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Chapter 3

Cognitive decline in Huntington's disease expansion gene carriers

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Abstract

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

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

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

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

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

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

Introduction

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

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

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

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

Methods

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

Participants

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

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

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

Assessments

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

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

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

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

Statistical analysis

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

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

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

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

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

Results

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

Cognitive task performance based on disease stage

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

Table 1: Group characteristics

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

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

^atotal number; significant difference between the groups marked with *

^bParticipants were grouped based on baseline characteristics; mean (range)

^cmean (standard deviation); significant difference between the groups marked with *

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

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

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

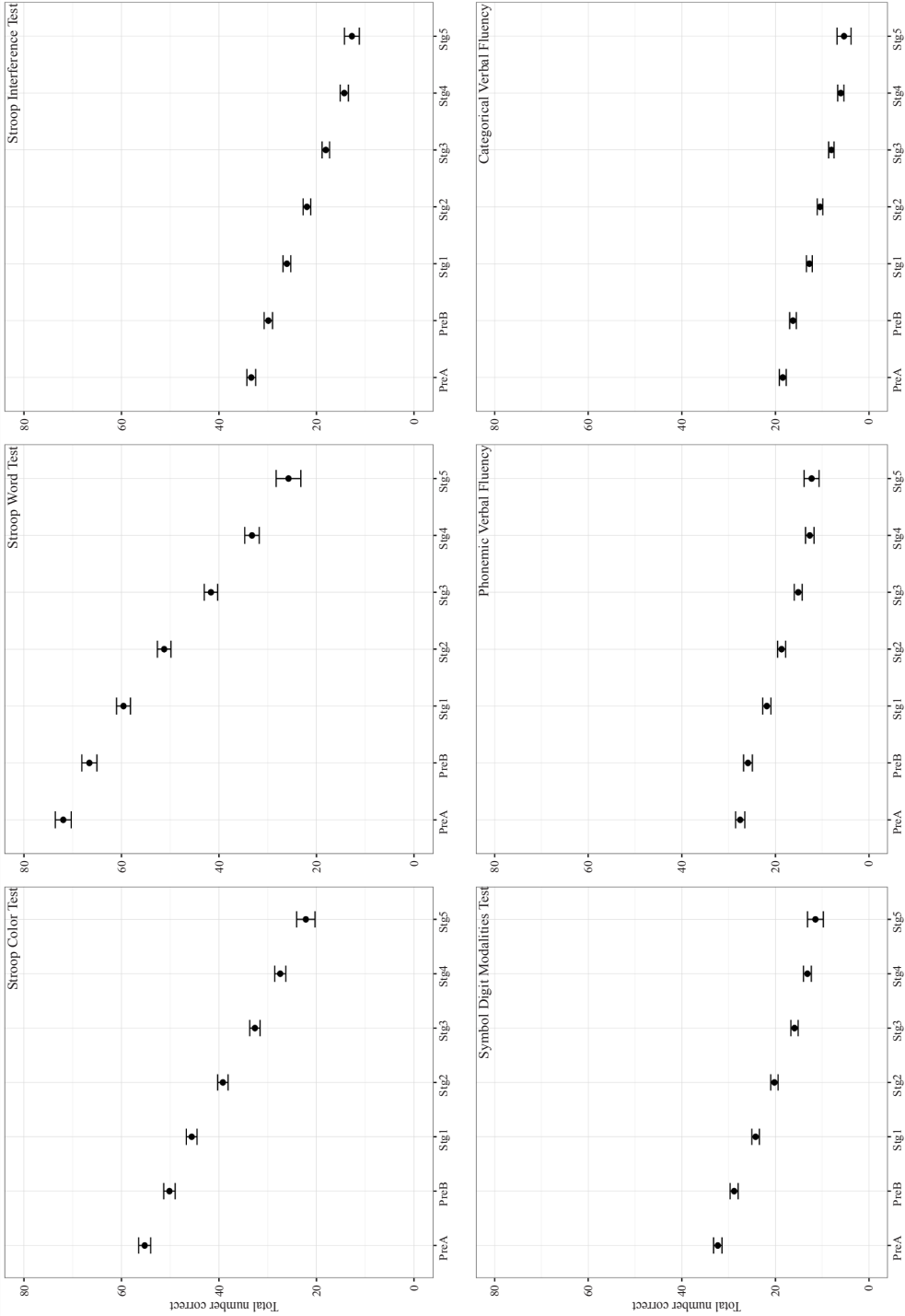
Table 2: Results of the linear mixed effects models; comparing subsequent disease stages per cognitive task

