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Validation Study of a German Cognitive Battery for Huntington's Disease: Relationship Between Cognitive Performance, Functional Decline, and Disease Burden

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Abstract

Objective: Cognitive decline is a key characteristic of Huntington's disease (HD). This study aimed to investigate the diagnostic accuracy of a cognitive battery with six tests used by most HD research centers to assess cognitive impairment in HD.
Method: In total, 106 HD patients in different disease stages with more (HD-CD, $N = 30$) and less cognitive impairments (HD-NC, $N = 70$) and 100 healthy controls (NC) were matched by age, sex, and education and were examined using a standardized protocol including cognitive, motor, and functional assessments.
Results: One-way between-groups analysis of variance showed that controls performed significantly better than HD patients and that HD-NC significantly outperformed HD-CD patients in all cognitive tests (NC > HD-NC > HD-CD), with all Games-Howell post-hoc tests $p < .001$. Analyses using area under the receiver-operating characteristic curve (AUC) disclosed the diagnostic accuracy of all tests included in the battery to discriminate between NC and HD patients with AUC ranging from 0.809 to 0.862 (all $p < .001$) and between HD-CD and HD-NC patients with AUC ranging from 0.833 to 0.899 (all $p < .001$). In both analysis, Stroop Color Naming Test showed the highest discriminative potential. Additional analyses showed that cognitive deficits in all domains progressed with disease duration. Moreover, cognitive performance correlated with the severity of motor and functional impairment (all $p < .001$) and with the Disease Burden Score regardless of disease duration and age.
Conclusion: Our results indicate that the cognitive battery is a suitable tool for assessing cognitive impairment in HD.

Keywords: Huntington's disease; Unified Huntington's Disease Rating Scale; Diagnostic accuracy; Neuropsychological test battery; Cognitive impairment

Introduction

Huntington disease (HD) is a progressive, autosomal dominant inherited, neurodegenerative disorder caused by an expansion in the trinucleotide cytosine-adenine-guanine (CAG) repeat in the huntingtin gene (*htt*) on chromosome 4 (Huntington's Disease Collaborative Research Group, 1993). It is characterized by a triad of clinical symptoms including progressive impairment of motor function, cognition, and behavior (Kirkwood et al., 2000; Roos, 2010; Stout et al., 2011). A clinical diagnosis of HD is typically based on the presence of the characteristic motor symptoms in combination with a positive genetic test for a pathological

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CAG expansion and a family history of HD. However, there is clear evidence from previous studies that subtle cognitive changes occur years before the motor disorder is severe enough to merit a clinical diagnosis of HD (Kirkwood et al., 2000; Paulsen & Long, 2014; Paulsen, Smith, & Long, 2013; Snowden, 2017; Stout et al., 2011). Hence, cognitive impairment can already be detected in the prodromal stages of the disease (Bachoud Lévi et al., 2001; Paulsen, 2011; Stout et al., 2011). Although neuropsychological assessment is not essential for differential diagnosis of HD, it is crucial for monitoring the cognitive status of HD patients from prodromal to manifest stages as cognitive decline is a suitable measure for detecting disease onset and is a robust indicator for disease progression (Paulsen & Long, 2014; Snowden, 2017; Stout et al., 2011). Furthermore, cognition is also a key issue for patients and families in everyday life, as even minor cognitive deficits can have a negative impact on everyday abilities such as driving (Beglinger et al., 2012), work performance and on patients' and caregivers' quality of life (Paulsen et al., 2014; Ready, Mathews, Leserman, & Paulsen, 2008; Snowden, 2017). The most salient cognitive alterations associated with HD are reduced psychomotor and processing speed, deficits in attention, working memory, executive functions, episodic memory, emotion processing, perception, and social cognition (Kirkwood et al., 2000; Paulsen, 2011; Snowden, 2017). Moreover, psychomotor slowing represents the first sign and most precise predictor for the disease progression (Snowden, 2017; Stout et al., 2011). It is most often measured with time-dependent tasks, such as Stroop-Test, Symbol Digit Modalities Test (SDMT) and Trail Making Test (TMT) (Snowden, 2017). Among the executive deficits in HD patients are difficulties in action planning (Lawrence, Sahakian, Hodges, & Rosser, 1996), organizing and sequencing (Snowden, Craufurd, Griffiths, Thompson, & Neary, 2001), as well as in cognitive flexibility, attention shifting (Lawrence et al., 1996), strategic search, phonemic and semantic fluency (Henry, Crawford, & Phillips, 2005; Rosser & Hodges, 1994; Snowden, 2017). Executive functions are often measured using the Stroop-Test (i.e., interference test; Hanes, Andrewes, Pantelis, & Chiu, 1996), the Categorical and Phonological Fluency Tests (Rosser & Hodges, 1994) and the TMT (i.e., part B; Snowden, 2017). A cognitive battery used to examine HD patients in prodromal and manifest stages should ideally contain a test for each of these key cognitive functions that have been shown to be sensitive indicators of HD (Snowden, 2017). An example of a cognitive battery for the evaluation of cognitive impairment in HD is the Huntington's Disease Cognitive Assessment Battery (HD-CAB), which consists of six tests and is explicitly designed for use in late premanifest and early manifest HD patients in clinical trials (Stout et al., 2014). Although, there are several different tests and assessment batteries for the neuropsychological evaluation of HD available, most HD centers rely in daily clinical practice on the cognitive battery used in Enroll-HD (Paulsen et al., 2013; Snowden, 2017), a worldwide observational study for HD (www.enroll-hd.org; Landwehrmeyer et al., 2017). There are about 16 Enroll-HD study sites in German speaking countries, which have examined more than 3,100 German-speaking participants so far (status in February 2019) and use the cognitive battery as part of the study protocol and also in clinical practice. The cognitive battery of Enroll-HD is based on the Unified Huntington's Disease Rating Scale (UHDRS). A clinical scale developed by the Huntington Study Group (HSG, 1996) to assess four main domains in HD: motor function, behavioral abnormalities, functional capacity and cognitive function. It includes the SDMT (Smith, 1982), the Stroop-Test with its three subtests color naming, word reading, and interference (HSG, 1996; Stroop, 1935), and the Phonological Fluency Test (Benton, Hamsher, Varney, & Spreen, 1994). The Enroll-HD cognitive battery additionally added the TMT (Reitan, 1958), the Categorical Fluency Test (Benton et al., 1994; Morris et al., 1989) and the Mini Mental Status Examination Test (MMSE; Folstein, Folstein, & McHugh, 1975). Thus, the Enroll-HD cognitive battery is suitable to examine HD patients in prodromal and manifest stages as it includes tests for each key cognitive function known to be sensitive indicators of HD, i.e. psychomotor and processing speed, attention, working memory, and executive functions. Moreover, it is well established in clinical practice and it is an essential tool for monitoring cognition in observational studies and clinical trials. However, so far it has not been investigated whether the German version of this battery is sufficiently specific and sensitive to discriminate normal cognitive functioning in healthy controls from cognitive deficits in HD patients and to differentiate HD patients with more from patients with less pronounced cognitive deficits. A validation of the battery in each available language is essential, as it guarantees correct use and application in clinical practice.

