Intra-individual Variability in Prodromal Huntington Disease and Its Relationship to Genetic Burden

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Abstract

The current study sought to examine the utility of intra-individual variability (IIV) in distinguishing participants with prodromal Huntington disease (HD) from nongene-expanded controls. IIV across 15 neuropsychological tasks and within-task IIV using a self-paced timing task were compared as a single measure of processing speed (Symbol Digit Modalities Test [SDMT]) in 693 gene-expanded and 191 nongene-expanded participants from the PREDICT-HD study. After adjusting for depressive symptoms and motor functioning, individuals estimated to be closest to HD diagnosis displayed higher levels of across- and within-task variability when compared to controls and those prodromal HD participants far from disease onset ($F_{ICV(3,877)} = 11.25$; $p < .0001$; $F_{PacedTiming(3,877)} = 22.89$; $p < .0001$). When prodromal HD participants closest to HD diagnosis were compared to controls, Cohen's *d* effect sizes were larger in magnitude for the within-task variability measure, paced timing (–1.01), and the SDMT (–0.79) and paced tapping coefficient of variation (CV) (–0.79) compared to the measures of across-task variability [CV (0.55); intra-individual standard deviation (0.26)]. Across-task variability may be a sensitive marker of cognitive decline in individuals with prodromal HD approaching disease onset. However, individual neuropsychological tasks, including a measure of within-task variability, produced larger effect sizes than an index of across-task IIV in this sample. (*JINS*, 2015, *21*, 8–21)

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INTRODUCTION

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder caused by expansion of the trinucleotide repeat cytosine-adenine-guanine (CAG) in the huntingtin (*HTT*) gene (MacDonald et al., 1993). Individuals with the CAG expansion can be identified through presymptomatic genetic testing, and there is an inverse relationship between the number of CAG repeats and HD age of onset (Lee et al., 2012). Huntington disease has been associated with changes in multiple brain regions, particularly fronto-subcortical circuits (Aylward et al., 2012; Paulsen et al., 2010a), and involves a triad of clinical features, including psychiatric disturbances,

impaired motor functioning, and cognitive deficits. Cognitive changes in HD include deficits in attention, working memory, executive functions, processing and motor speed, visuomotor integration (Brandt & Butters, 1986; Zakzanis, 1998; Paulsen, Smith, & Long, 2013), memory acquistion and retrieval, emotion processing, and manual dexterity (Zakzanis, 1998). Motor, cognitive, and psychiatric abnormalities have been associated with functional decline in prodromal HD (Beglinger et al., 2010).

A formal diagnosis of HD is made in the presence of unequivocal motor signs in an individual with a CAG expansion or an individual coming from a family with known HD. However, symptoms may be present before formal diagnosis. Individuals with expanded CAG repeats who have not met motor criteria for diagnosis are considered to be in the prodromal stages of HD (Paulsen et al., 2010b). The nature of cognitive deficits in prodromal HD is similar to the deficits

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noted after diagnosis, though the degree of prodromal impairment is more modest (Johnson et al., 2007; Kirkwood et al., 1999, Paulsen et al., 2001, 2008, 2013; Pirogovsky et al., 2007; Stout et al., 2012). Nearly 40% of 575 individuals with prodromal HD in the PREDICT-HD study met criteria for mild cognitive impairment (MCI) in at least one cognitive domain, with higher rates found in individuals estimated to be closer to motor diagnosis (Duff et al., 2010). Paulsen and colleagues (2008) reported cognitive deficits are difficult to detect in earlier stages of prodromal HD, and cognitive impairment in those estimated to be 15–20 years from diagnosis is generally minimal (Paulsen et al., 2013). For example, Stout and colleagues (2011) reported individuals who were fewer than nine years from estimated diagnosis showed broad cognitive impairment on an extensive battery, whereas impairment in persons estimated to be 9–15 years from diagnosis was observed in approximately half of the variables, and individuals estimated to be greater than 15 years from diagnosis demonstrated impairments only in emotion recognition. Novel metrics and measures of cognition that are sensitive to the earliest neuropathological changes in individuals with prodromal HD may prove to be useful markers of disease progression for clinical trials. Clinically, novel metrics and measures of cognition may provide additional information about the nature of the cognitive deficits in individuals with prodromal HD and how those deficits impact daily functioning, ideally leading to more effective interventions.

