 12 degrees of freedom[38]. 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 FSL[39].

### *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, buproprion, 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.

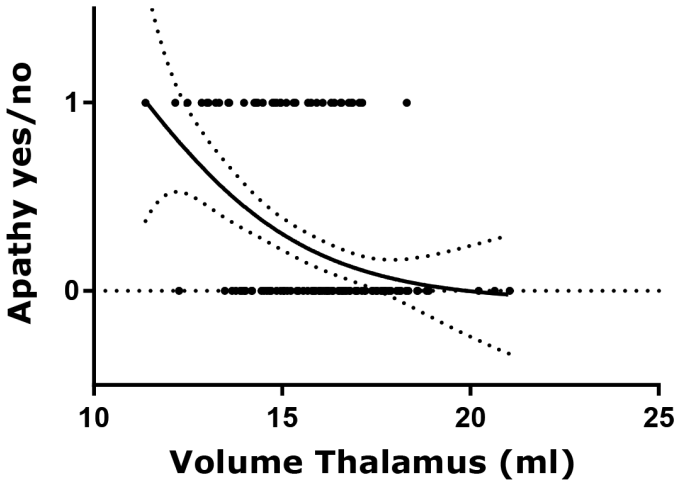
The logistic model showed that only a smaller volume of the thalamus (OR=0.57; 95% CI:0.38–0.84; p=0.004) was associated with the presence of apathy; i.e. smaller thalamus indicates a higher probability of presence of apathy, see figure 1. No other associations were found, and the results did not change 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
[a]total number
[b]mean (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 increases[3] 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 previously[11]. 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 improved[44]. 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 apathy[45]. 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 years[1]. This is supported by Thompson et al.'s study[3] 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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# References


1. Roos RA. Huntington‘s disease: a clinical review. OrphanetJRareDis 2010;5:40.
2. Hamilton JM, Salmon DP, Corey-Bloom J, et al. Behavioural abnormalities contribute to functional decline in Huntington‘s disease. JNeurolNeurosurgPsychiatry 2003;74:120-122.
3. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington‘s disease. JNeuropsychiatry ClinNeurosci 2012;24:53-60.
4. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington‘s disease gene carriers. JNeuropsychiatry ClinNeurosci 2007;19:441-448.
5. Martinez-Horta S, Perez-Perez J, van Duijn E, et al. Neuropsychiatric symptoms are very common in premanifest and early stage Huntington‘s Disease. Parkinsonism Relat Disord 2016;25:58-64.
6. Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington‘s disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol 2013;12:637-649.
7. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. JNeurolNeurosurgPsychiatry 2008;79:1088-1092.
8. Leroi I, Harbishettar V, Andrews M, McDonald K, Byrne EJ, Burns A. Carer burden in apathy and impulse control disorders in Parkinson‘s disease. IntJGeriatrPsychiatry 2012;27:160-166.
9. Aubeeluck AV, Buchanan H, Stupple EJ. ‚All the burden on all the carers‘: exploring quality of life with family caregivers of Huntington‘s disease patients. QualLife Res 2012;21:1425-1435.
10. Kingma EM, van DE, Timman R, van der Mast RC, Roos RA. Behavioural problems in Huntington‘s disease using the Problem Behaviours Assessment. GenHospPsychiatry 2008;30:155-161.
11. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington‘s disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801.
12. Thompson JC, Snowden JS, Craufurd D, Neary D. Behavior in Huntington‘s disease: dissociating cognition-based and mood-based changes. JNeuropsychiatry ClinNeurosci 2002;14:37-43.
13. Levy R. Apathy: a pathology of goal-directed behaviour: a new concept of the clinic and pathophysiology of apathy. Rev Neurol (Paris) 2012;168:585-597.
14. Haegelen C, Rouaud T, Darnault P, Morandi X. The subthalamic nucleus is a key-structure of limbic basal ganglia functions. MedHypotheses 2009;72:421-426.
15. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. JPsychosomRes 2002;53:647-654.
16. Cummings JL. Frontal-subcortical circuits and human behavior. ArchNeurol 1993;50:873-880.
17. Riba J, Kramer UM, Heldmann M, Richter S, Munte TF. Dopamine agonist increases risk taking but blunts reward-related brain activity. PLoS One 2008;3:e2479.