Against this background, the present study aimed to evaluate the diagnostic accuracy of the German version of the Enroll-HD cognitive battery to distinguish between, first, HD patients and healthy controls and, second, between HD patients with more and less pronounced cognitive impairments. In addition, the study aimed to explore the effects of disease burden on the cognitive performance of HD patients and to examine the relation between cognitive, motor, and functional status.

Methods

Participants

A total of 256 participants were recruited between 2011 and 2017. For the present study, we included a patient group (HD) and a healthy control group (NC). Only data from subjects who met predefined inclusion criteria were used. The patient group was composed of 106 participants (56 males, 50 females) with genetically verified HD. All, first, had a positive molecular genetic

Table 1. Mean characteristics of the Huntington's disease (HD) (N = 106) and the NC (N = 100) group

	HD (N = 106)		NC (N = 100)		
	$M \pm SD$	Range	$M \pm SD$	Range	p
Age (Y)	48.80 ± 13.39	20–79	48.47 ± 13.53	21–80	.970*
Education (Y)[a]	12.92 ± 2.30	8–20	13.41 ± 2.09	9–19	.054*
Gender (% male)	52.8		39.0		.064**
MMSE[b]	25.46 ± 4.39	9–30	29.58 ± 0.76	27–30	<.001*
UHDRS-FIS	18.37 ± 6.58	3–25			
UHDRS-TFC	8.63 ± 4.15	1–13			
UHDRS-TMS	31.42 ± 22.21	0–78			
CAG repeats[c]	17.86 ± 2.77	12–28 (normal allele)			
	44.22 ± 3.78	39–57 (mutant allele)			

[a]Analyses based on sample size of N = 99 (NC).
[b]Analyses based on sample size of N = 100 (HD) and N = 100 (NC).
[c]Analyses based on sample size of N = 86 (normal allele) and N = 90 (mutant allele).
Notes: *Mann–Whitney U-test for two independent samples was used to test for significance of group differences. **χ^2-test for independence (with Yates continuity correction) was used to test for significance of group differences. Y = years; MMSE = mini-mental state examination; UHDRS = unified Huntington's disease rating scale; UHDRS-FIS = functional independence scale (rating from 0 to 100% based on 25 questions (yes/no), which evaluate the ability of a subject to carry out everyday activities independently); TFC = total functional capacity (possible range 1–13, based on five questions concerning occupation, finances, domestic chores, activities of daily living, and care level); TMS = total motor score (possible range 0–124, this score is used to characterize the clinical HD motor phenotype based on ratings on 15 standardized examinations [e.g. oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability], which evaluate the presence and characteristic of motor features of HD in a given subject); CAG = Cytosine-Adenine-Guanine.

test for HD (confirming a CAG repeat length of >36 repeats in the *htt*-gene); second, were capable of completing the entire cognitive test battery (without missing values); third, had no other neurological disorder that might have pathologically affected their cognition; fourth, were in stable psychiatric and physical condition during the test administration and motivated to complete the study protocol; fifth, had no severe speech, motor, or behavioral deficits that might have affected neuropsychological testing; sixth, and all patients who were undergoing therapy were given long-term continuous medication at the time of the examination. As an indicator of the pathological burden caused by lifetime exposure to mutant huntingtin, we used the Disease Burden Score (DBS; Penney, Vonsattel, MacDonald, Gusella, & Myers, 1997; Sampedro et al., 2019). The DBS is calculated by using the following formula: DBS = $(CAG_n – 35.5) \times$ age.

The control group (NC) consisted of 100 healthy volunteers (39 males, 61 females), who were matched to the patient group in terms of age, gender, and education. All of them met the following inclusion criteria: first, no cognitive impairment, i.e. MMSE ≥ 27, second, no past or present severe psychiatric, neurological, sensory, metabolic deficits, or other disorders known to affect cognition; third, no consumption of any drugs that may impair cognitive abilities; sixth, and capable of completing the entire neuropsychological test battery (without missing values) and medical examination.

Demographic and clinical characteristics of the patient and control group are summarized in Table 1.

Moreover, additional descriptions of the sample, including demographic information of patients in different disease stages are provided in Supplementary Tables S2–S5.

Design

Data were collected in the framework of Enroll-HD, a multinational, prospective, and observational study of HD intended to accelerate progress toward therapeutics. All participants provided written informed consent for their participation. The study has been approved by the local ethics committee and conducted in accordance with the ethical standards described in the Helsinki Declaration of 1964. Any information that could disclose the identity of the examined subjects was omitted.

Neuropsychological, Functional, and Motor Assessment

All participants were examined using the standardized UHDRS assessment protocol for HD including neuropsychological, motor, psychiatric, and functional assessments. The tests and clinical examinations were performed by professionally trained and experienced personnel (i.e., clinicians, psychologists) in the local language (i.e., German).