One measurement that might be relevant to early detection of cognitive deficits in HD is intra-individual variability (IIV), an indicator of short-term within-person fluctuations in cognition hypothesized to be an early marker of brain pathology (MacDonald, Backman, & Li, 2009; Stuss, Murphy, Binns, & Alexander, 2003). IIV is hypothesized to reflect the efficiency of cognitive control, and more specifically, top-down executive control (Bellgrove, Hester, & Garavan, 2004; Kaiser et al., 2008; Stuss, Murphy, & Binns, 1999) under the direction of prefrontal circuits (Bellgrove et al., 2004; Bunce et al., 2007; Stuss et al., 2003). Broadly, there are two different methods used to measure IIV: (1) dispersion of scores across a neuropsychological battery (across-task IIV), and (2) inconsistency in performance within an individual task (within-task IIV). Dispersion and inconsistency in reaction times are correlated, indicating individuals who exhibit more variability within tasks also demonstrate more variability across tasks (Hilborn, Strauss, Hultsch, & Hunter, 2009; Hultsch, MacDonald, & Dixon, 2002). Increased IIV, when compared to healthy individuals, has been noted in several disorders such as attention deficit hyperactivity disorder (ADHD) (Castellanos et al., 2005; Klein, Wendling, Huettner, Ruder, & Peper, 2006), traumatic brain injury (Stuss et al., 1989), human immunodeficiency virus (HIV) (Morgan, Woods, Grant, & The HIV Neurobehavioral Research Program (HNRP) Group, 2012a; Morgan et al., 2012b), schizophrenia (Cole, Weinberger, & Dickinson, 2011; Rentrop et al., 2010), and dementia (Ballard et al., 2001; Christensen et al., 1999; Duchek et al., 2009; Holtzer, Verghese, Wang, Hall, & Lipton, 2008; Hultsch

et al., 2000; Murtha, Cismaru, Waechter, & Chertkow, 2002). Studies indicate IIV may be associated with cognitive decline and disease progression in MCI and dementia (Christensen et al., 1999; Cherbuin, Sachdev, & Anstey, 2010). Dispersion across neuropsychological tasks has also been found to be associated with functional abilities in schizophrenia (Cole et al., 2011), HIV (Morgan et al., 2012a), and aging (Christensen et al., 1999). Of relevance to the investigation of prodromal HD, IIV has been proposed to represent a unique construct to study top-down attentional control. It may also be of value in individuals with genetic predispositions for certain disorders including ADHD (Frazier-Wood et al., 2011) and Alzheimer disease (Duchek et al., 2009).

The aforementioned research supports IIV as a cognitive construct that is affected by central nervous system disease and is associated with real-world outcomes and future cognitive decline across a variety of patient populations. However, IIV has not previously been investigated in prodromal HD. Accordingly, the objective of the current study was to examine IIV as a potential early marker of cognitive changes in individuals with prodromal HD. Our objective is based on the hypothesis that individuals with prodromal HD will demonstrate increased IIV, as measured by within-task variability on a motor programming task, and across-task variability among 15 neuropsychological tasks, compared to healthy adults (individuals with a family history of HD but without the CAG expansion). Considering prior research regarding IIV's sensitivity to a genetic predisposition to other neuropsychiatric disorders, it was also expected that within-task and across-task IIV would increase in individuals with prodromal HD who were closer to diagnosis. As a check on sensitivity, we also compared the ability of IIV to discriminate among HD groups with different estimated times to disease onset to that of an individual cognitive variable shown to be a good measure in discriminating gene-expanded from nongene-expanded individuals, the Symbol Digit Modalities Test (SDMT) (Paulsen et al., 2013).

METHOD

The PREDICT-HD study is designed to identify markers for HD onset in individuals with prodromal HD, with the goal of advancing clinical trials research (Paulsen, 2001). PREDICT-HD involves longitudinal data collection of gene-expanded individuals and controls. The study collects neuropsychological, motor, functional, psychiatric, genetic, and imaging data for these individuals to determine the most appropriate markers of disease progression.

