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Neurocognitive Signs in Prodromal Huntington Disease

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Abstract

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Objective—PREDICT-HD is a large-scale international study of people with the Huntington Disease CAG-repeat expansion who are not yet diagnosed with HD. The objective of this study was to determine *at what stage* in the HD prodrome cognitive differences from CAG-normal controls can be reliably detected.

Method—For each of 738 HD CAG-expanded participants, we computed estimated years to clinical diagnosis and probability of diagnosis in five years, based on age and CAG repeat expansion number (Langbehn, Brinkman, Falush, Paulsen, & Hayden, 2004). We then stratified the sample into groups: "NEAR," estimated to be ≤ 9 years, "MID," between 9 and 15 years, and "FAR," ≥ 15 years. The control sample included 168 CAG-normal participants. Nineteen cognitive tasks were used to assess attention, working memory, psychomotor functions, episodic memory, language, recognition of facial emotion, sensory-perceptual functions, and executive functions.

Results—Compared to the controls, the NEAR group showed significantly poorer performance on nearly all, and the MID group on about half of the cognitive tests ($p = 0.05$, *Cohen's d* Near as large as −1.17, Mid as large as −0.61). One test even revealed significantly poorer performance in the FAR group (*Cohen's d* = −0.26). Individual tasks accounted for 0.2% to 9.7% of the variance in estimated proximity to diagnosis. Overall, the cognitive battery accounted for 34% of the variance; in comparison, the UHDRS Motor Score accounted for 11.7%.

Conclusions—Neurocognitive tests are robust clinical indicators of the disease process prior to reaching criteria for motor diagnosis of HD.

Keywords

cognitive assessment; presymptomatic; neuropsychology; psychomotor; prediagnosis

Huntington disease (HD) is a progressive, fatal, autosomal dominant neurodegenerative disease that primarily affects movement, cognition, and psychiatric functions. Diagnosis of HD is based on the presence of unequivocal motor signs of HD, in conjunction with a positive genetic test for the HD CAG expansion or a confirmed family history of HD. Most people with the HD gene appear healthy throughout their youth and early adulthood, and then gradually develop signs and symptoms of HD, often leading to a diagnosis in middle age. The age of diagnosis varies in accordance with the number of CAG repeats on the expanded allele, although there is also substantial individual variability not accounted for by this genetic factor (Andrew et al., 1993; Gusella, MacDonald, Ambrose, & Duyao, 1993). A growing community of researchers is directing efforts at finding treatments to delay onset or slow the progression of early pathological changes in an attempt to reduce the tremendous personal and social costs of HD. Finding effective therapeutic or preventive treatments for HD depends critically on the ability to reliably and sensitively measure clinical signs of disease.

Cognitive measures have excellent potential both for identifying individuals beginning to show subtle signs prior to the diagnosis of HD who might be suitable for clinical trials, and as sensitive outcome measures in HD trials. Cognition is an important target for therapeutic trials because even subtle cognitive changes can affect functional abilities like work performance, driving, and financial management. Cognition is actively studied in the HD prodrome, with more than 150 empirical reports of neurocognitive function published since the genetic mutation for HD was identified in 1993. In early studies, the evidence of cognitive dysfunction was inconsistent. But more recent, adequately powered studies have revealed that people with the HD prodrome have poorer performance on measures of attention, working memory, processing speed, psychomotor functions, episodic memory, emotion processing, sensory-perceptual functions, and executive functions (Johnson et al.,

2007; Kirkwood et al., 2000; Paulsen et al., 2006a; Paulsen et al., 2008; Paulsen et al., 2001; Pirogovsky et al., 2007; e.g., Stout et al., 2007).

The use of cognitive measures in clinical trials requires a substantial knowledge base, indicating when in the HD prodrome cognitive changes can be reliably detected, and which measures show adequate sensitivity. The PREDICT-HD study was designed to address these questions. PREDICT-HD is a 31-site international study of potential clinical and biological markers of HD in individuals with the CAG-expansion for HD, but who did not meet criteria based on motor impairment for diagnosis at the time of enrolment. The PREDICT-HD cohort is large, with more than 700 non-diagnosed CAG-expanded (prodromal) participants. For each participant, age-conditioned estimates of time to onset of motor disease were derived using a survival analysis regression equation based on CAG repeat length (Langbehn et al., 2004). Estimated time to motor disease onset in the sample varies from 5 to 25 years. The size and diversity of this sample makes it possible to stratify participants based on their estimated proximities to diagnosis, allowing an estimation of when, in the extended period leading up to HD diagnosis, cognitive signs can be detected, and which cognitive measures appear to have the most promise for detecting change in longitudinal studies.

We report findings based on three stratified prodromal HD groups, a far from diagnosis group (FAR) estimated to be more than 15 years from diagnosis, a middle group, estimated to be between 9 and 15 years from diagnosis (MID), and a near diagnosis group, estimated to be less than 9 years from diagnosis (NEAR). For each of these groups compared to controls, we computed effect sizes for individual cognitive measures, allowing a direct comparison of all the tasks in our cognitive assessment. This allows a determination of *which* tasks are most adversely affected during the HD prodrome, and an upper-limit estimate of *how early* in the prodromal phase significant effects could be detected (Paulsen et al., 2008). Additionally, we examined the associations between cognitive findings and results of the clinical motor examination, which also reveals subtle signs prior to diagnosis (Biglan et al., 2009). Thus, this study provides a comprehensive depiction of the cognitive prodrome for HD.

Method

Participants

Data from 906 participants in the PREDICT-HD study, including 738 prodromal HD participants and 168 control participants, were included in these analyses. These data were collected at 32 sites in the United States, Canada, Australia, Germany, Spain, and the United Kingdom from 2002 to 2008. Consent was obtainted according to the Declaration of Helsinki and study protocol was approved by the Institutional Review Board at The University of Iowa as well as instituional review boards at each participating institution.

All participants had a family history of HD and prior voluntary, independent genetic testing for the HD CAG expansion; prodromal HD participants had the expansion (≥ 36 CAG repeats) and control participants did not (< 36 CAG repeats). Exclusion criteria included clinical evidence of unstable medical or psychiatric illness, alcohol or drug abuse within the previous year, learning disability or mental retardation requiring special education, history of other central nervous system disease or events such as seizures or head trauma, pacemaker or metallic implants, age less than 18 years, prescription of antipsychotic medications within the past six months, and use of phenothiazine-derivative anti-emetic medications more than three times per month. Other prescribed, over-the-counter, and natural remedies were not restricted.

Genetic Status

Confirmatory DNA testing was completed using blood drawn at the baseline visit. CAG-repeat length for each participant was determined using a polymerase chain reaction method (Warner, Barron, & Brock, 1993).

Motor Examination

Participants were evaluated using a standardized neurological examination, the Unified Huntington Disease Rating Scale (UHDRS) (The Huntington Study Group [HSG], 1996), which includes 31 items assessing chorea, bradykinesia, rigidity, dystonia, and oculomotor function. Item scores range from 0 (no impairment) to 4 (impairment), and all item scores are summed to create total motor scores (see Table 1). In addition to the motor scores, the motor examiner also assigned a rating indicating the level of the examiner's confidence that any observed motor signs were a manifestation of HD. Confidence level ratings ranged from 0 = normal, indicating no abnormalities, to 4, indicating motor abnormalities that are unequivocal signs of HD (≥ 99% confidence). Only participants with diagnostic confidence level ratings < 4 are included in the current report.

Proximity to Clinical Diagnosis

For each participant, we computed estimated years to diagnosis (as defined by the presence of unequivocal motor signs of HD), and the probability of diagnosis in five years, based on the participant's age and the number of CAG repeats on the expanded allele (Langbehn et al., 2004; Langbehn, Hayden, & Paulsen, 2009; Paulsen et al., 2008). Given previous findings indicating that neurocognitive symptoms are more prominent in individuals with the HD genetic mutation who are estimated to be closer to diagnosis (Paulsen et al., 2008; Paulsen et al., 2001; Stout et al., 2007), we stratified our prodromal HD sample into three groups to allow a focused examination of neurocognitive differences in the HD prodrome: NEAR to diagnosis (< 9 years), MID (9 to 15 years), and FAR from diagnosis (> 15 years). The groups represent approximate terciles of CAG-expanded participants, rounded to the nearest estimated year to diagnosis.

Demographics

Approximately two-thirds of the PREDICT-HD study participants were female; however, female overrepresentation is common in observational studies of HD, and the ratio of females to males did not differ across the NEAR, MID, FAR, and control groups, $p = 0.09$. For prodromal HD participants, those participants who were estimated to be nearer to the clinical diagnostic threshold were older, on average, than participants farther from their estimated age of diagnosis ($p < 0.0001$). This was relationship was anticipated because age and CAG length interact to determine estimated years to diagnosis. The control group was older than the MID group and younger than the NEAR group. Education levels did not differ significantly by group, $p = 0.13$ (see Table 1).