The neuropsychological assessment protocol was used to assess the cognitive state of the participants. It included the German version of the following six neuropsychological tests. The MMSE (Folstein et al., 1975) was used to provide a measure of general cognitive functioning; the SDMT (Smith, 1982, 1991) was used as a measure for cognitive processing speed; the Stroop-Test

(Treisman & Fearnley, 1969) and its three subtests (color naming, word reading, and interference) were employed as metric for cognitive flexibility and for inhibition of irrelevant responses (resistance to interference); the TMT (Kelland & Lewis, 1994) consisting of TMT-A and TMT-B were used as indicator of psychomotor speed (TMT-A), visual attention (TMT-A and -B), cognitive flexibility and selective attention abilities, such as task switching (TMT-B); the Phonological Fluency Test (Benton & Hamsher, 1989) and Categorical Fluency Test (Benton et al., 1994; Morris et al., 1989) were used as measures of frontal mental flexibility and semantic knowledge.

The motor assessment protocol from the UHDRS (HSG, 1996) was applied to evaluate the presence and characteristic of neurological motor symptoms of HD in a given subject including chorea, oculomotor function, dysarthria, rigidity, dystonia, finger tapping, gait, postural stability using a 15-item scale. First, each motor sign was rated on a 0 to 4 scale. By summing up all motor ratings the total motor score (TMS) was obtained, ranging from 0 to 124 points, whereby higher scores indicate more severe motor impairment. The TMS is commonly used to characterize the clinical HD motor phenotype.

The functional status of the participants was assessed by means of two scales included in the UHDRS (HSG, 1996): the Functional Independence Scale (UHDRS-FIS) and the Total Functional Capacity Scale (UHDRS-TFC). Both scales provide an indicator of an individual's independence in activities of daily living. The TFC score ranges between 1 and 13 and is based on the evaluation of five questions concerning occupation, finances, domestic chores, activities of daily living, and care level, with lower scores indicating more severe impairment of the functional status. The FIS score ranges from 0% to 100% based on 25 questions (yes/no), which evaluate the ability of a subject to carry out everyday activities independently. The level of disease severity was classified into five stages and evaluated based on the TFC score with TFC scores from 11 to 13 representing stage I (least severe); scores from 7 to 10 reflecting stage II; scores from 3 to 6 indicating stage III; scores from 1 to 2 representing stage IV; and a score of 0 reflecting stage V (most severe) (Beglinger et al., 2010).

Statistical Analyses

Continuous variables are expressed as mean, SD, and range, while categorical variables are expressed as percentages, and ordinal variables as medians. Normality was evaluated by visual inspection of Quantile-Quantile plots (Q-Q plots) and the Shapiro-Wilk test. Spearman correlation coefficients r were used to evaluate the strength and direction of the linear relationships between two or more ordinal variables. The strength and direction of correlations between two or more continuous variables were calculated using Pearson correlation coefficients r. The Pearson chi-square (χ^2) test was used for dichotomous variables. To evaluate differences among groups, independent-samples t-tests were applied. Effect sizes were reported in form of Eta-Squared (η^2) and Cohen's d (as proposed by Cohen, 1988). The Bonferroni correction for multiple comparisons was applied in between-groups analyses. Receiver Operating Characteristic (ROC) curves with area under curve (AUC) and 95% Confidence Intervals (CIs) were calculated and used to compare the diagnostic accuracy of the neuropsychological tests included in the cognitive battery to assess cognitive impairment in HD. A one-way between-groups analysis of variance (ANOVA) was conducted to explore the impact of cognitive impairment in HD on the discriminative potential of each test included in the cognitive battery. Significant findings were followed by post-hoc analyses using Games-Howell due to the violation of homogeneity of variance (i.e., heterogeneity of variance). The level of significance was set at $\alpha = 0.05$. All reported analyses were performed using IBM SPSS Statistics Software for Windows (Version 22.0, Armonk, NY: IBM Inc.).

Results

Demographic and clinical characteristics of HD patients and NC can be found in Table 1. A Mann-Whitney U-test revealed a significant difference in the global cognitive performance based on the MMSE total score between HD patients ($M = 25.46$, median = 26, $SD = 4.39$) and NC ($M = 29.58$, median = 30, $SD = 0.76$), $U = 1684.00$, $z = -8.551$, $p < .001$. Regarding all other demographic variables (i.e., gender, education, age), no significant a priori differences were found between HD patients and NC (all p's > .05, see Table 1).

Diagnostic Accuracy in Detecting Cognitive Impairment

First, we examined the diagnostic accuracy of all tests included in the cognitive battery to assess cognitive impairment in HD and to discriminate between HD patients and NC. Therefore, an independent-samples t-test was conducted to compare the cognitive performance of HD patients and NCs on each test included in the battery. There were significant differences in all cognitive test scores for HD and NC (all p's < .001; two-tailed) even after the Bonferroni correction for multiple comparisons with HD patients showing significantly worse cognitive performance than controls. The magnitude of differences in the means was large in each measure (for Cohen's d see Table 2). Subsequently, we applied ROC analysis to examine the discriminative

Table 2. Between-group differences in the cognitive battery between Huntington's disease (HD) (N = 106) and NC (N = 100)

	HD (N = 106)	NC (N = 100)			
	$M \pm SD$	$M \pm SD$	$t(df)$	p	d
Phonemic Fluency (three letters)[a]	21.58 ± 13.50	39.39 ± 12.71	−9.15 (180)	<.001*	1.359
Stroop-C	44.05 ± 20.00	74.11 ± 12.71	−12.948 (179.3)	<.001*	1.794
Stroop-W	62.40 ± 28.76	102.70 ± 13.36	−13.014 (150.2)	<.001*	1.797
Stroop-I[b]	27.30 ± 13.30	42.83 ± 9.44	−9.326 (166.8)	<.001*	1.347
SDMT	24.37 ± 16.07	47.35 ± 11.51	−11.851 (190.5)	<.001*	1.644
Categorical fluency	13.79 ± 7.05	23.81 ± 5.43	−11.461 (196.2)	<.001*	1.592
TMT-A[c]	69.36 ± 53.84	25.44 ± 8.51	8.058 (103.9)	<.001*	−1.140
TMT-B[d]	144.54 ± 79.50	59.88 ± 29.46	9.762 (118.2)	<.001*	−1.412

