Cognitive predictors of HD diagnosis: A prospective study of phenoconversion

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Background

Early treatment of Huntington's Disease (HD) requires having measures of a candidate compound's abilities to delay clinical onset and/or slow disease progression. To date, there are no known measures of manifest HD prior to receiving a clinical diagnosis based on measures of motor and functional abnormality. The Predict-HD was designed to characterize early measures of HD so that intervention can be pursued within the earliest course of disease pathology.

Methods

- *Predict-HD* is a 32-site longitudinal study evaluating persons who have a CAG HD gene expansion but do not yet manifest disease and do not yet show any functional decline.
- *Participants:* *543* pre-HD individuals participated in the Predict-HD study.
- Over the course of annual evaluations, 68 participants have converted from being considered pre-HD to receiving a diagnosis of HD with 100% confidence by a movement disorder specialist.
- Using a log logistic survival analyses we examined the utility of 16 neurocognitive tests to predict diagnosis in 543 pre-HD individuals in Predict-HD.

Measures

Digit symbol

Stroop Color Word Test

Trail Making Test

Facial Recognition Test

Smell Identification

Letter Number Sequencing

ANART

Verbal Fluency

Hopkins Verbal Learning

Tapping Speed

Self-paced Timing

Button Task

Emotional Recognition

Choice Reaction Time

Tower Task

Serial Motor Learning

Data Analysis

A log logistic model was used for survival analyses of diagnosis on baseline data; results in Odds Ratio.

Interval censoring used due to annual exams.

Broader class of accelerated life models used to replicate each analysis; results in Time change.

Results

- Performances on 13 of 16 tests studied significantly increased the probability of receiving a diagnosis of HD.
- Twelve cognitive tests were significant predictors of diagnosis even after well-known predictors of clinical onset (CAG repeat length and current age) were considered.
- Nine of our 16 cognitive tests made significant contributions to the prediction of HD diagnosis after controlling for motor exam.

Cognitive Test	**DX**	**ProbDX After CAG, Age**	**ProbDX After CAG, Age, Motor Score**
Digit symbol	**2.5**	**1.8**	**1.5**
Stroop Color Word Test	**2.5**	**2.1**	**2.0**
Trail Making Test	**1.6**		
Facial Recognition Test			
Smell Identification	**4.2**	**1.4**	
Letter Number Sequencing	**1.9**	**1.6**	
ANART			
Verbal Fluency	**2.0**	**1.8**	**1.7**
Hopkins Verbal Learning	**1.9**	**1.5**	
Tapping Speed	**2.7**	**1.9**	**3.4**
Self-paced Timing	**4.8**	**3.2**	**2.6**
Button Task	**2.1**	**1.7**	**1.4**
Emotional Recognition	**2.3**	**1.7**	**2.5**
Choice Reaction Time	**1.9**	**1.4**	
Tower Task	**1.6**	**1.5**	**1.5**
Serial Motor Learning			

Conclusions

Our findings suggest that a number of neurocognitive measures may be useful in the design of clinical trials in pre-HD. Findings will be addressed in terms of increased power calculations, reduced sample sizes, and greater efficiency these results offer to preventive trials.

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