Estimate of Premorbid Intellectual Functioning

Participants in the USA, Canada, and Australia completed the American National Adult Reading Test (ANART; Grober & Sliwinski, 1991; Schwartz & Saffran, 1987) and participants in the UK completed the National Adult Reading Test (NART-2; Nelson & Willison, 1991). These tests assess pronunciation of non-phonetic, low frequency English words such as "prelate" and "chamois" and are used to retrospectively estimate an individual's verbal premorbid intelligence. Such tests are used to control for individual differences in intelligence that are unrelated to illness. The Word Accentuation Test, used in Spain, assesses pronunciation of low frequency Spanish words, absent written accents to guide pronunciation (Del Ser, Gonzalez-Montalvo, Martinez-Espinosa, Delgado-Villapalos,

& Bermejo, 1997). German participants completed the Wortschatztest (WST; Schmidt & Metzler, 1992), which involves discriminating written German words from non-word alternatives. An estimated premorbid verbal intelligence quotient (IQ) was calculated based on raw scores. For the NART-2, ANART, and WST, look-up tables from test manuals allowed conversion from raw errors to estimated verbal IQ. We were unable to identify standards for conversion to verbal IQ for the WAT, so we estimated IQ by standardizing the participants' raw WAT scores to the mean and SD of estimated verbal IQs for all other participants in the study. This is admittedly a rough method for estimating verbal IQ from the WAT; however, it affects only 1% of our sample and we chose to use this rough estimate over dropping the Spanish speakers from our analyses. Estimated premorbid verbal IQ did not differ across the NEAR, MID, FAR, and control groups ($p = 0.49$).

Procedure

Neurocognitive Assessment—Neurocognitive performance was assessed using a comprehensive battery of neuropsychological and cognitive tasks designed to maximize sensitivity to fronto-striatal neural circuitry. Tasks were selected to assess a broad range of cognitive functions that are known to be affected in the early stages of HD. The PREDICT-HD neurocognitive battery alternates between a longer battery administered in odd-numbered years (Year 1, 3, 5, etc.) and a shorter battery administered in even-numbered years (Year 2, 4, 6). We report cross-sectional baseline data corresponding to the initial administration of each task, most of which occurred at Visit 1, but which also included several tasks administered for the first time at Visit 2 (see Table 2).

The cognitive assessment included a total of 19 separate tasks, each of which we report on here. Because each of the tasks yielded several variables, we employed a data reduction strategy to select variables to include in this report. This data reduction strategy included: (1) for standardized clinical tests, selection of the variable known to have the best sensitivity and measurement characteristics (i.e., for Trails, number of seconds instead of number of errors); (2) for tests with multiple conceptually distinct measures, a variable that represented each component (i.e., for finger tapping tests, one variable indicating the speed of tapping and another indicating tapping variability); and (3) where necessary, using statistical methods to exclude variables having little evidence of sensitivity. This latter approach involved computing results on all summary variables for a given computerized test. Using this approach, for the 19 tasks which each yielded several variables, we identified a set of 51 variables, with at least one variable from each of the 19 original tasks. These 51 variables were used in our main presentation of effect sizes. Then, for the final set of analyses that examined the relationship between cognitive findings and the clinical motor examination, we reduced this number further while still maintaining at least one variable from each of the 19 tasks. From the total of 51 variables above, we reduced the set to to 29 variables, one from each conceptually distinct task component (e.g., one each for Trail A and Trail B), or difficulty level in the cognitive battery (e.g., Tower Tasks in the three disk and four disk versions).

All testing was conducted in the native language spoken at the study site. Thirty of the 32 sites were English speaking, and there was one site in Germany and another in Spain. Translation of the cognitive assessment battery, which was developed first in English, consisted of translations of all stimulus materials and instructions used with study participants. Translation of these materials generally occurred in three stages. First, translations were completed by a local translator involved in HD research who was also fluent in English. Next, a second translator, either local to the site, or a native speaker working with the study team and familiar with cognitive assessment, checked the original translations and identified any elements for which alternative translations could be

warranted. Third, discussion ensued between the two translators, and when necessary, included one of the authors (J.C.S. or S.A.J) to arrive at a consensus for the wording thought to best capture the nuances in the original English version. Translations of some tests had additional considerations, and these are noted where relevant within the description of those tests below.

Two computerized *Tower Tasks*, similar to Saint-Cyr et al. (1988), were used to assess planning and reasoning. For the first task, "Tower 3," participants viewed three vertical pegs. On one peg was a stack of three disks of increasing sizes, with the largest on the bottom. Participants attempted to relocate the stack, in exactly the same configuration, to a different peg, following two rules: only the topmost peg could be moved, and larger disks could not be placed on smaller disks. Participants also completed "Tower 4," a three-peg task that used four disks and the same rules as described above. Tower 3 and Tower 4 each included four identical trials; overall performance was assessed separately for Tower 3 and 4 by computing the mean number of moves performed across the four trials within each task. Learning was also assessed as the difference in the number of moves from the first to the fourth trial for each task.

A computerized *Serial Response Time Task* (Willingham, Nissen, & Bullemer, 1989) was used to assess implicit learning of a motor sequence. Throughout the task, asterisks were presented serially in one of four locations. When an asterisk appeared, participants responded by pressing one of four buttons located on an external response device. Response buttons were aligned with the four screen positions where the asterisks could appear. Participants responded using index and middle fingers from both hands, keeping their fingers positioned above the four buttons throughout the task. For the first four blocks, asterisks appeared serially in a fixed 12-asterisk sequence which was repeated 8 times to allow learning. In a fifth (interference) block, asterisks appeared in the four locations in random order. Finally, in the sixth block, asterisks again appeared in the previously presented repeating sequence to ascertain whether the random block affected any learning gains that had been achieved by the fourth block. Participants were never informed that it was a repeating sequence. Learning was assessed as the difference in response time between blocks 5 (random sequence) and block 4 (4^{th} repetition of the same sequence). The impact of the random block (interference effect) was assessed by the difference between blocks 6 and 4.

To examine rule-based learning of categories, participants were tested using the computerized *Category Learning Task*, for which the decision rule can be verbalized (Ashby & Maddox, 2005). Participants attempted to assign visual stimuli to either category A or B on the basis of the width and orientation of darker and lighter bands inside a circular frame. They were not told how to categorize the stimuli, but were given corrective feedback after each trial to facilitate learning. In the verbalizable Category Learning Task, categories A and B were differentiated by a simple rule such that width exceeding a criterion belonged to one category and width less than that criterion belonged to the other category. Stimuli were presented in blocks of 50 trials. Participants completed the task by achieving 92% accuracy in any given block, or the task continued for a maximum of six blocks (300 trials) if the accuracy criterion was not met. We used two measures of performance: 1) percent correct in the block with the highest accuracy, and 2) percentage of blocks completed to reach the accuracy criterion.

To examine associative learning of categories, participants completed a version of the computerized *Category Learning Task* in which the decision rule is non-verbalizable (Ashby & Maddox, 2005). The task works similarly to the rule-based Category Learning Task except that: 1) the optimal decision rule requires integrating information from both width

and orientation in a manner that could not be described verbally, 2) the accuracy criterion was 80%, and 3) there were ten possible blocks. The accuracy criterion was reduced and number of blocks increased due to the greater level of difficulty of this task; however, the same two performance measures as assessed in the rule-based version of the task were collected: 1) percent correct in the block with the highest accuracy, and 2) percentage of blocks completed to reach the accuracy criterion.

A computerized *Emotion Recognition* task (Johnson et al., 2007) was used to assess facial emotion recognition. Participants viewed photographs of faces expressing one of six emotions or a neutral expression (Ekman & Friesen, 1976). They then selected the emotion label that identified the expression from a multiple choice response set which included the words: fear, disgust, happy, sad, surprise, anger, and neutral. There were ten stimuli per emotion. The dependent variable was the total number correct using only the negative emotions: anger, disgust, fear, and sadness (maximum = 40). We opted to include only the negative emotion trials in the total score based on our earlier work in a subset of this sample, which suggested a relative deficit in recognition of negative emotions (Johnson et al., 2007).

In a separate task, *Dynamic Emotion Recognition*, we examined emotion recognition using a set of facial stimuli with and without simulated movement. Again, participants chose from a multiple choice response set including anger, disgust, fear, happy, sad, and surprise (Spencer-Smith et al., 2001). For the trials without simulated movement, an emotional expression of moderate intensity was presented for one second. For the trials with simulated movement, a emotional expression of mild intensity was presented for 500 ms, followed by an emotional expression of moderate intensity for another 500 ms. Again, only the four negative emotions were included in the total score (max = 40).

A computerized *N-back Task* (Kirchner, 1958) was used to assess verbal working memory. Participants viewed a series of letters, three seconds apart, and were asked to judge whether the current letter matched the previous letter (1-back condition) or the letter presented 2-back (2-back condition). The 1-back and 2-back conditions were presented separately in 100 randomly ordered trials. Participants responded to every trial using the external response device, selecting either MATCH or NON-MATCH responses. Trials were of three types: matches, non-match foils, and non-match lures. Foils were unambiguous non-matches. Lures, more easily confused with matches, were defined as trials in which the current trial's letter was presented near the N-back position. For the 1-back condition, lures were in the 2-back position, and for the 2-back condition, lures were in either the 1-back or 3-back position. Discriminability indexes, comparing the ability to discriminate either lures from matches, or foils from matches, were computed separately for the 1-back and 2-back conditions.

Precision of movement timing was examined in a *Self-timed Finger Tapping task*, which used a response box interfaced to the computer (Hinton et al., 2007; Paulsen et al., 2004). Participants listened to a tone repeated at 1.8 Hz, and when ready, began tapping along with the tone. The tone then continued for 11 more taps. After the tone stopped, participants were to continue tapping, at the same rate, until 31 taps had occurred without the pacing tone, at which point the trial ended. This sequence was repeated for five trials. Means and standard deviations of intertap intervals over the five trials are reported for two conditions: dominant hand index finger and thumbs in alternation.

