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RESEARCH PAPER

Cognitive domains that predict time to diagnosis in prodromal Huntington disease

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ABSTRACT

Background Prodromal Huntington's disease (prHD) is associated with a myriad of cognitive changes but the domains that best predict time to clinical diagnosis have not been studied. This is a notable gap because some domains may be more sensitive to cognitive decline, which would inform clinical trials.

Objectives The present study sought to characterise cognitive domains underlying a large test battery and for the first time, evaluate their ability to predict time to diagnosis.

Methods Participants included gene negative and gene positive prHD participants who were enrolled in the PREDICT-HD study. The CAG—age product (CAP) score was the measure of an individual's genetic signature. A factor analysis of 18 tests was performed to identify sets of measures or latent factors that elucidated core constructs of tests. Factor scores were then fit to a survival model to evaluate their ability to predict time to diagnosis.

Results Six factors were identified: (1) speed/inhibition, (2) verbal working memory, (3) motor planning/speed, (4) attention—information integration, (5) sensory—perceptual processing and (6) verbal learning/memory. Factor scores were sensitive to worsening of cognitive functioning in prHD, typically more so than performances on individual tests comprising the factors. Only the motor planning/speed and sensory—perceptual processing factors predicted time to diagnosis, after controlling for CAP scores and motor symptoms.

Conclusions The results suggest that motor planning/speed and sensory—perceptual processing are important markers of disease prognosis. The findings also have implications for using composite indices of cognition in preventive Huntington's disease trials where they may be more sensitive than individual tests.

INTRODUCTION

A formal diagnosis of Huntington's disease (HD) is made at the appearance of unequivocal motor signs. However, changes in the brain decades before a diagnosis not only produce subtle motor and psychiatric symptoms, but also cognitive changes. With the development of treatments that delay the onset or slow progression of symptoms, international studies (PREDICT-HD, TRACK-HD and REGISTRY/COHORT) have made a concerted effort to characterise cognition in prodromal HD (prHD) and determine when changes can be detected to evaluate the potential of cognitive measures as outcomes in clinical trials. Cognitive decline in prHD has been reported on tests of attention, working memory, processing speed, learning and memory, executive functions, sensory—perceptual functions and emotion perception.[1–13] Most studies focus on a sole task or a few tests so that the relative sensitivity of different cognitive domains cannot be ascertained, which would inform selection of measures in clinical trials. Only one study has evaluated the prognostic significance of two cognitive tests in predicting time to diagnosis using a survival model.[14] However, genetic mutation information that determines whether a subject was at risk for developing HD was unavailable on the majority of cases and therefore not used in the analysis. This may reduce the prognostic importance of cognitive measures. In addition, the value of multiple cognitive domains in predicting time to diagnosis has not been investigated, which is vital for identifying behavioural markers of disease prognosis.

With these issues in mind, the present study sought to characterise cognitive domains underlying a large test battery and evaluate their sensitivity to time to diagnosis in prHD participants enrolled in the PREDICT-HD study. We first performed a factor analysis (FA) of prHD participant data from cognitive and sensorimotor tests to identify sets of tests or latent factors that would help conceptualise core constructs of tests and potentially serve as more sensitive indices of functioning than single measures.[15] Then we investigated the cognitive domain(s) that best predicted time to diagnosis. This topic has been difficult to tackle due to the dearth of studies that track prHD individuals until they receive a clinical diagnosis. PREDICT-HD is the first study to prospectively follow genetically tested prHD participants, evaluating them yearly on a large cognitive battery until a manifest diagnosis is made. Thus the present study contains a large cohort of newly diagnosed HD subjects with baseline assessments, enabling an investigation of this issue for the first time.

METHODS

Participants

Study participants were enrolled in PREDICT-HD,[6] and included gene positive prHD individuals and gene negative controls with a family history of HD. Data were collected at 32 sites in the USA, Canada, Australia, Germany, Spain and the UK, from 2001 to 2008. Consent was obtained according to the Declaration of Helsinki. The study protocol was approved by the institutional review boards at the University of Iowa and participating sites.