[a]Analyses based on sample size of N = 83 (HD) and N = 99 (NC).
[b]Analyses based on sample size of N = 94 (HD).
[c]Analyses based on sample size of N = 100 (HD).
[d]Analyses based on sample size of N = 95 (HD).
Notes: *Significant after Bonferroni correction for multiple comparisons (p < .006). M = mean; SD = standard deviation; Stroop-C = Stroop Color Naming Test; Stroop-W = Stroop Word Reading Test; Stroop-I = Stroop Interference Test; SDMT = Symbol Digit Modalities Test; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; an independent-samples t-test (Welch's test) was used to test for significance of differences; classification and interpretation of effect size measure Cohen's d according to Cohen (1988): d = |0.2| (small effect); d = |0.5| (moderate effect); d = |0.8| (large effect); df = degrees of freedom.

Table 3. Diagnostic accuracy of the cognitive battery to assess cognitive impairment in Huntington's disease patients (N = 106) compared to normal cognitive functioning in healthy controls (NC, N = 100)

	AUC	95% CI	p
Phonemic fluency (three letters)	**.821**	.758–.884	<.001
Stroop-C	**.862***	.807–.917	<.001
Stroop-W	**.844**	.780–.908	<.001
Stroop-I	**.809**	.740–.877	<.001
SDMT	**.819**	.752–.887	<.001
Categorical fluency	**.818**	.754–.882	<.001
TMT-A	**.831**	.771–.891	<.001
TMT-B	**.813**	.751–.875	<.001

Notes: AUC = area under the curve (measures showing high discriminative potential with AUC > .80 are in bold; *neuropsychological test with the highest AUC); 95% CI = 95% confidence interval; Stroop-C = Stroop Color Naming Test; Stroop-W = Stroop Word Reading Test; Stroop-I = Stroop Interference Test; SDMT = Symbol Digit Modalities Test; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B.

potential of each neuropsychological test included in the cognitive test battery to assess cognitive impairment in HD patients compared to NC (see Table 3, Fig. 1 and Supplementary Figure S1). All tests showed high discriminative potential with all AUC > 0.80 and all p < .001. Based on the AUC the Stroop Color Naming Test showed the highest potential to discriminate between HD and NC (AUC = .862), followed by Stroop Word Reading Test (AUC = .844), TMT-A (AUC = .831), Letter Fluency Test (AUC = .821), SDMT (AUC = .819), Categorical Fluency Test (AUC = .818), TMT-B (AUC = .813) and Stroop Interference Test (AUC = .809) with the lowest discriminative potential.

Second, we investigated the diagnostic accuracy of all tests included in the cognitive battery to discriminate between HD patients with more (HD-CD) and less cognitive impairment (HD-NC). Hence, the HD patient group was split into two subgroups HD-NC (MMSE ≥ 24) and HD-CD (MMSE < 24) according to their MMSE score. The MMSE was used as a proxy to distinguish between HD patient groups with more and less cognitive impairments, as it is considered to be an established, conservative instrument to distinguish between moderate, and severe cognitive deficits (Klempíř, Klempířová, Spačková, Židovská, & Roth, 2006; Mestre et al., 2018). Demographic and clinical characteristics of the subgroups are displayed in Supplementary Table S2. One-way between-groups ANOVA was applied to analyze the differences between the two patient subgroups and the control group in their cognitive performance on each test. There were statistically significant differences (all p < .001) in all test scores between all three groups showing that controls performed significantly better than both HD patients subgroups and that HD-NC performed significantly better than HD-CD patients in all cognitive tests (NC > HD-NC > HD-CD), with all Games-Howell post-hoc tests p < .001. Results of the ANOVA are displayed in Supplementary Table S1 and the corresponding descriptive statistics are shown in Supplementary Table S4. Subsequently, ROC analysis was performed to investigate the sensitivity and specificity of each test to discriminate between HD-NC and HD-CD patients based on their cognitive performance. All tests showed high discriminative potential with all AUC > 0.80 and all p < .001. The highest discriminative potential was detected

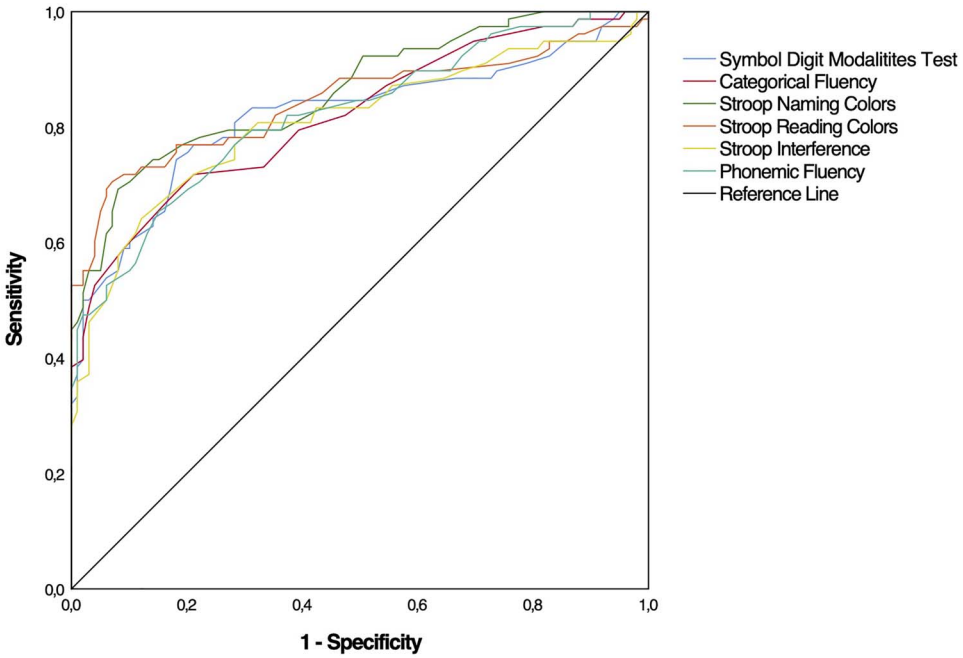

Fig. 1. Receiver-operating characteristic (ROC) discloses diagnostic accuracy of the cognitive battery to assess cognitive impairment and discriminate between HD patients (HD, $N = 106$) and healthy controls (NC, $N = 100$). Diagonal segments are produced by ties. *y*-axis = sensitivity; *x*-axis = 1 – specificity.