The *Speeded Tapping Task*, which is another computerized task with the response box, requires participants to tap as quickly as possible for five 10-second trials. Results are reported as the mean and standard deviation of the intertap intervals, separately for the index

fingers on each hand, as well as for the tapping of the thumbs, in alternation, on two adjacent response buttons.

A computerized *Cued Movement Sequence Task*, based on Georgiou, Bradshaw et al. (1995), was used to assess the impact of advance cuing on response times. Filled blue circles, arranged in twelve vertical pairs, were displayed along the bottom of a touch screen. At the left side was a single circle which indicated a start location, and which was illuminated (i.e., changed from blue to white) to initiate the trial. Trials proceeded from left to right, with one circle in each vertical pair illuminating at a time. Participants were asked to press each illuminated circle in order. Three conditions provided varied levels of advance information. In the *low cue level* condition, when the finger was lifted from the illuminated circle, a circle in the next column illuminated to indicate the next response location. In the *medium cue level* condition, the cue regarding the next response location occurred slightly earlier; as soon as the finger pressed the illuminated circle, a circle in the adjacent pair illuminated simultaneously. The *high cue level* condition was similar to the medium cue level in that as soon as the finger pressed the illuminated circle, a circle in the adjacent pair illuminated simultaneously. In addition, however, as the participant's finger lifted, a circle two pairs over from the current pair also illuminated, and the illuminated circle in the adjacent pair extinguished. Up to 28 attempts were allowed to complete either 8 (low and medium cue level conditions) or 16 (high cue level condition) error-free trials. We report the mean and standard deviation of the response times within accurate trials for each cue-level condition.

Simple and Two-Choice Response Times (RT) were examined using the computer and a response device fitted with a single start button at the bottom and two adjacent response buttons at the top. Participants initiated trials by placing the dominant index finger on the start button. For simple RT, a single hollow circle appeared on the computer screen, then filled in green between 0 and 3.2 s later. Participants responded to the filled circle by pressing the right-sided response button as quickly as possible. The two-choice RT condition was similar except that *two* adjacent hollow circles appeared. One of the circles then filled in green between 0 and 3.2 s later, and the participant pressed the corresponding response button. For both simple and 2-choice RT, we report means and standard deviations of response times.

The *Letter-Number Sequencing* subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III LN; Wechsler, 1997) was used to assess auditory-verbal working memory. The examiner read a series of numbers and letters, in mixed order. Participants attempted to repeat back the numbers first in numerical order, followed by the letters in alphabetical order. Three trials were presented at each set length (a total of 2 to 8 letters and numbers), with increasing set sizes across the task. The dependent measure was the number of correct trials (max = 21).

The *Benton Facial Recognition Test* (Benton & Hamsher, 1978; Benton, Hamsher, Varney, & Spreen, 1983) assesses visuoperceptual processing and face recognition abilities. Participants viewed an image of a face (frontal view, with either the full face, a partial ¾ face, or in darkened conditions) and then selected, from the six alternatives in the multiple choice response set, the face that matched the target. We report total correct (max = 27).

The *University of Pennsylvania Smell Identification Test* (UPSIT; Doty, Shaman, Kimmelman, & Dann, 1984; Sensonics, Inc., Haddon Heights, New Jersey, USA) assesses olfactory recognition. For the German and Spanish sites, translated versions of the test were sourced from the manufacturer. Participants "scratched and sniffed" odor patches and

attempted to identify the odors from a multiple choice response set. We report total correct (max = 40).

The *Stroop Task* (Stroop, 1935) assesses processing speed and executive functions. Participants rapidly named colors (Color naming condition), read color names (Word reading condition), and finally named colors while inhibiting the dominant reading response (e.g., correct response to the word "blue" printed in red ink is "red"; Interference condition). We report total correct separately for each of the three conditions.

The *Symbol Digit Modalities Test* (SDMT; Smith, 1991) assesses psychomotor speed and working memory. Participants were presented with a key at the top of the page, which paired the digits 1 through 9 with unique symbols, such as X and =. Below the key, they were presented with the symbols, arranged in rows, and they were required to write below each symbol the corresponding digit. We report the number of correct matches completed in 90 seconds.

The *Trail Making Test* (Reitan, 1958) assesses psychomotor speed and executive functions. For Trail A, participants connected circles containing numbers in ascending numerical order. In Trail B, participants connected circles containing numbers and letters by alternating between numbers and letters in ascending order (e.g., 1-A-2-B, etc.). We report time to completion for each condition.

Phonemic Verbal Fluency (Benton et al., 1983) asked participants to say as many words as possible beginning with a specified letter within 60 seconds. In the English language, two forms of the task (B, W, R and L, D, T) were randomly assigned by site. For the German site, P, K, and T were used, and for the Spanish site F, A, and S. The selection of these three letters for the non-English sites were made in conjunction with neuropsychologists native to the region. We report the sum of correct words across three trials.

The *Hopkins Verbal Learning Test-Revised* (HVLT-R; Brandt & Benedict, 2001) assesses verbal episodic memory. Forms 2 and 4 were used and counterbalanced across all sites including non-English sites. German and Spanish forms were developed and tested in small pilot studies locally at the site using samples of ~ 30 healthy controls. For the HVLT-R, twelve words were presented and recalled over three trials to measure learning. Additionally, the words were recalled after a 20-minute delay, which was followed by a recognition trial. A subset of these data was also reported in greater detail by Solomon et al. (2007).

The *Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence* (Wechsler, 1999) assesses abstract nonverbal reasoning. For each item, the participant examined a matrix of images that was missing one component and selected the response option that best completed the matrix. We analyzed the total correct (max = 35 or 32 for participants aged 18–44 and 45–79, respectively). This test was not administered at the German or Spanish site.

The *Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence* (WASI Vocab) (Wechsler, 1999) assesses vocabulary knowledge by asking participants to define a series of words of increasing difficulty. Each item was scored as 0, 1, or 2 points, based on completeness of the definition. We report total correct (max = 42). This test was not administered at the German or Spanish site.

Statistical Analyses

Descriptive statistics on the cognitive measures indicated that variability measures from the following timed tests were positively skewed: Self-Timed Tapping, Cued Movement Sequencing, Simple RT, 2-Choice RT, and Speeded Tapping. For these measures, we computed reciprocals to improve their normality. Also, we computed arcsine transformations of the discriminability indexes from the N-back task to improve their normality. The analyses described below used a standard set of covariates consisting of gender, age, estimated verbal IQ, years of education, and bivariate (yes/no) indications of self-reported typing and musical expertise. The latter two covariates were intended to control for expertise in fine motor abilities that could add disease irrelevant noise to our psychomotor task measures; to keep a consistent method of analysis across all measures, we included the typing and musical expertise measures in the covariate set for all analyses.

Primary analyses: Sensitivity of cognitive measures in prodromal HD NEAR, MID, and FAR from diagnosis.

Effect Size Estimates—To identify the most sensitive cognitive measures, we computed effect sizes to produce a common metric, the number of standard deviations of difference between prodromal HD group and control group performance. We then assessed effect sizes for the NEAR, MID, and FAR from diagnosis groups to determine when in the prodromal timeline specific cognitive measures become sensitive. Effect sizes were computed based on separate univariate linear regression equations for each neurocognitive variable, adjusting for the standard set of covariates. From these regression models, we derived least-squares means for each group, and we estimated performance variability pooled across all four groups (root mean square error). These values were then used to calculate effect sizes (Cohen's *d*; Cohen, 1988) for each prodromal HD group (NEAR, MID, FAR) compared to controls:

$$\text{Effect Size}_{\text{pre-HDgroup}} = \frac{\text{Mean}_{\text{pre-HDgroup}} - \text{Mean}_{\text{control}}}{\text{PooledStandardDeviation}}$$

We re-coded effect size estimates so that poorer performance of the prodromal HD groups compared to controls was indicated by negatively signed effect sizes, and superior performance of the prodromal HD group compared to controls was indicated by positively signed effect sizes. In total, we computed 51 effect size comparisons for each of the prodromal HD groups, allowing us to build a reasonably comprehensive view of all variables in the test battery that we thought had the potential to be sensitive.

Detection of Significant Group Effects—We used Dunnett's test to determine the statistical significance of differences between each prodromal HD group and controls for each cognitive variable. Because the effect sizes are simply the differences between the mean of the prodromal HD and control groups divided by an estimate of variability, Dunnett's test is also conceptually equivalent to testing whether effect sizes differ from zero.

Secondary Analyses: Sensitivity of Cognitive Measures and UHDRS Motor Scores—We investigated whether cognitive measures tap unique variance in proximity to diagnosis that is not captured by the routinely administered UHDRS motor exam. We limited these analyses from 51 to 29 variables, one from each conceptually distinct *task component* in the cognitive battery (e.g., Trails A *and* Trails B). From each of the 29 task components, we selected the variable with the largest effect size in the NEAR group. We then computed separate univariate linear regressions for each of these variables, predicting probability of HD diagnosis within 5 years, after controlling for UHDRS motor score and

the standard set of covariates. Finally, we examined the extent to which the full set of cognitive measures, in aggregate, was associated with estimated proximity to diagnosis. To address this, we computed three additional univariate linear regression models in which we predicted the probability of diagnosis within 5 years based on UHDRS total motor score alone (Model 1), based on the full set of neurocognitive measures as listed in Table 3, excluding UHDRS motor score (Model 2), and based on the full set of neurocognitive measures in addition to UHDRS motor score (Model 3). In each case, the models included our standard set of covariates. For these models, the relative contributions of the motor and neurocognitive assessments were based on the percent of variance explained relative to covariates alone (partial $r^2$and partial F test) and on the total variance explained by the model including covariates (adjusted R^2).