Participants

Participants included 884 individuals from PREDICT-HD (See Table 1) who had complete data for the 15 variables used to compute the across-task IIV measure (see below). PREDICT-HD data have been collected from 2002 to date,

Table 1. Demographic information for participants

Variable	Control	Low[a]	Medium[a]	High[a]
n	191	186	246	261
% Male	35.60	32.26	33.33	43.68
% Caucasian	100.00	96.79	97.01	97.20
Age	43.11 (11.32)	35.20 (7.45)	40.90 (9.51)	44.09 (9.87)
Education (years)	14.70 (2.69)	14.53 (2.53)	14.54 (2.65)	14.22 (2.71)
CAG repeat length	20.08 (3.53)	40.82 (1.54)	42.21 (2.06)	43.74 (2.73)
UHDRS score[b]	2.34 (2.90)	3.06 (3.42)	4.11 (4.19)	6.67 (6.03)
Confidence in motor diagnosis	0.35 (0.55)	0.59 (0.67)	0.72 (0.75)	1.09 (0.94)

Note. CAG = cytosine-adenine-guanine; UHDRS = Unified Huntington's Disease Rating Scale.
[a]Classification of participants into Low, Medium, and High is based on the CAG-age product (CAP) (see "Method" section). Low: low probability (>15 years from diagnosis); Medium: medium probability (9–15 years from diagnosis); High: high probability of near-future diagnosis (estimated to be <9 years from diagnosis).
[b]The UHDRS assesses motor functioning. Scores range from 0 to 124, with higher scores reflecting more impairment.

but we considered only the single baseline cross-sectional data for this analysis. Data were included from 693 gene-expanded participants and 191 control participants collected across 32 sites in the United States, Canada, Australia, Germany, Spain, and the United Kingdom. All participants provided informed written consent for participation in the PREDICT-HD study and permission for de-identified data to be analyzed at collaborative institutions. All procedures complied with the Helsinki Declaration and were approved by Institutional Review Boards at each participating site.

Inclusion criteria for PREDICT-HD were adults 18 years of age or older with a family history of HD and previous, voluntary genetic testing for CAG expansion. At study entry, no participants met formal criteria for clinically definitive HD. Participants were included in the prodromal HD group if they had CAG expansion ≥36 repeats. For every six prodromal HD participants recruited, a comparison participant, defined as someone with a parent who had HD but who did not have the gene expansion themselves (i.e., <36 CAG repeats) was recruited. Individuals were excluded from PREDICT-HD if they had evidence of an ongoing unstable medical or psychiatric condition, reported substance abuse within the past year, had a history of learning disability or intellectual disability requiring special education classes, a history of other central nervous system disease (e.g., seizures, TBI), or if they had a pacemaker or metallic implants. Individuals were also excluded if they had used prescription antipsychotic medications within the past six months or if they used phenothiazine-derivative antiemetic medications more than three times per month. No other prescription or over-the-counter medications or natural remedies were restricted.

Procedure

All participants underwent comprehensive baseline evaluations including blood draw, neurological/motor examination, cognitive assessment, psychiatric and psychological questionnaires, and brain MRI. All site data were sent to a centralized location and subjected to quality assurance/control methods, including double or triple scoring of all protocols by different reviewers trained by PREDICT-HD, and double data entry.

Genetic Status and Estimating Years to Clinically Definitive Diagnosis

Progression group was determined for each participant based on the CAG-Age Product (CAP) developed by Zhang et al. (2011) using the larger PREDICT-HD database. CAP is similar to the "genetic burden" score of Penney et al. (1990) and purports to index cumulative toxicity of the mutant *huntingtin*. CAP is calculated as CAP = (Age at entry) × (CAG – 33.66). Using the algorithm of Zhang et al. (2011), participants were classified as High probability of near-future diagnosis (estimated to be <9 years from diagnosis), Medium probability (9–15 years from diagnosis), and Low probability (>15 years from diagnosis).

Motor Examination

Participants' motor functioning was assessed using the Unified Huntington's Disease Rating Scale (UHDRS) (Huntington Study Group, 1996). The UHDRS total motor score (TMS) is a standardized assessment consisting of 31 items rated on a scale from 0 to 4 with a score of 0 indicating no abnormalities and 4 indicating the most severe impairment. Motor scores have been shown to distinguish controls from gene-expanded participants, with the presence of motor abnormalities associated with a closer estimated time to disease diagnosis (Kieburtz et al., 1996; Long et al., 2013). The TMS is computed by summing the individual items (range is 0 to 124).