18. Martinez-Horta S, Sampedro F, Pagonabarraga J, et al. Non-demented Parkinson's disease patients with apathy show decreased grey matter volume in key executive and reward-related nodes. Brain Imaging Behav 2016.
19. Aylward EH, Nopoulos PC, Ross CA, et al. Longitudinal change in regional brain volumes in prodromal Huntington disease. JNeurolNeurosurgPsychiatry 2011;82:405-410.
20. Hobbs NZ, Henley SM, Ridgway GR, et al. The progression of regional atrophy in premanifest and early Huntington's disease: a longitudinal voxel-based morphometry study. JNeurolNeurosurgPsychiatry 2010;81:756-763.
21. Douaud G, Gaura V, Ribeiro MJ, et al. Distribution of grey matter atrophy in Huntington's disease patients: a combined ROI-based and voxel-based morphometric study. Neuroimage 2006;32:1562-1575.
22. Paulsen JS, Magnotta VA, Mikos AE, et al. Brain structure in preclinical Huntington's disease. BiolPsychiatry 2006;59:57-63.
23. Thieben MJ, Duggins AJ, Good CD, et al. The distribution of structural neuropathology in pre-clinical Huntington's disease. Brain 2002;125:1815-1828.
24. Bohanna I, Georgiou-Karistianis N, Hannan AJ, Egan GF. Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for Huntington's disease. Brain ResRev 2008;58:209-225.
25. Georgiou-Karistianis N, Scahill R, Tabrizi SJ, Squitieri F, Aylward E. Structural MRI in Huntington's disease and recommendations for its potential use in clinical trials. NeurosciBiobehavRev 2013;37:480-490.
26. Montoya A, Price BH, Menear M, Lepage M. Brain imaging and cognitive dysfunctions in Huntington's disease. JPsychiatry Neurosci 2006;31:21-29.
27. Aylward EH, Codori AM, Barta PE, Pearlson GD, Harris GJ, Brandt J. Basal ganglia volume and proximity to onset in presymptomatic Huntington disease. ArchNeurol 1996;53:1293-1296.
28. Paulsen JS, Langbehn DR, Stout JC, et al. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. JNeurolNeurosurgPsychiatry 2008;79:874-880.
29. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP, Jr. Neuropathological classification of Huntington's disease. JNeuropatholExpNeurol 1985;44:559-577.
30. van den Bogaard SJ, Dumas EM, Acharya TP, et al. Early atrophy of pallidum and accumbens nucleus in Huntington's disease. JNeurol 2011;258:412-420.
31. van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. JNeuropsychiatry ClinNeurosci 2010;22:287-294.
32. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. ClinGenet 2004;65:267-277.
33. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1-3.

34. Callaghan J, Stopford C, Arran N, et al. Reliability and Factor Structure of the Short Problem Behaviors Assessment for Huntington's Disease (PBA-s) in the TRACK-HD and REGISTRY studies. JNeuropsychiatry ClinNeurosci 2015;27:59-64.
35. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23 Suppl 1:S208-219.
36. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 2011;56:907-922.
37. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17:143-155.
38. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17:825-841.
39. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17:479-489.
40. O'Callaghan C, Bertoux M, Hornberger M. Beyond and below the cortex: the contribution of striatal dysfunction to cognition and behaviour in neurodegeneration. JNeurolNeurosurgPsychiatry 2013.
41. Tabrizi SJ, Reilmann R, Roos RA, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. Lancet Neurol 2012;11:42-53.
42. Tabrizi SJ, Scahill RI, Durr A, et al. Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. Lancet Neurol 2011;10:31-42.
43. McNally G, Rickards H, Horton M, Craufurd D. Exploring the Validity of the Short Version of the Problem Behaviours Assessment (PBA-s) for Huntington's disease: A Rasch Analysis. J Huntingtons Dis 2015;4:347-369.
44. Reedeker N, Bouwens JA, van DE, Giltay EJ, Roos RA, van der Mast RC. Incidence, course, and predictors of apathy in Huntington's disease: a two-year prospective study. JNeuropsychiatry ClinNeurosci 2011;23:434-441.
45. van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. J Neuropsychiatry Clin Neurosci 2010;22:287-294.

# Chapter 6
## Huntington's disease gene expansion carriers are aware of their degree of apathy

Verena Baake[1, 2], Erik van Duijn[3] and Raymund A.C. Roos[1]

1 Leiden University Medical Center, Department of Neurology, Leiden, The Netherlands

2 Huntington Center Topaz Overduin, Katwijk, The Netherlands

3 Leiden University Medical Center, Department of Psychiatry, Leiden; and Mental Health Care Centre Delfland, Delft, The Netherlands

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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 4[1]. HD is clinically characterized by a triad of symptoms: motor abnormalities, behavioural symptoms, and cognitive deterioration[2]. 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 sings 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 signs[4].