Participants were 18 years of age or older and completed independent genetic testing for the HD

Table 1 Characteristics of participants included in ANCOVAs that compared the control and prodromal Huntington's disease groups on factor scores

	Controls (n=233)	Low (n=222)	Medium (n=281)	High (n=318)	p Value
Estimated years to diagnosis		>12.8	7.6–12.8	<7.6	
% Women	63.5	68.0	65.1	58.8	0.151
Age (years)	43.5 (11.6)	35.0 (7.7)	41.2 (9.5)	44.2 (9.8)	<0.0001
Education (years)	14.7 (2.7)	14.5 (2.5)	14.3 (2.7)	14.2 (2.8)	0.160
CAG repeat length	20.0 (3.5)	40.9 (1.6)	42.2 (2.1)	43.8 (2.8)	<0.0001
UHDRS motor score	2.6 (3.3)	3.0 (3.4)	4.0 (4.3)	6.8 (6.3)	<0.0001

Note, stratification of the prodromal Huntington's disease participants into low, medium, and high groups was based on the CAG–age product (CAP) score.[18]
UHDRS, Unified Huntington's Disease Rating Scale.

CAG expansion prior to study entry. Confirmatory DNA testing was conducted on blood drawn at the baseline PREDICT visit. A polymerase chain reaction method determined CAG repeat length.[16] Gene positive prHD participants had the expansion (≥36 CAG repeats) and gene negative controls did not (<36 CAG repeats). Exclusion criteria included alcohol or substance abuse within the previous year, learning disability or mental retardation requiring special education, a history of seizures, head trauma or other neurological disease, a pacemaker or metallic implants, use of antipsychotic medications within the past 6 months and use of phenothiazine derivative antiemetic medications more than three times per month. Other prescribed and over the counter medicines were not restricted.

Another exclusion criterion concerned ratings on the Unified Huntington's Disease Rating Scale (UHDRS) motor scale,[17] which contains 31 items that assess chorea, bradykinesia, rigidity, dystonia and oculomotor function. Item scores range from 0 (normal) to 4 (motor abnormalities, impairment) and are summed for a total motor score. Trained specialists in movement disorders performed the examination and rated their level of confidence that any observed motor sign was a manifestation of HD (question 17). Confidence ratings ranged from 0 (no abnormalities) to 4 (motor abnormalities, unequivocal signs, or ≥99% chance of HD). Participants with a diagnostic confidence level rating of 4 were excluded when they entered PREDICT-HD.

A prHD individual's genetic signature at the time of study entry was based on the CAG–age product (CAP) score.[18] CAP is computed by multiplying age at study entry (Age_0) by a scaling of the CAG repeat length ($CAP=Age_0 \times (CAG-33.66)/432.3326$). Scaled CAP scores <1, 1 and >1 indicate a 5 year diagnosis probability of <0.5, 0.5 and >0.5, respectively. The scaled CAP score is a proxy variable for time to diagnosis in a survival model containing only CAG and Age_0. Hence the CAP score is an index of the scaled cumulative mutation toxicity, with the scaling in reference to a 50–50 chance of diagnosis by 5 years. For one analysis, we stratified the prHD sample into low, medium and high CAP groups. The CAP for the control group was assigned 0, the low group was >0 and ≤0.67, the medium group ≥0.67 and <0.85 and the high group >0.85.[18]

Data from three samples of participants were analysed. For the FA, the sample included 580 prHD participants with complete data: 157, 197 and 226 had low, medium and high CAP scores, respectively. In a second intermediate analysis that examined the internal validity of factor scores, prHD participants were stratified into low, medium and high CAP groups. Table 1 shows the characteristics of the 233 gene negative and 821 prHD participants in these analyses. The groups were balanced in terms of gender and years of education but differed in age and CAG repeat length as these variables are part of the CAP score. UHDRS motor scores increased with CAP group, as they correlate with CAG length. The sample for the main analysis that tested the ability of factor scores to predict time to diagnosis included 730 prHD participants that had at least one follow-up assessment; 137 (16.7%) were judged as having converted to HD based on a score of 4 on question 17 of the UHDRS during a follow-up examination. Follow-up periods ranged between 0.85 and 6.59 years. Table 2 details the characteristics of the two groups at the baseline assessment.