Table 4. Diagnostic accuracy of the cognitive battery to discriminate between Huntington's disease (HD) patients with more (HD-CD, $N = 30$) and less cognitive impairments (HD-NC, $N = 70$)

	AUC	95% CI	*p*
Phonemic fluency (three letters)	**.848**	.749–.947	<.001
Stroop-C	**.899***	.810–.988	<.001
Stroop-W	**.887**	.803–.970	<.001
Stroop-I	**.894**	.791–.997	<.001
SDMT	**.892**	.808–.976	<.001
Categorical Fluency	**.863**	.781–.945	<.001
TMT-A	**.833**	.748–.917	<.001
TMT-B	**.835**	.754–.915	<.001

Note. AUC = area under the curve (measures showing high discriminative potential with AUC > .80 are in bold; *neuropsychological test with the highest AUC); 95% CI = 95% confidence interval; Stroop-C = Stroop Color Naming Test; Stroop-W = Stroop Word Reading Test; Stroop-I = Stroop Interference Test; SDMT = Symbol Digit Modalities Test; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B.

for the Stroop Color Naming Test (AUC = .899) followed by Stroop Interference Test (AUC = .894), SDMT (AUC = .892), Stroop Word Reading Test (AUC = .887), Categorical Fluency Test (AUC = .863), Letter Fluency Test (AUC = .848), TMT-B (AUC = .835) and TMT-A (AUC = .833) with the lowest discriminative potential. All results of the ROC analysis including AUC, CIs and *p*-values are presented in Table 4, Fig. 2 and Supplementary Figure S2.

Effect of Individual Factors on Cognitive Performance and Relationship of Cognitive, Motor, and Functional Status

In addition, partial correlational analyses were performed: first, to analyze the effects of individual factors on the cognitive performance of HD patients, second, and to examine the relationship between cognitive performance, motor impairment, and functional status. All results including correlation coefficients *r*- and *p*-values are presented in Table 5.

Results showed that the cognitive deficits, identified in nearly all neuropsychological tests (except MMSE score), progressed with the duration of the disease. Moreover, results indicate that the DBS, an indicator for the pathological burden of a patient caused by lifetime exposure to mutant huntingtin (i.e., disease burden), was significantly correlated with the cognitive performance on nearly all neuropsychological tests (except MMSE with $r = -.227$, $p = .102$) regardless of disease duration and current age: SDMT ($r = -.596$, $p < .001$), Stroop Word Reading Test ($r = -.556$, $p < .001$), Stroop Color Naming Test

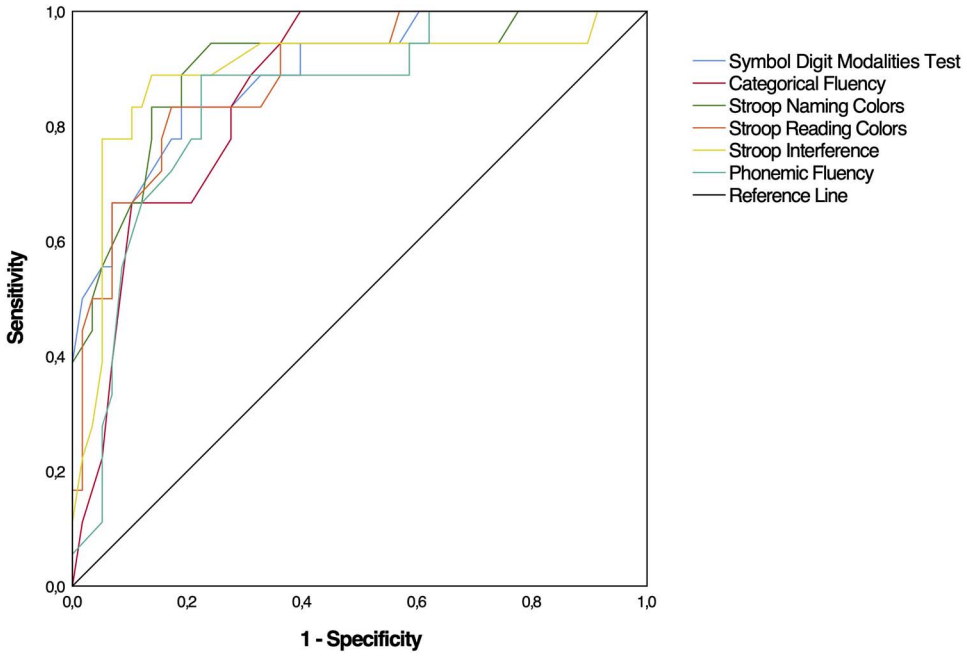

Fig. 2. Receiver-operating characteristic (ROC) discloses diagnostic accuracy of the cognitive battery to assess cognitive impairment and discriminate between HD patients with more (HD-CD, N = 30) and less cognitive impairment (HD-NC, N = 70). Diagonal segments are produced by ties. y-axis = sensitivity; x-axis = 1–specificity.