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

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

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

Figure 1: Performance on all cognitive tasks per disease stage



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

Cognitive task performance based on CAG length and age

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

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

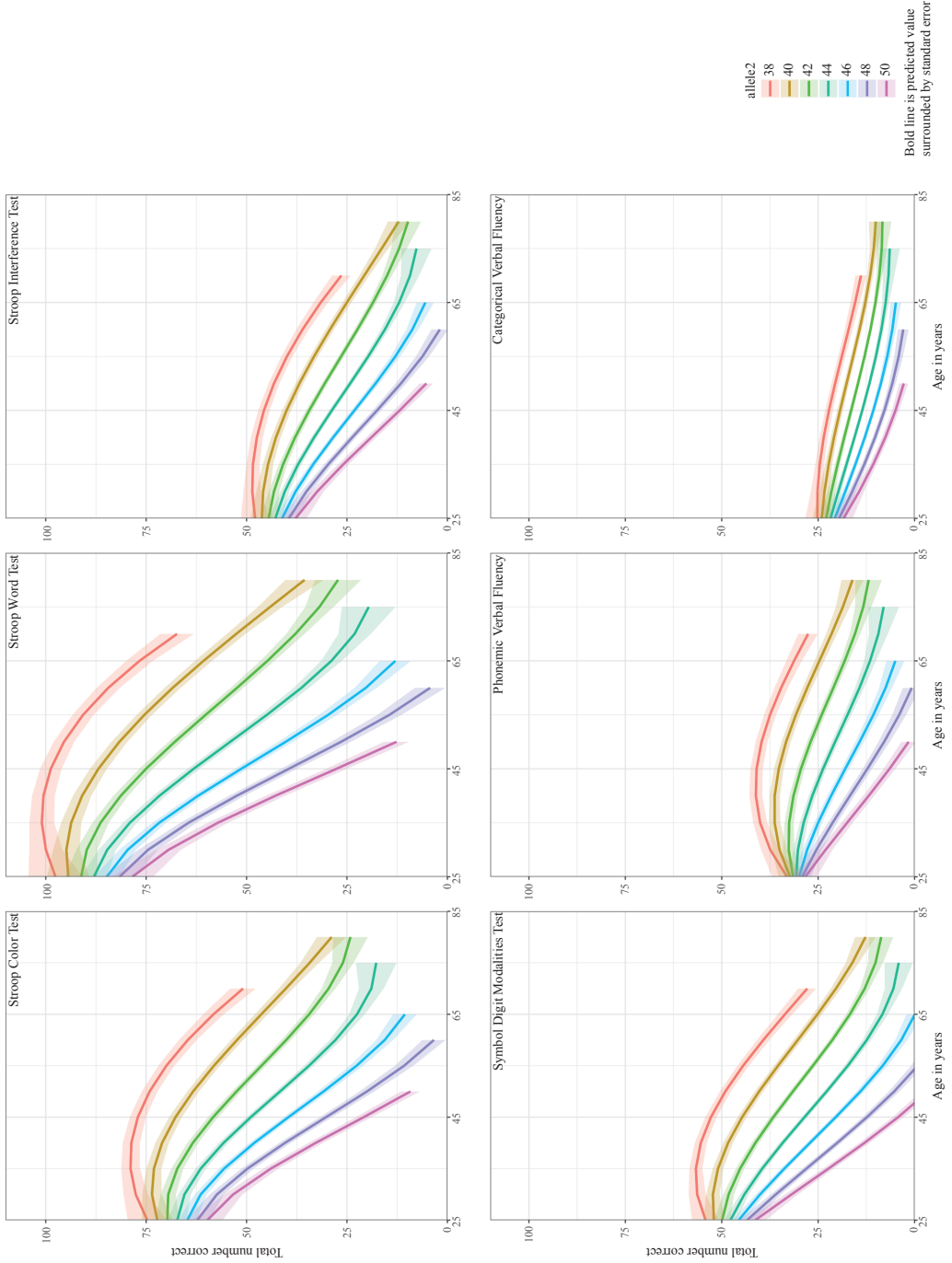
In contrast to the Stroop Word Test the Categorical Verbal Fluency Test did not discriminate well between the different CAG lengths. As participants aged the performance worsened but the different lines stay close to each other (see figure 2). For the Stroop Color Test, Stroop Interference Test, Symbol 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
Phonemic verbal fluency ^a	2548	2.39 (0.29)*	5.75 (0.22)*	6.77 (0.36)*
Stroop Color ^a	2554	4.05 (0.37)*	9.37 (0.28)*	12.26 (0.46)*
Stroop Word ^a	2526	5.09 (0.50)*	11.90 (0.36)*	16.03 (0.60)*
Stroop Interference ^a	2540	2.70 (0.27)*	5.63 (0.20)*	6.84 (0.34)*
Symbol Digit Modalities Test ^a	2521	4.08 (0.27)*	8.09 (0.21)*	8.95 (0.34)*
Categorical Fluency ^a	1410	1.80 (0.22)*	2.88 (0.15)*	2.83 (0.23)*

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

Figure 2: Cognitive performance plotted against age and CAG length



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

Discussion

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

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

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

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

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

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

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

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