Assessment battery

The battery contained 18 measures from standardised clinical tests and computerised cognitive tests more commonly used in research. A detailed description of the tasks is provided by Stout *et al*.[4] We selected tests and dependent variables that were the most sensitive in distinguishing gene negative control and the prHD groups in a recent study[4] and in our latest unpublished internal analysis of the PREDICT-HD database. Three clinical tests contained more than one subtest that was conceptually distinct (ie, Stroop Test, Trail Making Test and Hopkins Verbal Learning Test). For these tests, multiple measures were included

Table 2 Characteristics of prodromal Huntington's disease participants at baseline who did and did not receive a clinical diagnosis at a follow-up examination

	Not diagnosed (n=593)			Diagnosed (n=137)			
	Low (n=179)	Medium (n=226)	High (n=188)	Low (n=9)	Medium (n=25)	High (n=103)	p Value
% Women	65.9	65.0	55.9	88.9	68.0	65.0	0.069
Age (years)	35.6 (7.6)	41.7 (9.2)	43.9 (9.6)	37.4 (5.5)	42.8 (10.2)	45.1 (10.1)	0.205
Education (years)	14.6 (2.5)	14.6 (2.7)	14.2 (2.9)	13.8 (2.0)	12.8 (2.4)	14.3 (2.6)	0.113
CAG repeat length	40.8 (1.6)	42.0 (1.9)	43.5 (2.6)	40.8 (1.3)	42.2 (2.5)	44.1 (3.0)	0.072
UHDRS motor score	2.8 (3.1)	3.6 (3.7)	5.0 (5.2)	7.8 (5.1)	10.4 (5.4)	10.1 (7.0)	0.0001
Follow-up period (years)	3.6 (1.5)	3.6 (1.4)	3.6 (1.5)	4.2 (1.1)	4.2 (1.3)	4.4 (1.2)	0.0001

Note, stratification of the prodromal Huntington's disease participants into low, medium, and high groups was based on the CAG–age product (CAP) score.[18] The p values are from comparisons between prodromal Huntington's disease participants who did and did not receive a diagnosis, adjusting for CAP group. The significant group difference in the follow-up period further stressed the importance of using survival analysis, for which the follow-up time is taken into consideration.
UHDRS, Unified Huntington's Disease Rating Scale.

because they distinguished between the control and prHD groups. The present study reports baseline data from the first task administration for all analyses.

Eleven well known clinical tests/subtests and their measures included the Stroop Test (colour naming, word reading and interference; total correct in 45 s)[19]; the Trail Making Test (parts A and B; time to complete)[20]; the Wechsler Adult Intelligence Scale-III Letter–Number Sequencing (total correct); Phonemic Verbal Fluency (letters; total correct over three trials)[21]; the Symbol Digit Modalities Test (total correct in 90 s)[22]; the Hopkins Verbal Learning Test-revised (HVLT-R; immediate (total learning) and delayed recall; total correct)[23]; and the University of Pennsylvania Smell Identification Task (per cent correct).[24]

There were seven computerised tests. In the Dual Verbal Working Memory task,[25 26] participants name the colour of digits presented serially every 1500 ms, and then recall the serial order of the digits. The set size begins at two and increases by one after two trials. The task is discontinued when recall fails for both trials of a set size; the measure is total correct recall. In the Emotion Recognition task, participants match the facial expression of faces with a verbal description of the emotion.[5] The measure is total correct negative emotions, which is sensitive in prHD. In the N-Back Working Memory task,[27] participants match the current letter with a letter presented two back in the series. Letters are presented every 3 s and lures occur in the one back and three back positions. The measure is the discrimination score in the condition with lures. In the Maximum Tapping Speed task, participants tap at their maximum speed for 10 s using the non-dominant hand. Five trials are administered and the measure is the mean of the inter-tap intervals. In the Paced Timing task,[2] participants begin tapping in synchrony with a 550 ms isochronous tone and then continue tapping without the tone at the same pace (continuation phase). The measure is the reciprocal of the within subject inter-tap interval during the continuation phase, which reflects timing proficiency. In the Two Choice Reaction Time task, one of two adjacent circles on a touch screen turns green and participants immediately press the circle. The measure is mean movement time, which reflects response selection processes. In the Cued Movement Sequence task,[28] filled circles are displayed in 12 vertical pairs along the bottom of a touch screen. Participants press sequentially illuminated circles. The next circle is illuminated when the finger is lifted from the previous circle. Eight error free trials are administered; the measure is movement time, which reflects motor planning and sequencing skills.