Table 5. Pairwise partial correlations between the respective neuropsychological tests of the cognitive battery (shown in rows) and clinical variables (shown in columns) by taking into account and controlling for the influence of the tertiary variables disease duration and age

Clinical variables	UHDRS TMS	UHDRS TO	UHDRS TB	UHDRS TR	UHDRS TD	UHRDS TCH	TFC	FIS	DBS
MMSE	**−.575*****	**−.512*****	**−.592*****	−.318*	−.425**	−.420**	**.575*****	**.603*****	−.227
Phonemic fluency	**−.589*****	**−.513*****	**−.621*****	−.298*	−.345*	**−.521*****	**.501*****	.486***	−.488***
Stroop-C	**−.666*****	**−.593*****	**−.693*****	−.464***	−.447**	−.494***	**.572*****	**.640*****	**−.516*****
Stroop-W	**−.619*****	**−.560*****	**−.647*****	−.363**	−.437**	−.442**	**.609*****	**.566*****	**−.556*****
Stroop –I	**−.648*****	**−.586*****	**−.673*****	−.400**	−.448**	−.473***	.476***	**.617*****	−.325*
SDMT	**−.660*****	**−.638*****	**−.674*****	−.411**	−.387**	**−.521*****	**.627*****	**.615*****	**−.596*****
Categorical fluency	−.472***	−.391**	**−.500*****	−.184	−.304*	−.426**	.427**	.461**	−.315*
TMT-A	**.573*****	**.613*****	**.589*****	.392**	.356**	.337*	**−.512*****	**−.569*****	.331*
TMT-B	**.550*****	**.556*****	**.616*****	.384**	.275*	.338*	**−.559*****	**−.615*****	.422**

Notes: CAG = Cytosine-Adenine-Guanine, DBS = Disease Burden Score, DBS = (CAG_n-35.5) x age; MMSE = Mini-Mental State Examination; Stroop-C = Stroop-Test, Color Naming; Stroop-W = Stroop-Test, Word Reading; Stroop-I = Stroop-Test, Interference; SDMT = Symbol Digit Modalities Test; UHDRS = Unified Huntington's Disease Rating Scale; UHDRS-FIS = functional independence scale (possible range: 0–100); TFC = Total Functional Capacity (possible range: 1–13). TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; UHDRS-TMS = UHDRS-Total Motor Score (possible range: 0–124); UHDRS-TO = UHDRS-Total Oculomotor; UHDRS-TB = UHDRS-Total Bradykinesia; UHDRS-TR = UHDRS-Total Rigidity; UHDRS-TD = UHDRS-Total Dystonia; UHDRS-TCH = UHDRS-Total Chorea; analyses based on N = 55 observations of HD patient group; interpretation of effect size according to Cohen (1988, pp. 79–80): $r < 0.1$ may be interpreted as no effect; $0.1 \leq r < 0.3$ indicates a small effect size; $0.3 \leq r < 0.5$ refers to a moderate effect size; $r \geq 0.5$ is equivalent to a strong effect size; correlations coefficients equivalent to a strong effect size are written in bold; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

($r = -.516$, $p < .001$), Letter Fluency Test ($r = -.488$, $p < .001$), TMT-B ($r = .422$, $p < .01$), TMT-A ($r = .331$, $p < .05$), Stroop Interference Test ($r = -.325$, $p < .05$) and Categorical Fluency Test ($r = -.315$, $p < .05$). An overview of all coefficients is displayed in Table 5.

Concerning the relation of motor and cognitive status, the results showed that the severity of overall motor impairment (UHDRS-TMS; r ranging from −.472 to −.666; all p's < .001), bradykinesia (UHDRS-TB; r ranging from −.500 to −.693; all p's < .001), oculomotor impairment (UHDRS-TO; r ranging from −.391 to −.638, all p's < .001 except categorical fluency with $p < .01$), dystonia (UHDRS-TD; r ranging from .275 to −.448, all p's at least < .05), chorea (UHDRS-CH; r ranging from .337 to −.521; all p's at least < .05) and rigidity (UHDRS-TR; r ranging from −.184 to −.464; all p's < .05 except categorical fluency with $p = .187$) were significantly correlated with performance on all cognitive tests. Hence, the degrees of rigidity

(UHDRS-TR) and dystonia (UHDRS-TD) were less strongly related to cognitive performance (see Table 5). Thus, the severity of motor impairment in different domains (UHDRS: TMS, oculomotor, bradykinesia, rigidity, dystonia, and chorea) was closely associated with the severity of cognitive deficits.

In terms of the link between functional and cognitive status, correlation analysis showed that TFC and FIS were significantly correlated with performance on all neuropsychological tests with moderate to large correlation coefficients r ranging from .427 to .627 (TFC; all p's < .001 except categorical fluency with $p < .01$) and from .461 to .640 (FIS; all p's < .001 except categorical fluency with $p < .01$). Thus, the severity of deficits in all cognitive functions were strongly associated with the severity of functional disabilities.

Discussion

The main objective of the present study was to examine the diagnostic accuracy of the Enroll-HD cognitive battery to assess cognitive impairment and to distinguish between HD patients and healthy controls and between HD patients with more and less pronounced cognitive impairment. Moreover, it aimed to explore the relation between cognitive, motor, and functional status as well as the effect of disease burden on cognition.

Diagnostic Accuracy of the Cognitive Battery to Assess Cognitive Impairment in HD Compared to Normal Cognitive Functioning in Healthy Controls