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 stage[6]. 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 HD[5]. Therefore, it is suggested that apathy is caused by the neurodegenerative process in HD and could be seen as a marker of disease progression[8]. In HD, apathy is also associated with cognitive dysfunction and the use of psychotropic medication[9]. In their review of rating scales for behavioural symptoms in HD, Mestre et al.[10] discuss three scales for assessing apathy in HD. Several studies[11-13] 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 stage[16]. 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 proxies[11], but the second study did not find a difference in the total apathy score between pre-manifest and manifest HDGECs and their proxies[17]. 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 AES[18], 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 HD[10]. 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 study[19] 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) score[21]. 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 72[14]. 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 apathy[9], 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, buproprion, 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
[a]significant difference between pre-motormanifest and early motormanifest
[b]significant difference between pre-motormanifest and late motormanifest
[c]significant difference between early motormanifest and late motormanifest

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

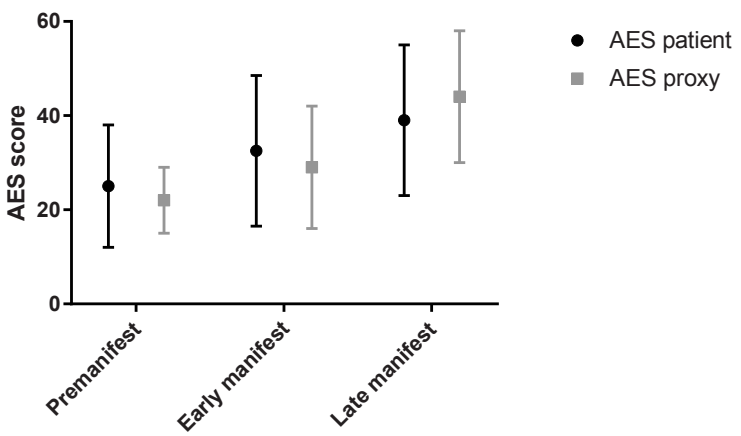
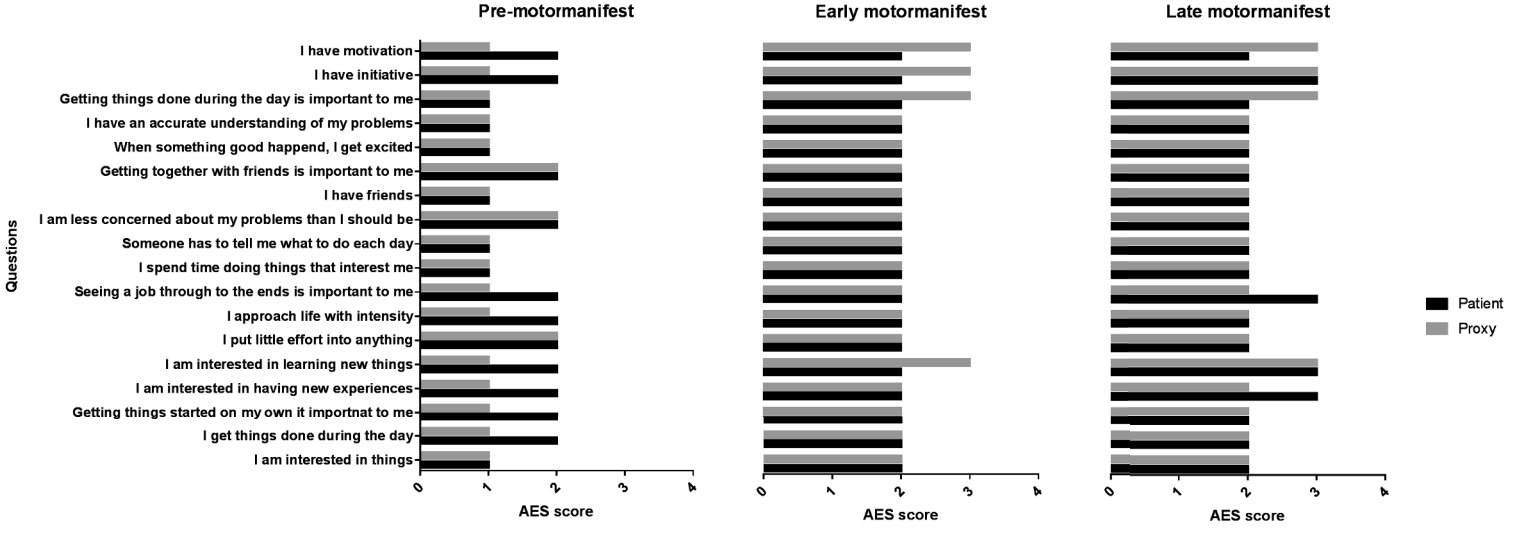


**Figure 2: Average score on each question per participant group**




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 stage[5]. 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.