Statistical analyses

We first conducted an exploratory FA with varimax rotation to elucidate the dimensional structure underlying the 18 tests. The FA used data from 580 prHD participants with complete observations. Measures that comprised a factor were those with factor loadings of ±0.40 or greater, indicating that at least 16% of the variation in a variable was explained by an individual factor. Factors were not retained if a minimum of two variables failed to load on a factor. For each retained factor, factor scores were computed by (1) standardising each cognitive variable, (2) multiplying the standardised variable by the factor coefficient for variables that loaded 0.40 or greater on the factor and (3) summing over the weighed standardised variables.

In an intermediate analysis, an ANCOVA evaluated the internal validity of the factor scores by comparing the control, low CAP, medium CAP and high CAP groups (table 1) on each factor score, covarying age. Follow-up ANCOVAs were performed on each individual test comprising a factor score to qualitatively compare their sensitivity with the factor scores, as indexed by the adjusted R^2 for the main effect of group.

A log-logistic accelerated failure time (AFT) survival model was used to predict time to diagnosis using data from 730 prHD participants with at least one follow-up assessment (table 2). This model is an improvement over others because it directly models time to diagnosis in years since study entry to a HD diagnosis or to the last follow-up assessment for individuals who did not receive a diagnosis. A detailed description of the model is given by Zhang *et al*.[18] The present study extended the model by including the UHDRS motor score and the factor scores as predictor variables, in addition to the CAP score. The ability of cognitive factor scores to predict time to diagnosis was assessed adjusting for the CAP and motor symptoms, which potentially confound associations between cognitive functioning and the primary endpoint. A stepwise variable selection procedure was used wherein each factor score was sequentially added to the AFT model that included the CAP and the UHDRS motor score to identify the combination of factors that were the strongest unique predictors of time to diagnosis. Age at study entry did not add significantly to the model, so it was excluded in the final model.

RESULTS

Factor analysis

Seven factors were identified that accounted for 51% of the total variance. Factor 7 was discarded as all variable loadings were lower than ±0.40 (ie, ±0.01 to 0.23). The first six factors were retained for further analyses. Table 3 summarises variables that loaded on each factor, which accounted for 9–21.6% of the total common variance. Factor 1 was described as speed and inhibition but consisted only of the three Stroop subtests. Although not a latent variable, subtests did not load with other factors, indicating they represent a different component of cognition that should be treated separately. This was also seen for factor 6, verbal learning and memory, which consisted of the two HVLT-R subtests. Latent variables were suggested by the remaining factors. Factor 2 was characterised by three tests of verbal working memory and phonemic verbal fluency, which involves tracking previously named words (ie, monitoring contents of working memory). Factor 3 was characterised by tests of motor planning, but also motor speed (maximum tapping speed). Factor 4 was described by tests of attention and information integration. Factor 5 was characterised by tests of sensory and perceptual processing, including negative emotion recognition, smell perception and timing.

Internal validity of factor scores

Intermediate ANCOVAs tested for group differences (control, low CAP, medium CAP, high CAP) in each factor score, covarying for age. All six factor scores differed significantly among the groups (factor 1: $F(4,1041)=34.59$, $p<0.0001$; factor 2: $F(4,812)=14.71$, $p<0.0001$; factor 3: $F(4,948)=51.23$, $p<0.0001$; factor 4: $F(4,1027)=45.20$, $p<0.0001$; factor 5: $F(4,984)=58.21$, $p<0.0001$; and factor 6: $F(4,1044)=16.16$, $p<0.0001$). Figure 1 plots the age adjusted standardised effect sizes (ie, effect size/SE of the effect size) for each CAP group, which were obtained from pairwise comparisons with the control group. Greater negative effect sizes for factors 1, 2, 5 and 6 and greater positive effect sizes for factors 3 and 4 reflect worse performance. This figure shows the strong relationship between the CAP groups and factor scores. Although none of the factor scores discriminated the low CAP group from controls, all factors were significantly sensitive to worse performance in the medium and high CAP groups, similar to findings for individual tests.[4] These results verified the internal validity of