According to our results, all tests included in the cognitive battery are sufficiently sensitive and specific to capture cognitive deficits in HD patients compared to healthy controls (see Tables 2 and 3). The highest discriminative properties to distinguish between healthy controls and HD patients were found in the following tests in descending order: Stroop Color Naming Test, Stroop Word Reading Test, TMT-A, Letter Fluency Test, SDMT, Categorical Fluency Test, TMT-B, and Stroop Interference Test (Table 3). These results are consistent with the findings of Paulsen et al. (2014) who identified the Stroop Word Reading Test as the strongest cognitive predictor for the motor diagnosis of HD. Thus, tests that are simpler in administration seem to be more sensitive in assessing cognitive deficits in early stages of the disease. Typical cognitive deficits in the early stages of HD include psychomotor slowing and disruption of automated activities, such as speech, reading, and coding (Snowden, 2017; Thompson et al., 2010). SDMT has been considered a highly sensitive and consistent task for tracking decline in HD. In previous studies, statistically significant differences in SDMT were found in premanifest and manifest HD and psychomotor speed was identified as the earliest and the best predictor of HD progression (Georgiou-Karistianis et al., 2013; Larsen, Vinther-Jensen, Gade, Nielsen, & Vogel, 2015; Paulsen et al., 2013; Stout et al., 2011). In the early stages, the Categorical Fluency Test appears to be more sensitive in detecting cognitive deficits than the Letter Fluency Test. Although the Letter Fluency Test places greater demands on executive function, the Categorical Fluency Test is subject to more automated processes and uses the existing semantic links between the words retrieved (Shao et al., 2014). In contrast, the letter fluency task requires words to be retrieved from a phonemic category so that the activation of semantically related words is suppressed and novel retrieval strategies are applied that are demanding on decision making and obtained education (Feigin et al., 1995; Friesen, Luo, Luk, & Bialystok, 2015; Katzev, Tuscher, Hennig, Weiller, & Kaller, 2013). Although there is not a significant cognitive deficit in sematic memory in HD (Snowden, 2017), a crucial problem in the verbal fluency assessment is the time to respond to the task and the speech tempo of an affected person. In the early stages, patients with mild cognitive deficits, who are mainly affected by slow psychomotor speed, are able to compensate their attention deficits due to the cognitive reserves and relatively well-preserved functions of the frontal lobes (Giralt, Saavedra, Alberch, & Pérez-Navarro, 2012; Stout et al., 2011). The striatum and the fronto-striatal network degeneration subsequently leads to depletion of cognitive reserves, in particular, to executive control dysfunction, leading to significant deficits in assessments of demand for executive functions, such as TMT-A, TMT-B, Letter Fluency Test and Stroop Interference Test (see Table 2 and 3; Paulsen, Miller, Hayes, & Shaw, 2017; Rüb, Vonsattel, Heinsen, & Korf, 2015; Sánchez-Cubillo et al., 2009; Snowden, 2017; Stout et al., 2011). Overall, our results indicate that the simplest tests for assessing psychomotor speed and executive functions already allow continuous monitoring of cognitive performance and disease progression (see Table 3).

Diagnostic Accuracy of the Cognitive Battery in the Diagnosis of HD with more (HD-CD) and less Advanced Cognitive Impairments (HD-NC)

MMSE plays an important role in assessing and monitoring the progression of cognitive decline and remains a part of everyday clinic due to its time efficiency and simple administration. However, a more precise assessment of functional and cognitive abilities is required to warrant a diagnosis of dementia. The MMSE provides information on the orientation and ability of the patient to participate in further cognitive testing (Mestre et al., 2018; Peavy et al., 2010). The present results show that in

contrast to the other tests included in the Enroll-HD battery the MMSE is not correlated with the DBS, an indicator for disease progression (see Table 5). This is remarkable as it emphasizes the non-specificity of the MMSE versus the specificity of the Enroll-HD battery for assessing characteristic cognitive deficits in HD patients. The present ANOVA results showed that every test included in the Enroll-HD cognitive battery has a very high diagnostic accuracy for differencing cognitive impairment in HD (see Supplementary Table S1 and Supplementary Table S5). Notably, the differences between the two subgroups with more (HD-CD) and less cognitive impairments (HD-NC) were highly significant, resulting in high levels of classification accuracy based on ROC space (see Table 4). According to our results, all tests included in the cognitive battery are sufficiently sensitive and specific to capture cognitive deficits in HD patients with more cognitive impairment (HD-CD) compared to HD patients with less cognitive impairments (HD-NC) (see Table 4). The highest discriminative properties to distinguish between those patient subgroups were found in the following tests in descending order: Stroop Color Naming Test, Stroop Interference Test, SDMT, Stroop Word Reading Test, Categorical Fluency Test, Letter Fluency Test, TMT-B and TMT-A (see Table 4). Overall, it appears that more complex tests to assess cognitive performance are needed to distinguish between HD patients in different disease stages with more and less severe cognitive impairments (see Table 4).

Relation Between Cognitive Performance, Motor Impairment, Functional Decline, and Disease Burden

Cognitive Performance and Motor Impairments. The partial correlation analysis was performed after excluding the variables for age and disease duration to reveal the relationship between motor and cognitive deficits. Results showed that cognitive deficits were most significantly correlated with the level of bradykinesia, oculomotor deficits, and chorea. The degrees of dystonia and rigidity were less strongly associated with cognitive deficits (see Table 5). This is reasonable, because the brain regions involved in motor and cognitive performance are the regions that are predominantly affected by the neurodegenerative process in HD (Bonelli & Cummings, 2007; Georgiou-Karistianis et al., 2013; Rüb et al., 2015) and the cortical loops serve to coordinate motor and cognitive function integrated in the basal ganglia (Alexander, 1986; Klempíř, Klempířová, Štochl, Špačková, & Roth, 2009; Ross, Pantelyat, Kogan, & Brandt, 2014). Moreover, our findings seem to be consistent with clinical practice and studies, which demonstrated that motor impairment, especially bradykinesia, is a factor contributing to the decline in cognitive performance of HD (Baake et al., 2017; Long et al., 2014; van Vugt et al., 2004).

Cognitive Performance and Functional Abilities. In our study, we additionally examined the association between cognition and functional abilities in patients with more (HD-CD) and less cognitive impairments (HD-NC). The results showed that the cognitive performance of HD patients on all neuropsychological tests was significantly correlated to their functional abilities (see Table 5). Thus, higher cognitive impairment is associated with higher loss of functional abilities. These results are consistent with the results of previous studies (Baake et al., 2017; Duff, Beglinger, Theriault, Allison, & Paulsen, 2010; Peavy et al., 2010) and with the statements of relatives of HD patients that cognition is one of the most decisive factors for the everyday life abilities of HD patients. In this respect, our results additionally seem to support the frequently used criteria for the diagnosis of dementia in HD patients, according to which the presence of dementia is determined by significant functional deficits leading to the following scores UHDRS-TFC > Stage II and UHDRS-FIS < 80% (Peavy et al., 2010). Therefore, the present results provided further evidence that although HD is classically considered to be a motor disorder, cognitive decline already occurs in early stages of the disease (Paulsen, 2011; Stout et al., 2011) and is highly associated to the deterioration of the patients' functional abilities (Beglinger et al., 2012; Paulsen et al., 2014; Ready et al., 2008; Snowden, 2017). This early detectable cognitive decline reflects the impairment of additional neuronal populations, such as cortical and hippocampal neurons, by the presence of mutant *htt* and its toxic effect, which increase with the polyglutamine chain (Giralt et al., 2012; Nopoulos et al., 2011; Quarrell et al., 2013; Zuccato, Valenza, & Cattaneo, 2010). In general, there are interactions among striatal, cortical, and hippocampal systems and the final cognitive outcome depends on compensatory and cooperative interactions between those systems (Giralt et al., 2012). Consequently, the impairments in cognitive functions contribute to the deterioration of motor performance and functional capacity.