Results

Dunnett's tests revealed that the NEAR group performed more poorly than controls on 40 of the 51 cognitive variables (16 of the 19 tasks), with the largest effect size being −1.17 (see Table 2 for effect size estimates and Table 3 for least squares means and confidence intervals). The only tests that were not sensitive were the 3-disk Tower Task, Serial Response Time Task, and the WASI Matrix Reasoning subtest. The MID group performed more poorly than controls on 28 of the 51 cognitive variables (13 of 19 tasks), with the largest effect size being −0.61. The FAR group showed the least impairment, with significantly worse performance than controls on only one task (the Emotion Recognition Task) with an effect size of −0.26. Importantly, several of the largest effect sizes for neurocognitive tasks (maximum Cohen's d = −1.17 in NEAR group) were of similar magnitude to the effect size for the UHDRS motor score (Cohen's d = −1.10 in NEAR group). Tasks showing the greatest sensitivity (largest effect sizes) were reasonably consistent across the NEAR, MID, and FAR groups and included speeded and self-timed tapping measures and recognition of negative facial emotions. It is worth noting that the prodromal HD groups did not perform significantly *better* than the control group on any of the 51 cognitive variables.

Subtle motor changes are often evident in the HD prodrome, and because these changes are intrinsically related to clinical diagnosis, UHDRS motor scores account for significant variability in estimates of proximity to diagnosis. We investigated whether cognitive variables account for additional variability, independent of UHDRS motor scores. To address this question, we selected a subset of 29 cognitive variables (from the 51 total variables) that showed the largest effect sizes in the NEAR group, and that were either different tasks or conceptually distinct measures from within a given task. We found that, after controlling for the UHDRS motor score (as well as our standard set of covariates), probability of diagnosis in 5 years was significantly associated with 17 of 29 neurocognitive variables (see Table 4). Interestingly, tests of motor/psychomotor function yielded the largest partial R^2s even after accounting for UHDRS motor score. For instance, the largest partial R^2s were observed for the Speeded Tapping task ($F[1,328] = 35.28$, <0.001) and Timed Tapping task ($F[1,328] = 32.66$, <0.001), which accounted for 9.7% and 9.1%, respectively (or 14.5% when examined in combination), of the variance in estimated proximity to diagnosis. Sensory/perceptual tasks also accounted for variance over and above the motor score, with the UPSIT explaining 7.4% and Emotion Recognition explaining 5.5% of the variance in estimated proximity to diagnosis, $F(1,328) = 36.17$, <0.001 and $F(2,327) = 9.50$, <0.001, respectively. Additional findings indicated that the Stroop test (overall, for the three variables) accounted for 3.8% of the variance, $F(3,326) = 4.40$, 0.005, with individual conditions accounting for 3.4% (Color Naming; $F[1,328] = 11.50$, 0.001), 1.9% (Word Reading; $F[1,328] = 6.34$, 0.012), and 2.6% (Interference; $F[1,328] = 8,74$, 0.003).

We also examined the variance accounted for by the neurocognitive battery as a whole. The neurocognitive battery and the UHDRS motor score, together, accounted for 34.4% of the variance in probability of diagnosis within 5 years (*partial* R^2, F[30,300] = 5.24, $p < 0.001$; full model with covariates *adjusted* R^2= 0.42, F[36,300] = 7.75, $p < 0.0001$). When considered in the absence of information from the UHDRS motor examination (i.e., after removing the UHDRS motor score from the equation), the neurocognitive battery accounted for 34.0% of the variance in probability of diagnosis within 5 years (*partial* R^2, F[29,301] = 5.35, $p < 0.0001$; full model including covariates *adjusted* R^2= 0.42, F[35,301] = 7.90, $p < 0.0001$), whereas the motor score alone predicted 11.7% of the variance (*partial* R^2, F[1,329] = 43.55, $p < 0.001$; full model including covariates *adjusted* R^2= 0.29, F[7,329] = 20.38, $p < 0.0001$).

Discussion

This study demonstrates conclusively, that with sufficient sample sizes and a neurocognitive assessment battery designed to maximize sensitivity to HD, neurocognitive signs of the disease are detectable prior to clinical diagnosis. Our results also show that these cognitive changes occur independently of motor signs (detectable using a standard clinical motor examination). To our knowledge, this is the largest and most comprehensive study ever undertaken of neurocognitive signs of HD prior to diagnosis. Our data not only lend support to several prior reports of neurocognitive effects in the HD prodrome (Johnson et al., 2007; Kirkwood et al., 2000; Lawrence et al., 1998; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2004; Snowden, Craufurd, Thompson, & Neary, 2002; Solomon et al., 2007; Tabrizi et al., 2009), but provide a much more comprehensive and detailed picture of the cognitive signs of disease prior to diagnosis.

This study included a large cognitive assessment, with 19 distinct tasks that required about three hours of assessment, yielding a comprehensive picture of cognition in the HD prodrome. In particular, tests assessing psychomotor performance, emotion recognition, and working memory were the most sensitive to prodromal HD neurocognitive effects. Specifically, the speeded finger tapping, self-timed finger tapping, emotion recognition, and N-back working memory tasks had the largest effect sizes near to diagnosis and accounted for the greatest degree of variance in proximity to diagnosis. These findings are generally consistent with our understanding of the early pathological changes in the basal ganglia in the HD prodrome (Vonsattel & DiFiglia, 1998; Vonsattel et al., 1985). It is important to note, however, that recent brain imaging studies suggest that brain changes in prodromal HD are more widespread than previously thought, and occur outside of the striatum. In particular, findings have included reductions in thalamic volumes (Harris et al., 1999; Paulsen et al., 2006b), the parietal, occipital, and cerebellar cortices (Beste et al., 2008), bilateral insula and posterior intraparietal sulcus (Kipps et al., 2005), and cortical thinning in the middle and superior frontal regions, the superior parietal region, occipital cortex, and the temporal cortex (Rosas et al., 2005). Although it may eventually be possible to link the timing of specific neurocognitive and brain changes to developmental stages of HD, the nature of these relationships remains unclear at this point.

Our data reveal graded findings across the pre-diagnosis period in HD, with neurocognitive effects most consistent and largest in magnitude in individuals estimated to be relatively closer to diagnosis (i.e., within 9 years). In addition, significant effects were found for more than half of the neurocognitive variables in the MID group, which comprised individuals estimated to be between 9 and 15 years from diagnosis. However, we detected less evidence of cognitive effects in individuals estimated to be far from diagnosis, with only one neurocognitive test, the emotion recognition test, showing a significant effect. This is consistent with several other reports (Brandt, Shpritz, Codori, Margolis, & Rosenblatt, 2002;

Paulsen et al., 2001; Paulsen et al., 2004; Robins Wahlin, Lundin, & Dear, 2007; Snowden et al., 2002), which indicate that symptoms are more difficult to detect in those far from diagnosis.

These findings suggest that the cognitive signs of HD develop gradually, perhaps over more than a decade in at least some individuals with prodromal HD. Our results do not support the possibility that prodromal HD is associated with cognitive differences throughout the life span (i.e., a trait marker for the HD CAG-expansion), in that we found sparse evidence for cognitive differences from controls in the prodromal HD group that is farthest from diagnosis. It remains possible, however, that additional cognitive changes may also occur in individuals very far from diagnosis but that we have not detected them, either because their effect sizes are below the threshold of detectability in our sample size, or because we failed to target the affected cognitive functions in our test battery. One important implication of this study is that a sample not stratified according to proximity to diagnosis may obscure effects present in those nearer to diagnosis, even if the sample is relatively large, when samples include a large proportion of individuals estimated to be far from diagnosis.

Many previous studies have failed to find differences in neurocognitive performance between prodromal HD and control groups (Brandt et al., 2002; Rosas et al., 2006; van der Hiele et al., 2007; Witjes-Ane et al., 2007) which may be attributable to several of the factors that were controlled for in the current study. These limitations include small sample sizes, prodromal HD samples far from diagnosis of the disease and the type and range of tests administered. Indeed, the most sensitive measures in this study tended not to be clinical neuropsychological measures, having originated instead from more experimental cognitive psychological literature (i.e., self-timed finger tapping, emotion recognition, N-back working memory task).

The size of the PREDICT-HD study, which thereby permitted the use of stratified groups with substantial sample sizes, made it possible to detect effect sizes that were small or medium in magnitude, in contrast to many previous studies which used sample sizes that were only ever powered to reveal large effect sizes. For example, the sample size of our MID group (n = 268) allowed us to detect a difference from controls as small as 0.37 standard deviations with 90% power.

We have shown that cognitive signs are a distinct measurable characteristic of the HD prodrome, and not attributable to or wholly redundant with the development of the measured motor features of the disease. Slowed information processing may contribute to explaining the effects found in this study; however, a conclusive analysis regarding this issue is elusive given that information processing speed is not a unitary construct (Chiaravalloti, Christodoulou, Demaree, & DeLuca, 2003), and there is no clear agreement on what neurocognitive test best indicates slowed information processing (Drew, Starkey, & Isler, 2009). Nonetheless, slowed sensory, perceptual, motor, memory scanning, and/or other aspects of cognitive processing may have contributed to our findings.