Table 3 Factor loadings for each test in the assessment battery

Tests	Factor 1 Speed and inhibition	Factor 2 Verbal working memory	Factor 3 Motor planning and speed	Factor 4 Attention and information integration	Factor 5 Sensory and perceptual processing	Factor 6 Verbal learning and memory
Stroop: colour	0.778					
Stroop: word	0.725					
Stroop: interference	0.575					
Letter–number sequencing		0.573				
2-back working memory		0.569				
Dual verbal working memory		0.551				
Phonemic verbal fluency		0.418				
Two choice reaction time			0.694			
Cued movement sequencing			0.615			
Maximum tapping speed			0.594			
Paced timing			−0.409		0.434	
Trail Making Test: part A				0.602		
Trail Making Test: part B				0.540		
SDMT				−0.433		
Emotion recognition					0.526	
UPSIT					0.456	
HVLT-R: delayed recall						0.581
HVLT-R: immediate recall						0.483
Per cent common variance	21.6	21.0	19.8	13.6	13.0	9.0

HVLT-R, Hopkins Verbal Learning Test-revised; SDMT, Symbol Digit Modalities Test; UPSIT, University of Pennsylvania Smell Identification Task.

the factor scores. Qualitatively, the age-adjusted standardised effect sizes for the medium and high CAP groups were largest for sensory–perceptual processing and motor planning/speed, and the smallest for verbal learning and memory.

Follow-up ANCOVAs examining group differences on each individual test comprising a factor showed that factor scores typically discriminated the groups as well or better than any single test. Table 4 shows that the adjusted R^2 for factor scores and the individual tests. Factors 2 (working memory), 3 (motor planning/speed) and 5 (sensory–perceptual processing) were more sensitive in discriminating among the groups than any single test comprising the factors. R^2 values for factors 1 (speed–inhibition) and 4 (attention–integration) were similar to those for one test comprising each factor score (Stroop Interference and Symbol Digit Modalities Test, respectively). Conversely, R^2 values were lower for factor 6 (verbal learning and memory) than the HVLT-R immediate recall subtest (ie, total recall).

Cognitive domains and proximity to diagnosis

A stepwise variable selection procedure determined the combination of factors that predicted time to diagnosis in the AFT model (table 5). The final prediction equation was

$$Y = \exp[3.339 - 1.217\times\text{CAPs} - 0.039\times\text{UHDRS Motor Score} - 0.099\times\text{F3} + 0.172\times\text{F5}]$$

where Y is the predicted time to HD diagnosis since study entry given the CAP score, the UHDRS motor score and scores on factors 3 (F3) and 5 (F5). The CAP and UHDRS motor scores were strongly related to time to diagnosis after adjusting for other variables in the equation. A half point increase in the CAP score decreases time to diagnosis by 46% (1−exp(−1.217*0.5) and a 1 point increase in the UHDRS motor score decreases time to diagnosis by 4% (1−exp(−0.039). The main results showed that motor planning/speed (factor 3) and sensory–perceptual processing (factor 5) were the strongest unique predictors of time to diagnosis, after adjusting for the CAP and UHDRS motor scores. A 1 point increase in the motor planning/speed factor score (worse performance) would be expected to decrease time to diagnosis by 9% (ie, 1−exp(−0.099). A 1 point increase in the sensory–perceptual factor score (better performance) would be expected to increase time to diagnosis by 19% (ie, exp (0.172)−1). The remaining factors did not add to the prediction of time to diagnosis.

DISCUSSION

The present study identified six conceptually meaningful cognitive domains that characterised functioning in prHD. Four latent factors (verbal working memory, motor planning/speed, attention–information integration and sensory–perceptual processing) were uncovered that elucidated the dimensional structure of 12 different tests. The two remaining factors (speed–inhibition and verbal learning/memory) were comprised of subtests from the same neuropsychological test, signifying that they should be treated separately. There was good definition between factors with all but one test clearly loading on one of the six factors. The paced timing task loaded on both the motor planning and the sensory–perceptual factors, which makes sense since timing proficiency is fundamental to planning and perception.