Cognitive Performance and Disease Burden. The present study results showed that disease burden was associated with cognitive performance regardless of age and disease duration, but not to the same extent for each test included in the battery (see Table 5). More precisely, the DBS, as a product of CAG length and age, was significantly correlated with the performance on the following cognitive tests in descending order: SDMT, Stroop Word Reading Test, Stroop Color Naming Test, Letter Fluency Test, TMT-B, TMT-A, Stroop Interference Test, Categorical Fluency Test. Thus, higher DBS was associated with poorer performance on these tests. This is consistent with findings from previous studies indicating that CAG length (an indicator for

genetic load) influences both the disease progression (Andrew et al., 1993) and the cognitive performance (Baake et al., 2017; Paulsen, Smith, & Long, 2013). Moreover, our results showed that the MMSE is the only neuropsychological test that is not significantly correlated to the DBS (see Table 5). Thus, the MMSE as a screening tool for assessing global cognitive functioning does not seem to reflect well the cognitive deterioration process in HD. This finding is in accordance with previous studies, which demonstrate the MMSE is not sufficiently specific and sensitive to assess and monitor cognitive decline in the course of the disease in HD patients (Bezdicek et al., 2013; Mestre et al., 2018; Peavy et al., 2010; Ringkøbing, Larsen, Jørgensen, Vinther-Jensen, & Vogel, 2020; Toh et al., 2014).

Limitations

There are several limitations concerning the present study. First, executive functions is a generic term for cognitive abilities that are thought to be mediated by the prefrontal cortex. These cognitive functions include for example the ability to plan, control and maintain attention, the ability to organize, abstract thinking, problem solving, control of actions, cognitive flexibility, and set shifting (Lezak, Howieson, Bigler, & Tranel, 2012). Because of this multitude of different cognitive abilities that are considered to be part of executive functions, there is no single measure of executive function available (Homack & Riccio, 2004). Therefore, the neuropsychological test battery used to assess the cognitive status of HD patients includes different tests to evaluate the different components of executive functions and psychomotor speed. However, it may be a limiting factor that the battery does not include tests for all cognitive abilities that are assumed to be part of executive functions. Another limitation of the investigated cognitive battery is that it does not examine memory, planning, and visuospatial function, although these are also cognitive functions which are often affected by HD. Furthermore, the cognitive battery includes the MMSE as a screening-tool to assess the global cognitive impairment in HD patients. This might be questioned as there is clear evidence that the MMSE is neither sufficiently sensitive to detect global cognitive impairment in HD nor is it sufficiently sensitive and specific to discriminate the cognitive functioning in HD from normal cognitive functioning or mild cognitive impairment in other neurodegenerative diseases, particularly in the executive functions (Bezdicek et al., 2013). Third, although the study sample was relatively small, the results were significant even with the use of rather conservative statistical thresholds. Fourth, some of the participants were undergoing therapy at the time they were recruited. Although they were given long-term continuous medication at the time of the examination, a possible effect of this medication with psychopharmaceuticals (e.g. antipsychotics, antidepressants) or of potentially present depression and anxiety states on the cognitive functioning of HD patients cannot be excluded. Fifth, it is desirable to be able to detect mild cognitive deficits in the early and presymptomatic stages of HD and to discriminate HD patients with pronounced and less pronounced cognitive impairment. Although, our sample did not include premanifest HD patients, it included two patient subgroups, i.e. HD patients with more (HD-CD, $N = 30$) and less cognitive impairments (HD-NC, $N = 70$), which were used to discriminate HD patients with pronounced and less pronounced cognitive impairment. However, the sample sizes were relatively small and thus, the results are of limited generalizability. Future studies should therefore examine larger samples to ensure the generalizability of the results.

Conclusion

In the present study, we performed a validation of the German version of the Enroll-HD cognitive battery by determining its diagnostic accuracy to assess cognitive impairment in HD patients. The study showed that every neuropsychological test included in the evaluated battery was sufficiently sensitive and specific to assess cognitive impairment in HD compared to normal cognitive functioning in healthy controls and to distinguish HD patients with more from patients with less pronounced cognitive deficits. Hence, the evaluated cognitive battery is suitable for the assessment and continuous monitoring of cognitive impairments in HD patients. Moreover, our results provide clear evidence for a close relationship between motor and cognitive performance. At the same time, they also confirm previous findings stating that functional capacity is strongly dependent on cognitive functioning and that disease burden expressed by DBS, regardless of age and disease duration, has an impact on cognitive performance.

Collaborators:

Colleagues at the Huntington Center South at kbo-Isar-Amper-Klinikum Taufkirchen (Vils): Prof. Matthias Dose, Rudolf Dengler, Michael Bachmeier, Roy Limpert, Jeanette Glassl, Alexandra Jovanovic, Erna Jobst, Daniel Stojicic, Gabriele Leythäuser.

Supplementary Data

Supplementary material is available at Archives of Clinical Neuropsychology online.

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Conflict of Interest

The authors declare the following potential conflict of interests:

A. Mühlbäck: Her institution, the Department of Neurology at the University of Ulm, has received grants from the following companies in the context of clinical trials: CHDI Foundation, Hoffmann-La Roche, Isis (IONIS) and Teva. Lecture fee from Desitin. Non-financial support (reimbursement of travel and accommodation costs) from Actelion, EHDN and a fee for scientific advice from TEVA.

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