Findings of clear cognitive signs in the prodromal period are important because they substantiate the fact that HD must be re-defined to incorporate the neurocognitive aspects of the disease. A depiction of HD that emphasizes the motor signs fails to do justice to the experience of people with prodromal HD, who report experiencing a whole host of symptoms, including not only motor symptoms but also cognitive and psychiatric symptoms. Consistent with this notion, our group recently reported on a subset of the participants studied here that, using cutoffs similar to those applied in research on mild cognitive impairment (MCI), revealed that nearly 40% of prodromal HD participants would be classified as having MCI (see also Duff et al., in press).

It is also worthy of note that our *staging* of the pre-diagnosis period did not take into account motor signs, and instead relied only on the CAG- and age-based estimates of proximity to diagnosis. Given the correlation of cognitive signs and genetically estimated proximity to diagnosis, after adjusting for motor signs in our data, we would anticipate that even if we had excluded individuals with subtle pre-clinical motor signs, evidence of cognitive effects would still have been detected. However, this report does not explicitly address whether cognitive signs appear differently in individuals with and without emerging motor features.

Consistent with previous findings in the literature, our results add substantial evidence that differences in cognition emerge in advance of the clinical diagnosis of HD. An important point, however, is that we and others have demonstrated such effects in *groups*, and as such, these findings do not translate into definite prognoses for *individuals* with the HD CAG expansion. The aim of our study was to identify the very early and often subtle changes that herald the progression toward disease diagnosis, rather than to develop an algorithm for the diagnosis of a cognitive disorder prior to diagnosis of HD. Also, given that more than half of the statistically significant findings in the study relied on tests not typically included in clinical neuropsychological assessment, we would not expect these findings to be replicable on individual patients within the clinical setting if only standard neuropsychological assessment strategies were used. The findings from this study are instructive, however, about how clinical neuropsychological methods might be developed or adapted to enhance sensitivity to cognitive signs that emerge prior to formal HD diagnosis. Importantly, thus far the findings cannot be taken as a clear indication of *clinically significant cognitive impairment* prior to disease diagnosis. The clinical significance of pre-diagnosis cognitive test performance must be evaluated in the context of evidence for its links to functional impairment in daily activities, a matter which we did not address in the current analyses.

General Conclusions

The ability to study neurocognitive markers prospectively, which will be possible in future years of the PREDICT-HD study using actual rather than estimated proximities to diagnosis, will more precisely define the relationship between neurocognitive function and HD diagnosis. Given that neurocognitive signs account for unique variability in estimated proximity to diagnosis beyond age, CAG length and motor signs, it is reasonable to expect that neurocognitive measures will enhance stratification of individuals in the HD prodrome. Importantly, however, for neurocognitive findings to be useful disease markers or to reveal drug effects, the significance of longitudinal changes must be ascertained over the relatively brief intervals used in therapeutic trials. This goal is an essential component of the PREDICT-HD study.

Overall, our findings show that with adequate power and sensitive assessment tools, neurocognitive signs are measurable in groups of individuals with the HD prodrome well in advance of clinical diagnosis of HD. These signs are more marked in individuals who are estimated to be relatively closer to the diagnostic threshold, but may be detectable more than a decade before estimated disease diagnosis.

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References

Andrew SE, Goldberg YP, Kremer B, Telenius H, Theilmann J, Adam S, Hayden MR. The relationship between trinucleotide (CAG) repeat length and clinical-features of Huntington's disease. Nature Genetics 1993;4(4):398–403. doi:10.1038/ng0893-398. [PubMed: 8401589]

Ashby EG, Maddox WT. Human category learning. Annual Review of Psychology 2005;56:149–178. doi:10.1146/annurev.psych.091103.070217.

Benton, AL.; Hamsher, K. Multilingual Aphasia Examination Manual. Iowa City: University of Iowa; 1978.

Benton, AL.; Hamsher, K.; Varney, N.; Spreen, O. Contributions to Neuropsychological Assessment: A Clinical Manual. New York: Oxford University Press; 1983.

Beste C, Saft C, Konrad C, Andrich J, Habbel A, Schepers I, Falkenstein M. Levels of error processing in Huntington's disease: A combined study using event-related potentials and voxel-based morphometry. Human Brain Mapping 2008;29(2):121–130. doi:10.1002/Hbm.20374. [PubMed: 17497629]

Biglan KM, Ross CA, Langbehn DR, Aylward EH, Stout JC, Queller S, Paulsen JS. Motor abnormalities in premanifest persons with Huntington's disease: the PREDICT-HD study. Movement Disorders 2009;24(12):1763–1772. doi:10.1002/mds.22601. [PubMed: 19562761]

Brandt, J.; Benedict, RHB. Hopkins Verbal Learning Test-Revised. Lutz: Psychological Assessment Resources; 2001.

Brandt J, Shpritz B, Codori AM, Margolis R, Rosenblatt A. Neuropsychological manifestations of the genetic mutation for Huntington's disease in presymptomatic individuals. Journal of the International Neuropsychological Society 2002;8(7):918–924. doi:10.10170S1355617702870060. [PubMed: 12405543]

Chiaravalloti ND, Christodoulou C, Demaree HA, DeLuca J. Differentiating simple versus complex processing speed: influence on new learning and memory performance. Journal of Clinical and Experimental Neuropsychology 2003;25(4):489–501. doi:10.1076/jcen.25.4.489.13878. [PubMed: 12911103]

Cohen, J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, N.J.: L. Erlbaum Associates; 1988.

Del Ser T, Gonzalez-Montalvo JI, Martinez-Espinosa S, Delgado-Villapalos C, Bermejo F. Estimation of premorbid intelligence in Spanish people with the Word Accentuation Test and its application to the diagnosis of dementia. Brain and Cognition 1997;33(3):343–356. doi:10.1006/brcg.1997.0877. [PubMed: 9126399]

Doty RL, Shaman P, Kimmelman CP, Dann MS. University of Pennsylvania Smell Identification Test: A rapid quantitative olfactory function test for the clinic. Laryngoscope 1984;94:176–178. doi:10.1288/00005537-198402000-00004. [PubMed: 6694486]

Drew MA, Starkey NJ, Isler RB. Examining the link between information processing speed and executive functioning in multiple sclerosis. Archives of Clinical Neuropsychology 2009;24:47–58. doi:10.1093/arclin/acp007. [PubMed: 19395356]

Duff K, Paulsen JS, Mills J, Beglinger LJ, Moser DJ, Smith MM. … the PREDICTHD Investigators and Coordinators of the Huntington Study Group. Mild cognitive impairment in pre-diagnosed Huntington disease. Neurology. (in press).

Ekman P, Friesen WV. Measuring facial movement. Environmental Psychology and Nonverbal Behavior 1976;1:56–75.

Georgiou N, Bradshaw JL, Phillips JG, Chiu E, Bradshaw JA. Reliance upon advance information and movement sequencing in Huntington's Disease. Movement Disorders 1995;10:472–481. doi:10.1002/mds.870100412. [PubMed: 7565829]

Grober E, Sliwinski M. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. Journal of Clinical and Experimental Neuropsychology 1991;13(6):933–949. doi:10.1080/01688639108405109. [PubMed: 1779032]

Gusella JF, MacDonald ME, Ambrose CM, Duyao MP. Molecular genetics of Huntington's disease. Archives of Neurology 1993;50(11):1157–1163. doi:10.1001/archneur.50.11.1157. [PubMed: 8215974]

Harris GJ, Codori AM, Lewis RF, Schmidt E, Bedi A, Brandt J. Reduced basal ganglia blood flow and volume in pre-symptomatic, gene-tested persons at-risk for Huntington's disease. Brain 1999;122:1667–1678. Retrieved from http://brain.oxfordjournals.org/. [PubMed: 10468506]

Hinton SC, Paulsen JS, Hoffmann RG, Reynolds NC, Zimbelman JL, Rao SM. Motor timing variability increases in preclinical Huntington's disease patients as estimated onset of motor symptoms approaches. Journal of the International Neuropsychological Society 2007;13(3):539–543. doi:10.1017/S1355617707070671. [PubMed: 17445303]

Johnson SA, Stout JC, Solomon AC, Langbehn DR, Aylward EH, Cruce CB, Paulsen JS. Beyond disgust: Impaired recognition of negative emotions prior to diagnosis in Huntington's disease. Brain 2007;130(7):1732–1744. doi:10.1093/brain/awm107. [PubMed: 17584778]

Kipps CM, Duggins AJ, Mahant N, Gomes L, Ashburner J, McCusker EA. Progression of structural neuropathology in preclinical Huntington's disease: A tensor based morphometry study. Journal of Neurology, Neurosurgery & Psychiatry 2005;76(5):650–655. doi:10.1136/jnnp.2004.047993.

Kirchner WK. Age-differences in short-term retention of rapidly changing information. Journal of Experimental Psychology 1958;55(4):352–358. doi:10.1037/h0043688. [PubMed: 13539317]

Kirkwood SC, Siemers E, Hodes ME, Conneally PM, Christian JC, Foroud T. Subtle changes among presymptomatic carriers of the Huntington's disease gene. Journal of Neurology, Neurosurgery & Psychiatry 2000;69(6):773–779. doi:10.1136/jnnp.69.6.773.

Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. Clinical Genetics 2004;65(4):267–277. doi:10.1111/j.1399-0004.2004.00241.x. [PubMed: 15025718]

Langbehn DR, Hayden MR, Paulsen JS. CAG-repeat length and the age of onset in Huntington disease (HD): A review and validation study of statistical approaches. American Journal of Medical Genetics Part B Neuropsychiatric Genetics 2009;153B:397–408. doi:10.1002/ajmg.b.30992.