Our main results indicated that motor planning/speed and sensory–perceptual processing were the best indicators of time to diagnosis after controlling for CAP and UHDRS motor scores. This is notable given that the CAP score is by far the most robust predictor of time to diagnosis. A worse motor planning/speed score was a risk factor, with a 1 point increase expected to decrease time to diagnosis by 9%. This finding likely relates to changes in neural systems that support cognitive aspects of planning, as it was not confounded by motor symptoms. Conversely, a better sensory–perceptual score was a protective factor, with a 1 point increase expected to increase time to diagnosis by 19%. Most tests comprising these two factors are utilised in research rather than clinically, as many lack normative data. Hence their use in clinical trials has been limited. Our

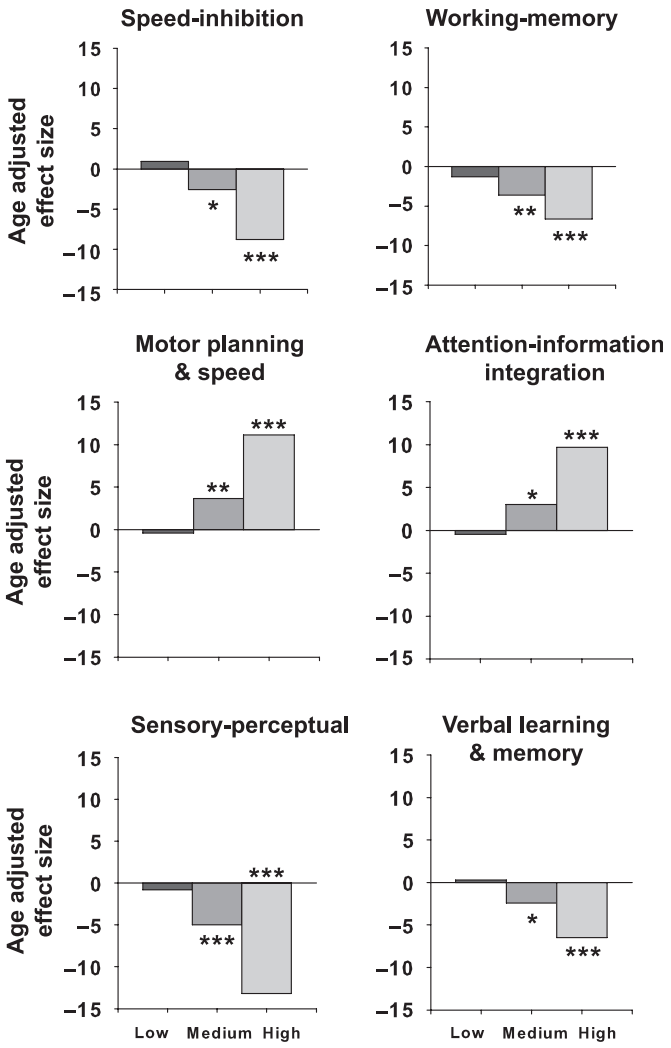

Figure 1 Age adjusted effect sizes for the six factor scores in the low, medium and high CAG—age product (CAP) groups. Standardised effect size=effect size/SE of effect size. Asterisks denote the significance of pairwise comparisons between the control group and each CAP group where *p<0.02, **p<0.001 and ***p<0.0001.

Table 5 Log-logistic accelerated failure time model results

Variable	Estimate	SD error	χ^2	p Value
CAP score	−1.217	0.299	16.565	<0.0001
UHDRS motor score	−0.039	0.008	21.437	<0.0001
Factor 3: motor planning and speed	−0.099	0.026	15.054	<0.0001
Factor 5: sensory—perceptual processing	0.172	0.054	10.049	<0.0015

CAP, CAG—age product; UHDRS, Unified Huntington's Disease Rating Scale.

results indicate that tests representative of these domains should be part of a clinical trials battery as they have more prognostic value than the other domains.

Factor scores are of limited utility for diagnosis. Changes in composite scores are also difficult to interpret for clinical purposes because they consist of linear combinations of variables. However, factor scores should be considered in clinical trials where the emphasis is on detecting treatment effects. Our results show that latent variables were more sensitive to cognitive decline than individual measures comprising the motor planning/speed and sensory—perceptual factors (ie, R^2), or for that matter any other factor. This is common when factors contain three or more measures from different tests.[15] Factor scores may also be more reliable as they are comprised of multiple measures, which would be advantageous for longitudinal designs. Sets of tests for the motor planning and sensory—perceptual factors are also feasible for use in clinical trials as they each take 15—20 min to administer.