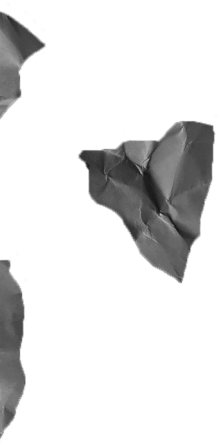
One limitation of our study is that we might have a selection bias. We asked all REGISTRY participants during a specific time period to participate in this study. It is possible that more severe apathetic or cognitively impaired participants declined to participate in this study. In addition, we assumed 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.

# References


1. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 1993;72:971-983.
2. Roos RA. Huntington's disease: a clinical review. OrphanetJRareDis 2010;5:40.
3. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801.
4. Reilmann R, Leavitt BR, Ross CA. Diagnostic criteria for Huntington's disease based on natural history. Mov Disord 2014;29:1335-1341.
5. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. JNeuropsychiatry ClinNeurosci 2012;24:53-60.
6. van Duijn E, Craufurd D, Hubers AA, et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). JNeurolNeurosurgPsychiatry 2014.
7. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. JNeurolNeurosurgPsychiatry 2008;79:1088-1092.
8. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington Disease. Neuropsychiatry NeuropsycholBehavNeurol 2001;14:219-226.
9. van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. JNeuropsychiatry ClinNeurosci 2010;22:287-294.
10. Mestre TA, van Duijn E, Davis AM, et al. Rating scales for behavioral symptoms in Huntington's disease: Critique and recommendations. Mov Disord 2016;31:1466-1478.
11. Chatterjee A, Anderson KE, Moskowitz CB, Hauser WA, Marder KS. A comparison of self-report and caregiver assessment of depression, apathy, and irritability in Huntington's disease. JNeuropsychiatry ClinNeurosci 2005;17:378-383.
12. Reedeker N, Bouwens JA, van DE, Giltay EJ, Roos RA, van der Mast RC. Incidence, course, and predictors of apathy in Huntington's disease: a two-year prospective study. JNeuropsychiatry ClinNeurosci 2011;23:434-441.
13. van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. J Neuropsychiatry Clin Neurosci 2010;22:287-294.
14. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res 1991;38:143-162.
15. McCusker E, Loy CT. The many facets of unawareness in huntington disease. Tremor Other Hyperkinet Mov (N Y) 2014;4:257.
16. Sitek EJ, Thompson JC, Craufurd D, Snowden JS. Unawareness of deficits in Huntington's disease. J Huntingtons Dis 2014;3:125-135.

17. Mason S, Barker RA. Rating Apathy in Huntington's Disease: Patients and Companions Agree. J Huntingtons Dis 2015;4:49-59.
18. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992;4:134-139.
19. Orth M, Handley OJ, Schwenke C, et al. Observing Huntington's disease: the European Huntington's Disease Network's REGISTRY. JNeurolNeurosurgPsychiatry 2011;82:1409-1412.
20. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. Mov Disord 1996;11:136-142.
21. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1-3.
22. Martinez-Horta S, Perez-Perez J, van Duijn E, et al. Neuropsychiatric symptoms are very common in premanifest and early stage Huntington's Disease. Parkinsonism Relat Disord 2016;25:58-64.



# 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 research[1-4]. These results emphasize that the recently published guidelines, which state that HD diagnosis can be given purely on cognitive and/or psychiatric symptoms[5], 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 diverse[8]. Apathy is common, is the only behavioral symptom closely related to disease progression[9-11] and is present in almost all late stage HDGECs[11]. 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 circuit[13]. 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 HD[14], 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 treatment[17]. Very recently, one trial has been launched which aims to lower the huntingtin level in the brain to stop or delay the neurogenerative process[18]. 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 replace 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.