Lawrence AD, Hodges JR, Rosser AE, Kershaw A, ffrench-Constant C, Rubinsztein DC, Sahakian BJ. Evidence for specific cognitive deficits in preclinical Huntington's disease. Brain 1998;121(Pt 7):1329–1341. Retrieved from http://brain.oxfordjournals.org/. [PubMed: 9679784]

Lemiere J, Decruyenaere M, Evers-Kiebooms G, Vandenbussche E, Dom R. Cognitive changes in patients with Huntington's disease (HD) and asymptomatic carriers of the HD mutation--a longitudinal follow-up study. Journal of Neurology 2004;251(8):935–942. doi:10.1007/s00415-004-0461-9. [PubMed: 15316797]

Nelson, HE.; Willison, J. The National Adult Reading Test (NART): Test manual. 2nd ed. Windsor, UK: NFER Nelson; 1991.

Paulsen JS, Hayden MR, Stout JC, Langbehn DR, Aylward EH, Ross CA, Penziner E. Preparing for preventive clinical trials: the Predict-HD study. Archives of Neurology 2006a;63(6):883–890. doi:10.1001/archneur.63.6.883. [PubMed: 16769871]

Paulsen JS, Langbehn DR, Stout JC, Aylward E, Ross CA, Nance M, Hayden M. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. Journal of Neurology, Neurosurgery & Psychiatry 2008;79(8):874–880. doi:10.1136/jnnp.2007.128728.

Paulsen JS, Magnotta VA, Mikos AE, Paulson HL, Penziner E, Andreasen NC, Nopoulos PC. Brain structure in preclinical Huntington's disease. Biological Psychiatry 2006b;59(1):57–63. doi:10.1016/j.biopsych.2005.06.003. [PubMed: 16112655]

Paulsen JS, Zhao H, Stout JC, Brinkman RR, Guttman M, Ross CA, Shoulson I. Clinical markers of early disease in persons near onset of Huntington's disease. Neurology 2001;57(4):658–662. Retrieved from http://www.neurology.org/. [PubMed: 11524475]

Paulsen JS, Zimbelman JL, Hinton SC, Langbehn DR, Leveroni CL, Benjamin ML, Rao SM. fMRI biomarker of early neuronal dysfunction in presymptomatic Huntington's Disease. AJNR American Journal of Neuroradiology 2004;25(10):1715–1721. [PubMed: 15569736]

Pirogovsky E, Gilbert PE, Jacobson M, Peavy G, Wetter S, Goldstein J, Murphy C. Impairments in source memory for olfactory and visual stimuli in preclinical and clinical stages of Huntington's disease. Journal of Clinical and Experimental Neuropsychology 2007;29(4):395–404. doi:10.1080/13803390600726829. [PubMed: 17497563]

Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. Perceptual and Motor Skills 1958;8:271–276.

Robins Wahlin TB, Lundin A, Dear K. Early cognitive deficits in Swedish gene carriers of Huntington's disease. Neuropsychology 2007;21(1):31–44. doi:10.1037/0894-4105.21.1.31. [PubMed: 17201528]

Rosas HD, Hevelone ND, Zaleta AK, Greve DN, Salat DH, Fischl B. Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. Neurology 2005;65(5):745–747. doi:10.1212/01.wnl.0000174432.87383.87. [PubMed: 16157910]

Rosas HD, Tuch DS, Hevelone ND, Zaleta AK, Vangel M, Hersch SM, Salat DH. Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. Movement Disorders 2006;21(9):1317–1325. doi:10.1002/mds.20979. [PubMed: 16755582]

Saint-Cyr JA, Taylor AE, Lang AE. Procedural learning and neostriatal dysfunction in man. Brain 1988;111(4):941–959. Retrieved from http://brain.oxfordjournals.org/. [PubMed: 2969762]

Schmidt, K.; Metzler, P. Wortschatztest (WST). Weinheim: Beltz Verlag; 1992.

Schwartz M, Saffran E. The American NART: Replication and extension of the British findings on the persistence of word pronunciation skills in patients with dementia. Unpublished manuscript. 1987

Smith, A. Symbol Digits Modalities Test. Los Angeles: Western Psychological Services; 1991.

Snowden JS, Craufurd D, Thompson J, Neary D. Psychomotor, executive, and memory function in preclinical Huntington's disease. Journal of Clinical and Experimental Neuropsychology 2002;24(2):133–145. doi:10.1076/jcen.24.2.133.998. [PubMed: 11992196]

Solomon AC, Stout JC, Johnson SA, Langbehn DR, Aylward E, Brandt J, Paulsen JS. Verbal episodic memory declines prior to diagnosis in Huntington's disease. Neuropsychologia 2007;45(8):1767–1776. doi:10.1016/j.neuropsychologia.2006.12.015. [PubMed: 17303196]

Spencer-Smith J, Wild H, Innes-Ker AH, Townsend J, Duffy C, Edwards C, Paik JW. Making faces: Creating three-dimensional parameterized models of facial expression. Behavior Research Methods, Instruments, and Computers 2001;33(2):115–123. Retrieved from http://brm.psychonomic-journals.org/.

Stout JC, Weaver M, Solomon AC, Queller S, Hui S, Johnson S, Foroud T. Are cognitive changes progressive in prediagnostic HD? Cognitive and Behavioral Neurology 2007;20(4):212–218. doi:10.1097/WNN.0b013e31815cfef8. [PubMed: 18091069]

Stroop JR. Studies of interference in serial verbal reactions. Journal of Experimental Psychology: General 1935;18(6):643–662. doi:10.1037/0096-3445.121.1.15.

Tabrizi SJ, Langbehn DR, Leavitt BR, Roos RA, Durr A, Craufurd D, Stout JC. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurology 2009;8(9):791–801. doi:10.1016/S1474-4422(09)70170-X. [PubMed: 19646924]

The Huntington Study Group. Unified Huntington's disease rating scale: Reliability and consistency. Movement Disorders 1996;11(2):136–142. doi:10.1002/mds.870110204. [PubMed: 8684382]

van der Hiele K, Jurgens CK, Vein AA, Reijntjes RH, Witjes-Ane MN, Roos RA, Middelkoop HA. Memory activation reveals abnormal EEG in preclinical Huntington's disease. Movement Disorders 2007;22(5):690–695. doi:10.1002/mds.21390. [PubMed: 17266047]

Vonsattel JP, DiFiglia M. Huntington disease. Journal of Neuropathology and Experimental Neurology 1998;57(5):369–384. doi:10.1002/mds.21390. [PubMed: 9596408]

Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP. Neuropathological classification of Huntingtons-disease. Journal of Neuropathology and Experimental Neurology 1985;44(6):559–577. [PubMed: 2932539]

Warner JP, Barron LH, Brock DJH. A new polymerase chain-reaction (PCR) assay for the trinucleotide repeat that is unstable and expanded on Huntingtons-disease chromosomes. Molecular and Cellular Probes 1993;7(3):235–239. doi:10.1006/mcpr.1993.1034. [PubMed: 8366869]

Wechsler, D. Wechsler Adult Intelligence Scale. 3 ed. San Antonio: The Psychological Corporation; 1997.

Wechsler, D. Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: The Psychological Corporation; 1999.

Willingham DB, Nissen MJ, Bullemer P. On the development of procedural knowledge. Journal of Experimental Psychology. Learning, Memory, and Cognition 1989;15(6):1047–1060. doi: 10.1037/0278-7393.15.6.1047.

Witjes-Ane MN, Mertens B, van Vugt JP, Bachoud-Levi AC, van Ommen GJ, Roos RA. Longitudinal evaluation of "presymptomatic" carriers of Huntington's disease. The Journal of Neuropsychiatry and Clinical Neurosciences 2007;19(3):310–317. doi:10.1176/appi.neuropsych.19.3.310. [PubMed: 17827417]

Appendix

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(September 2002–April 2008)

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Table 1

Participant Characterization

Characteristic	Near	Mid	Far	Controls	*p*-value
Visit 2 sample sizes	202	268	268	168	
Gender	118F, 84M	166F, 102M	181F, 87M	116F, 52M	0.09
Age (years)	44.5 ± 9.8	42.4 ± 9.9	37.0 ± 8.0	43.9 ± 11.1	<0.0001
Education (years)	14.1 ± 2.7	14.3 ± 2.7	14.5 ± 2.5	14.7 ± 2.7	0.13
Estimated IQ	111.8 ± 8.2	112.0 ± 8.2	112.3 ± 7.2	112.9 ± 7.4	0.49
CAG repeat length	44.3 ± 2.9	42.6 ± 2.1	41.1 ± 1.6	19.8 ± 3.5	<0.0001
UHDRS Motor score	7.4 ± 6.5	4.8 ± 4.8	3.5 ± 3.8	2.5 ± 3.1	<0.0001

Note. F = female; M = male; UHDRS = Unified Huntington Disease Rating Scale; Values shown are means ± standard deviations except gender and sample sizes which are counts. Scheffé tests indicate the following post-hoc findings: 1) For age, the Far group was younger than all other groups, and there were no other pairwise differences; 2) For CAG lengths, all pairwise comparisons are significant; 3) For UHDRS Motor Scores, all pairwise comparisons are significantly different except Controls compared to the Far group.