Although the neural bases of our findings are unknown, we speculate that motor planning/speed and sensory—perceptual processing may be mediated partly by different core networks that are especially weakened in prHD. For example, aspects of motor planning, including timing and sequencing are mediated by the motor circuit (putamen, thalamus, supplementary motor area and sensorimotor cortices) and parietal cortex.[29–31] Neuroimaging studies of timing and motor planning in prHD report abnormal activity in these systems, especially in individuals closer to diagnosis.[32 33] As for sensory—perceptual processing, the ventral striatum and the limbic system (orbitofrontal, cingulate and anterior insular cortex) mediate timing, emotion and odour recognition.[34–36] The insular cortex may be

Table 4 Adjusted R^2 from ANCOVA testing for group differences in factor scores and performances on individual tests comprising each factor

Factor/test	Adjusted R^2	Factor/Test	Adjusted R^2
Factor 1: speed—inhibition	0.114**	Factor 4: attention—integration	0.146**
Stroop: colour	0.095**	Trail Making Test: part A	0.074**
Stroop: word	0.081**	Trail Making Test: part B	0.099**
Stroop: interference	0.113**	SDMT	0.148**
Factor 2: working memory	0.063**	Factor 5: sensory—perceptual	0.188**
Letter—number sequencing	0.035**	Paced timing	0.132**
2-back working memory	0.049**	Emotion recognition	0.121**
Dual verbal working memory	0.039**	UPSIT	0.064**
Phonemic verbal fluency	0.030**		
Factor 3: motor planning and speed	0.174**	Factor 6: verbal learning and memory	0.055**
Two choice reaction time	0.097**	HVLT-R: immediate recall	0.091**
Cued movement sequencing	0.090**	HVLT-R: delayed recall	0.010*
Maximum tapping speed	0.126**		
Paced timing	0.134**		

The ANCOVAs adjusted for age. The main effect of group was significant for all factors and the measures comprising each factor at *p<0.006 or **p<0.0001.
HVLT-R, Hopkins Verbal Learning Test-revised; SDMT, Symbol Digit Modalities Test; UPSIT, University of Pennsylvania Smell Identification Task.

especially important as it integrates physiological states (eg, emotionally charged or arousing events), which alter estimates of time.[34 37] Indeed, anterior insula activity is abnormal during timing in prHD individuals who are more than 12 years from diagnosis.[32 38] Insula atrophy also correlates with impaired recognition of fear in early HD.[39]

Other cognitive domains identified by the present study appeared less affected in prHD, possibly because different neural systems assume a more central role in mediating core functions. However, emerging neuroimaging studies suggest that functional markers can be more sensitive barometers of decline than behavioural indices. For example, connectivity in working memory networks (frontostriatal and frontoparietal) is weakened in prHD individuals near to diagnosis, despite normal working memory performance.[40] Similarly, activation in a key inhibition hub (anterior cingulate) is abnormal in prHD despite normal performance on an interference task.[41] These findings may be due to the use of compensatory strategies which can mask performance difficulties. More challenging cognitive tests might reveal behavioural impairments in these areas.

Limitations and future directions

The results provide insight into cognitive domains that are important markers of time to diagnosis. Whether these domains will be sensitive to longitudinal cognitive decline is unknown although we plan to investigate this in the future. Our findings cannot be taken to mean that cognitive evaluations should focus only on motor planning/speed and sensory–perceptual processing. Rather, there are many facets to the constructs elucidated by the present study. More work is needed to address gaps in existing assessments. Domains that have been inadequately sampled by the PREDICT battery include inhibition and non-verbal working memory. The search for more sensitive indices of cognitive impairment is a vital endeavour as behavioural measures have considerable potential to serve as cost effective and sensitive outcomes in clinical trials, and are important for diagnosis and tracking of disease progression.

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Competing interests None.

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Data sharing statement There are no unpublished data from the study. All PREDICT-HD data are shared on the NIH dbGaP website and can also be obtained from the PI at the University of Iowa and the corresponding author on this paper.

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APPENDIX 1

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Cognitive domains that predict time to diagnosis in prodromal Huntington disease

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