# References


1. Dumas EM, van den Bogaard SJ, Middelkoop HA, Roos RA. A review of cognition in Huntington's disease. Frontiers in bioscience (Scholar edition) 2013;5:1-18.
2. Maroof DA, Gross AL, Brandt J. Modeling longitudinal change in motor and cognitive processing speed in presymptomatic Huntington's disease. JClinExpNeuropsychol 2011;33:901-909.
3. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801.
4. Witjes-Ane MN, Vegter-van der Vlis M, van Vugt JP, et al. Cognitive and motor functioning in gene carriers for Huntington's disease: a baseline study. JNeuropsychiatry ClinNeurosci 2003;15:7-16.
5. Reilmann R, Leavitt BR, Ross CA. Diagnostic criteria for Huntington's disease based on natural history. Mov Disord 2014;29:1335-1341.
6. Andrew SE, Goldberg YP, Kremer B, et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nat Genet 1993;4:398-403.
7. Penney JB, Jr., Vonsattel JP, MacDonald ME, Gusella JF, Myers RH. CAG repeat number governs the development rate of pathology in Huntington's disease. Ann Neurol 1997;41:689-692.
8. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. JNeuropsychiatry ClinNeurosci 2007;19:441-448.
9. Martinez-Horta S, Perez-Perez J, van Duijn E, et al. Neuropsychiatric symptoms are very common in premanifest and early stage Huntington's Disease. Parkinsonism Relat Disord 2016;25:58-64.
10. Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol 2013;12:637-649.
11. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. JNeuropsychiatry ClinNeurosci 2012;24:53-60.
12. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. JNeurolNeurosurgPsychiatry 2008;79:1088-1092.
13. Levy R. Apathy: a pathology of goal-directed behaviour: a new concept of the clinic and pathophysiology of apathy. Rev Neurol (Paris) 2012;168:585-597.
14. Martinez-Horta S, Perez-Perez J, Sampedro F, et al. Structural and metabolic brain correlates of apathy in Huntington's disease. Mov Disord 2018.
15. McCusker E, Loy CT. The many facets of unawareness in huntington disease. Tremor Other Hyperkinet Mov (N Y) 2014;4:257.
16. Sitek EJ, Thompson JC, Craufurd D, Snowden JS. Unawareness of deficits in Huntington's disease. J Huntingtons Dis 2014;3:125-135.
17. Sampaio C, Borowsky B, Reilmann R. Clinical trials in Huntington's disease: Interventions in early clinical development and newer methodological approaches. Mov Disord 2014;29:1419-1428.

18. Rodrigues FB, Wild EJ. Clinical Trials Corner: September 2017. J Huntingtons Dis 2017;6:255-263.

# 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 tegelijktijdig 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.
2. **Baake V**, van Duijn E, Roos RAC. Huntington's Disease Gene Expansion Carriers Are Aware of Their Degree of Apathy. J Neuropsychiatry Clin Neurosci 2018;30:183-187.
3. **Baake V**, Reijntjes R, Dumas EM, Thompson JC, Registry Investigators of the European Huntington's Disease Network, Roos RAC. Cognitive decline in Huntington's disease expansion gene carriers. Cortex 2017;95:51-62.
4. **Baake V**, Hart EP, Bos R, Roos RA. Participants at the Leiden Site of the REGISTRY Study: A Demographic Approach. J Huntingtons Dis 2016;5:83-90.
5. Booij SJ, Engberts DP, **Rodig V**, Tibben A, Roos RA. A plea for end-of-life discussions with patients suffering from Huntington's disease: the role of the physician. J Med Ethics 2013;39:621-624.
6. Booij SJ, **Rodig V**, Engberts DP, Tibben A, Roos RA. Euthanasia and advance directives in Huntington's disease: qualitative analysis of interviews with patients. J Huntingtons Dis 2013;2:323-330.

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Uiteraard wil ik ook al mijn vrienden en familie bedanken, zonder hun ondersteuning en geduld was dit proefschrift niet tot stand gekomen. Waarbij een groot dank aan iedereen uitgaat die in de laatste fase soms mijn kinderen heeft opgevangen zodat ik aan dit proefschrift kon werken.

Mijn bijzonder dank gaat naar mijn echtgenoot, Wouter, die altijd voor me klaar staat en me in alles liefdevol steunt, er zijn geen woorden om dit goed te kunnen omschrijven. En ik dank mijn kinderen, Sem en Mees, die me ook hebben laten zien dat er soms meer is dan werken.

# Curriculum Vitae

Verena Baake (meisjesnaam Rödig) 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.