Table 2

Effect Sizes (Cohen's d) in the Near, Mid, and Far Groups

	Effect Size		
Task and Variable	**Near**	**Mid**	**Far**
Benton Facial Recognition Test			
Total correct	−0.42[c,d]	−0.39[c]	−0.13
Category Learning Task: Rule-Based			
Max % correct in a block	−0.12	−0.11	−0.07
% blocks completed	−0.50[b,d]	−0.32	−0.20
Category Learning Task: Non-Verbalizable			
Max % correct in a block	−0.45[b,d]	−0.25	−0.21
% blocks completed	−0.11	−0.09	−0.02
Dynamic Emotion Recognition Task			
# correct (negative emotions only)	−0.84[c,d]	−0.41[c]	−0.05
Emotion Recognition Task			
# correct (negative emotions only)	−1.10[c,d]	−0.61[c]	−0.26[a]
Hopkins Verbal Learning Test-Revised			
Total learning (Trials 1–3)	−0.95[c,d]	−0.48[c]	−0.18
Delayed recall	−0.75[c]	−0.34[b]	−0.08
Delayed recognition discriminability	−0.77[c]	−0.41[c]	−0.22
N-Back Task: 1-Back Discriminability Indexes			
Foils	−0.57[c,d]	−0.27	−0.14
Lures	−0.44[b]	−0.20	0.02
N-Back Task: 2-Back Discriminability Indexes			
Foils	−0.56[c]	−0.13	−0.07
Lures	−0.64[c,d]	−0.18	−0.16
Phonemic Verbal Fluency			
Total correct	−0.51[c,d]	−0.29[a]	−0.09
Self-Timed Finger Tapping Task[f]			
Dominant index finger: Mean of ITIs	0.09	0.07	0.09
Dominant index finger: SD of ITIs	−1.06[c]	−0.50[c]	−0.10
Alternating thumbs: Mean of ITIs	0.09	0.12	0.07
Alternating thumbs: SD of ITIs	−1.17[c,d]	−0.61[c]	−0.24
Cued Movement Sequence Task: Low Cue Level[g]			
Mean	−0.69[c]	−0.23	−0.02
SD	−0.72[c,d]	−0.25[a]	0.04
Cued Movement Sequence Task: Medium Cue Level[g]			
Mean	−0.41[c]	−0.12	0.16

	Effect Size		
Task and Variable	**Near**	**Mid**	**Far**
SD	−0.775[c,d]	−0.181	0.075
Cued Movement Sequence Task: High Cue Level[g]			
Mean	−0.21	−0.18	0.03
SD	−0.48[c,d]	−0.26[a]	−0.05
Serial Response Time Task: Learning[f]			
Learning effect (B5-B4)	0.05[d]	−0.14	0.02
Interference effect (B6-B4)	0.02	0.01	−0.11
Simple Response Time Task[f]			
Mean	−0.77[c,d]	−0.40[c]	−0.10
SD	−0.59[c]	−0.29[a]	0.04
2-Choice Response Time Task[f]			
Mean	−0.80[c,d]	−0.43[c]	0.02
SD	−0.39[b]	−0.33[b]	−0.03
Speeded Tapping Task[f]			
Dominant index finger: Mean of ITIs	−0.77[c]	−0.38[c]	−0.14
Dominant index finger: SD of ITIs	−0.74[c]	−0.43[c]	−0.10
Nondominant index finger: Mean of ITIs	−1.14[c,d]	−0.39[c]	−0.10
Nondominant index finger: SD of ITIs	−0.82[c]	−0.61[c]	−0.19
Alternating thumbs: Mean of ITIs	−0.75[c]	−0.35[b]	−0.09
Alternating thumbs: SD of ITIs	−0.94[c]	−0.55[c]	−0.12
Stroop: Color			
Total correct	−0.75[c,d]	−0.39[c]	−0.11
Stroop: Word			
Total correct	−0.66[c,d]	−0.27[a]	0.03
Stroop: Interference			
Total correct	−0.62[c,d]	−0.32[b]	0.03
Symbol Digit Modalities Test			
Total correct	−0.96[c,d]	−0.49[c]	−0.05
Tower 3 Task			
Mean # moves (4 trials)	−0.24[d]	−0.08	0.11
Learning (T4-T1)	0.02	−0.03	−0.02
Tower 4 Task			
Mean # moves (4 trials)	−0.36[b,d]	−0.11	−0.15
Learning (T4-T1)	−0.02	−0.09	−0.07
Trail Making Test A			
Seconds to completion	−0.60[c,d]	−0.22	0.00

	Effect Size		
Task and Variable	**Near**	**Mid**	**Far**
Trail Making Test B			
Seconds to completion	$-0.80^{c,d}$	-0.33^{b}	-0.10
University of Pennsylvania Smell Identification Test			
Total correct	$-1.04^{c,d}$	-0.36^{b}	-0.12
WAIS-III Letter-Number Sequencing Subtest			
Total Score	$-0.51^{c,d}$	-0.43^{c}	-0.19
WASI Matrix[e] Reasoning Subtest			
Raw score	-0.24^{d}	-0.08	0.01
WASI Vocabulary[e] Subtest			
Raw score	$-0.47^{b,d}$	-0.180	-0.13
Unified Huntington Disease Rating Scale			
Motor score	-1.10^{c}	-0.50^{c}	-0.26^{a}

Note.

[a] $p < 0.05$,

[b] $p < 0.01$,

[c] $p < 0.001$ for Dunnett's test of mean differences in performance for each prodromal HD group compared to controls;

[d] designates the 29 variables that are included in models assessing neurocognitive plus motor;

[e] denotes tasks first administered at visit 2;

[f] denotes effect sizes for means and standard deviations of response times;

[g] denotes effect sizes for means and standard deviations of response times for accurately completed trials measured in ms. M = mean; S.D. = standard deviation; ITI = intertap interval measured in ms; B = block; WAIS-III = Wechsler Adult Intelligence Scale – Third Edition; WASI = Wechsler Abbreviated Scale of Intelligence.

Table 3

Least Squares Means and 95% Confidence Intervals

	GROUP			
Task and Variable	**Near**	**Mid**	**Far**	**Control**
Benton Facial Recognition Test				
Total correct				
M	22.2	22.2	22.8	23.0
95% CI lower	21.9	22.0	22.5	22.7
95% CI upper	22.5	22.5	23.0	23.3
Category Learning Task: Rule-Based				
Max % correct in a block				
M	95.9	96.0	96.2	96.5
95% CI lower	95.1	95.2	95.4	95.4
95% CI upper	96.7	96.7	97.0	97.7
% blocks completed				
M	33.1	30.2	28.2	25
95% CI lower	30.3	27.6	25.6	21.2
95% CI upper	35.8	32.8	30.9	28.9
Category Learning Task: Non-Verbalizable				
Max % correct in a block				
M	76.9	78.4	78.7	80.3
95% CI lower	75.5	77.2	77.4	78.5
95% CI upper	78.2	79.7	80.0	82.1
% blocks completed				
M	72.6	72.0	70.1	69.6
95% CI lower	67.8	67.5	65.5	63.0
95% CI upper	77.4	76.4	74.8	76.1
Dynamic Emotion Recognition Task				
# correct (negative emotions only)				
M	10.5	12.6	14.3	14.6
95% CI lower	9.7	12.0	13.7	13.8
95% CI upper	11.2	13.2	15.0	15.3
Emotion Recognition Task				
# correct (negative emotions only)				
M	22.6	25.1	26.9	28.2
95% CI lower	21.8	24.5	26.3	27.4
95% CI upper	23.4	25.8	27.5	29.0
Hopkins Verbal Learning Test-Revised				
Total learning (Trials 1–3)				
M	23.9	26.0	27.3	28.1
95% CI lower	23.2	25.4	26.8	27.4
95% CI upper	24.6	26.5	27.9	28.8

	GROUP			
Task and Variable	**Near**	**Mid**	**Far**	**Control**
Delayed recall				
M	8.5	9.4	9.9	10.1
95% CI lower	8.2	9.1	9.6	9.7
95% CI upper	8.8	9.6	10.2	10.4
Delayed recognition discriminability				
M	9.9	10.5	10.7	11.0
95% CI lower	9.7	10.3	10.5	10.8
95% CI upper	10.2	10.6	10.9	11.2
N-Back Task: 1-Back Discriminability Indexes[a]				
Foils				
M	.97	.98	.98	.98
95% CI lower	.97	.98	.98	.98
95% CI upper	.98	.98	.98	.99
Lures				
M	.95	.96	.97	.97
95% CI lower	.94	.95	.96	.96
95% CI upper	.96	.96	.97	.97
N-Back Task: 2-Back Discriminability Indexes[a]				
Foils				
M	.93	.94	.94	.95
95% CI lower	.92	.94	.94	.94
95% CI upper	.93	.95	.95	.96
Lures				
M	.79	.84	.84	.86
95% CI lower	.77	.82	.82	.84
95% CI upper	.81	.85	.86	.88
Phonemic Verbal Fluency				
Total correct				
M	37.7	40.1	42.2	43.1
95% CI lower	36.2	38.8	40.9	41.4
95% CI upper	39.3	41.3	43.5	44.7
Self-Timed Finger Tapping Task[b]				
Dominant index finger: Mean of ITIs				
M	515	515	515	518
95% CI lower	511	512	511	513
95% CI upper	519	519	519	522
Dominant index finger: SD of ITIs				
M	44	36	32	31
95% CI lower	41	35	31	30
95% CI upper	47	37	33	32

	GROUP			
Task and Variable	**Near**	**Mid**	**Far**	**Control**
Alternating thumbs: Mean of ITIs				
M	508	506	508	511
95% CI lower	502	502	503	505
95% CI upper	514	511	513	517
Alternating thumbs: SD of ITIs				
M	53	43	38	36
95% CI lower	50	41	37	34
95% CI upper	56	45	40	37
Cued Movement Sequence Task: Low Cue Level[c]				
Mean				
M	611	579	564	563
95% CI lower	601	570	555	552
95% CI upper	622	587	573	574
SD				
M	83	71	65	66
95% CI lower	79	68	63	63
95% CI upper	88	74	67	69
Cued Movement Sequence : Medium Cue Level[c]				
Mean				
M	537	516	496	508
95% CI lower	526	507	487	496
95% CI upper	548	525	506	519
SD				
M	91	74	69	70
95% CI lower	86	72	66	67
95% CI upper	97	77	72	74
Cued movement Sequence: High Cue Level[c]				
Mean				
M	353	350	333	335
95% CI lower	340	340	322	323
95% CI upper	366	361	343	348
SD				
M	89	79	72	70
95% CI lower	82	75	68	66
95% CI upper	98	85	76	76
Serial Response Time Task: Learning[b]				
Learning effect (B5-B4)				
M	99	88	97	96
95% CI lower	90	81	89	87
95% CI upper	107	95	104	105

	GROUP			
Task and Variable	**Near**	**Mid**	**Far**	**Control**
Interference effect (B6-B4)				
M	12	12	17	13
95% CI lower	6	7	12	7
95% CI upper	18	17	23	19
Simple Response Time Task				
Mean				
M	256	230	209	202
95% CI lower	245	221	200	191
95% CI upper	267	238	217	213
SD				
M	57	46	38	39
95% CI lower	51	43	36	36
95% CI upper	64	50	41	43
2-Choice Response Time Task[b]				
Mean				
M	295	268	236	238
95% CI lower	284	260	227	226
95% CI upper	306	277	245	249
SD				
M	76	73	59	58
95% CI lower	68	67	55	53
95% CI upper	87	80	64	64
Speeded Tapping Task[b]				
Dominant index finger: Mean of ITIs				
M	234	218	208	203
95% CI lower	228	213	203	196
95% CI upper	241	223	214	209
Dominant index finger: SD of ITIs				
M	57	47	39	38
95% CI lower	52	44	37	35
95% CI upper	63	50	42	41
Nondominant index finger: Mean of ITIs				
M	280	245	231	227
95% CI lower	273	239	225	220
95% CI upper	287	251	237	234
Nondominant index finger: SD of ITIs				
M	67	60	50	46
95% CI lower	62	57	47	43
95% CI upper	74	64	52	49
Alternating thumbs: Mean of ITIs				

	GROUP			
Task and Variable	**Near**	**Mid**	**Far**	**Control**
M	202	180	166	162
95% CI lower	194	174	159	153
95% CI upper	210	187	173	170
Alternating thumbs: SD of ITIs				
M	64	55	47	45
95% CI lower	60	52	45	43
95% CI upper	69	57	49	47
Stroop: Color				
Total correct				
M	72.1	76.8	80.4	81.8
95% CI lower	70.2	75.3	78.8	79.8
95% CI upper	74.0	78.4	82.1	83.8
Stroop: Word				
Total correct				
M	92.5	98.5	103.1	102.6
95% CI lower	90.3	96.7	101.1	100.2
95% CI upper	94.8	100.4	105.0	105.0
Stroop: Color				
Total correct				
M	41.3	43.9	47.0	46.7
95% CI lower	40	42.8	45.9	45.3
95% CI upper	42.6	44.9	48.1	48.1
Symbol Digit Modalities Test				
Total correct				
M	44.7	49.4	53.7	54.2
95% CI lower	43.3	48.2	52.5	52.7
95% CI upper	46.2	50.6	55.0	55.8
Tower 3 Task				
Mean # moves (4 trials)				
M	9.5	9.1	8.6	8.9
95% CI lower	9.1	8.8	8.3	8.5
95% CI upper	9.8	9.4	8.9	9.3
Learning (T4-T1)				
M	−1.7	−1.5	−1.6	−1.6
95% CI lower	−2.4	−2.0	−2.1	−2.3
95% CI upper	−1.1	−1.0	−1.0	−0.9
Tower 4 Task				
Mean # moves (4 trials)				
M	27.8	26.2	26.4	25.4
95% CI lower	26.8	25.4	25.6	24.4
95% CI upper	28.7	26.9	27.2	26.4

	GROUP			
Task and Variable	**Near**	**Mid**	**Far**	**Control**
Learning (T4-T1)				
M	−4.0	−3.2	−3.5	−4.3
95% CI lower	−5.8	−4.6	−5.0	−6.1
95% CI upper	−2.2	−1.7	−2.0	−2.4
Trail Making Test A				
Seconds to completion				
M	31.4	27.5	25.3	25.3
95% CI lower	29.9	26.3	24.0	23.7
95% CI upper	32.9	28.8	26.6	26.8
Trail Making Test B				
Seconds to completion				
M	81.7	67.6	60.8	57.8
95% CI lower	77.2	63.9	57.0	53.1
95% CI upper	86.2	71.3	64.6	62.5
University of Pennsylvania Smell Identification Test				
Total correct				
M	30.7	33.2	34.1	34.5
95% CI lower	30.1	32.8	33.6	34.0
95% CI upper	31.2	33.7	34.6	35.1
WAIS-III Letter-Number Sequencing Subtest				
Total Score				
M	11.2	11.4	12.0	12.5
95% CI lower	10.8	11.1	11.7	12.1
95% CI upper	11.6	11.7	12.3	12.9
WASI Matrix Reasoning Subtest				
Raw score				
M	25.3	26.0	26.4	26.4
95% CI lower	24.6	25.4	25.7	25.4
95% CI upper	26	26.7	27.1	27.3
WASI Vocabulary Subtest				
Raw score				
M	61.2	62.9	63.1	63.9
95% CI lower	60.3	62	62.3	62.7
95% CI upper	62.1	63.7	64.0	65.1
Unified Huntington Disease Rating Scale				
Motor score				
M	7.5	4.6	3.5	2.3
95% CI lower	6.8	4.1	2.9	1.6
95% CI upper	8.2	5.2	4.1	3.0

Note.

[a] denotes the ability to discriminate either lures or foils from matches, whereby 1.0 would indicate perfect discrimination and 0.5 would represent chance;

[b] denotes response times measured in ms;

[c] denotes mean response times for accurately completed trials measured in ms. M = mean; SD = standard deviation; CI = confidence interval; ITI = intertap interval; B = block; WAIS-III = Wechsler Adult Intelligence Scale –Third Edition; WASI = Wechsler Abbreviated Scale of Intelligence.

Table 4

% Variance in Probability of Onset in 5 Years Explained After Controlling for UHDRS Motor Score

Task – Conceptually distinct task component	% Variance Explained Above UHDRS Motor Score (Adj R-sq = 0.29)
Benton Facial Recognition Test: Total correct	0.8
Category Learning Tasks	(0.8)
Rule-based: % blocks completed	0.8
Non-verbalizable: Max % correct in a block	0.6
Emotion Tasks	(5.5)[b]
Emotion Recognition: # correct (negative)	1.3[a]
Dynamic Emotion Recognition: # correct (negative)	5.4[b]
HVLT-R – Total learning (Trials 1–3)	2.9[b]
N-Back Tasks	(2.0)[a]
1-back discriminability: Foils	1.0
2-back discriminability: Foils	1.3[a]
Phonemic Verbal Fluency: Total correct	0.4
Cued Movement Sequence Task	(8.8)[b]
Low cue level: SD	5.1[b]
Medium cue level: SD	8.3[b]
High cue level: SD	1.7[a]
Serial Response Time Task – Learning effect (B5-B4)	0.3
Simple and 2-Choice Response Time Task	(2.9)[b]
Simple Response Time: Mean	0.9
2-choice Response Time: Mean	2.7[b]
Stroop	(3.8)[b]
Stroop Color: Total correct	3.4[b]
Stroop Word: Total correct	1.9[a]
Stroop Interference: Total correct	2.6[b]
Symbol Digit Modalities Test: Total correct	4.3[b]
Tapping	(14.5)[b]
Speeded Tapping Nondominant Finger: Mean of ITIs	9.7[b]
Self Timed Tapping Alternating Thumbs: SD of ITIs	9.1[b]
Tower Tasks	(0.6)
Tower 3: Mean # moves (4 trials)	0.6
Tower 4: Mean # moves (4 trials)	0.2
Trail Making Tests	(3.4)[b]
Trails A: Seconds to completion	3.1[b]
Trails B: Seconds to completion	1.4[a]

Task – Conceptually distinct task component	% Variance Explained Above UHDRS Motor Score (Adj R-sq = 0.29)
UPSIT: Total correct	7.4[b]
WAIS-III Letter-Number	0.2
WASI – Matrix: Raw score	0.2
WASI – Vocab: Raw score	1.0

Note.

[a] indicates $p < 0.05$;

[b] indicates $p < 0.01$; Parentheses are used for linear regressions that involved multiple variables typically considered in conjunction with each other (e.g. Trials A and B), or a set of variables assessing highly related functions (e.g, Speeded and Self-Timed Tapping). SD = standard deviation; HVLT-R = Hopkins Verbal Learning Test – Revised; ITI = intertap interval; B = block; UPSIT = University of Pennsylvania Smell Identification Test; WAIS-III = Wechsler Adult Intelligence Scale – Third Edition; WASI = Wechsler Abbreviated Scale of Intelligence