Examiners also used the UHDRS diagnostic confidence level (DCL) to rate the degree of confidence that the observed motor signs were consistent with manifest HD. The DCL is a 4-point ordinal scale with the following format: 0 = no

abnormalities; 1 = non-specific motor abnormalities, less than 50% confidence; 2 = motor abnormalities that may be a sign of HD, 50–89% confidence; 3 = motor abnormalities that are likely signs of HD, 90–98% confidence; and 4 = motor abnormalities that represent unequivocal signs of HD, 99% confidence. Individuals with DCL = 4 at baseline were excluded because this study focused on premanifest HD.

Neurocognitive Assessment

PREDICT-HD uses a comprehensive battery of cognitive tests sensitive to fronto-striatal circuitry (see Paulsen et al., 2013). Table 2 lists the tests and a description of measures currently used in the study. All measures were administered in the native language where the study site was located. Information about translations of test materials and detailed descriptions of tasks are provided in Stout et al. (2011). The computer tests that were designed or modified for PREDICT-HD are described below. All measures used in this study with the exception of three tasks, the Benton Facial Recognition Test, the Towers 4 task, and the Serial reaction time task, were factor analyzed by Harrington et al. (2012). For tests that had multiple summary measures, the measures that demonstrated the highest factor loadings were chosen for across-task IIV analysis.

Measures

The emotion recognition task presents participants with faces that express one of six emotions or a neutral emotion (Ekman & Friesen, 1976). Participants are then asked to select the emotion from a multiple-choice list of words: disgust, anger, fear, sad, happy, surprise, or neutral. Ten stimuli are presented for each emotion. Raw scores are the total number of correct negative emotions identified (fear, disgust, anger, sad).

PREDICT-HD used two computerized Tower of Hanoi tasks to assess planning and reasoning. This study included the Towers 4 task, in which participants are presented with three vertical pegs, one of which contains four disks of increasing sizes with the largest disk on the bottom. Participants are asked to relocate all disks in exactly the same configuration to a different peg. However, they are required to follow two rules: only the top peg can be moved, and larger disks cannot be placed on top of smaller disks. Participants complete four trials.

The Cued Movement Sequencing task presents participants with ten vertical pairs of circles displayed along the bottom of a touchscreen. The start position circle is illuminated. Trials proceed from left to right with one of the vertical circles becoming illuminated at a time. Participants are asked to press an illuminated circle that appears at the bottom of the screen. There are three conditions: low-level, medium-level, and high-level of cueing. The high-level cue condition illuminates a circle in the adjacent pair simultaneously as the finger is pressed on the proceeding illuminated circle. But as the participant's finger is lifted, a circle two pairs over is also illuminated, and the illuminated circle in the adjacent pair is extinguished. Participants are given 28 attempts to complete either eight (low and medium cue-level conditions) or 16 (high cue-level condition) error-free trials.

In the simple and two-choice reaction times (RT) task, participants are presented with a computer fitted with a response device with a single button at the bottom and two adjacent buttons at the top. Participants initiate trials by placing the dominant index finger on the start button. For the simple RT, a single hollow circle appears on the screen then fills with green between zero and 3.2 s. The participant responds by pressing the right-sided button. For the two-choice reaction time task, participants are presented with two adjacent hollow circles and one filled with green. They are asked to press the response button on the corresponding side.

The serial reaction time task presents participants with asterisks in serial order in one of four locations. Participants respond to the asterisks by using their index and middle fingers to press one of four buttons on an external response device. The buttons are aligned with four screen positions. The first four blocks present asterisks serially in a fixed 12-asterisk sequence that is repeated eight times. A fifth block presents asterisks in four locations in random order. Finally, the sixth block presents the asterisks in the previously presented repeating sequence. Participants are not informed that that sequence was repeated.

The speeded tapping and paced timing tasks both use a response box interfaced with a computer. For the speeded tapping task, participants are asked to tap as quickly as possible for five consecutive 10-s trials. Participants complete separate trials with the index finger of each hand and a third trial where they tap with alternating thumbs. Paced timing is a self-timed tapping task during which participants listen to a metronome-like tone presented at an interval of one tone every 550 ms. Participants are asked to listen to the tone then tap along when ready. The tone continues for 11 taps then stops, at which time participants are asked to continue tapping at the same pace until signaled to stop by an alternate tone (31 taps). This procedure is completed for five trials, for a total of 155 self-paced taps. Paced timing tapping proficiency is calculated as the reciprocal of the standard deviation (1/standard deviation) because these scores are more normally distributed and better fit assumptions of linearity (Rowe et al., 2010). This measure indexes within-task IIV and has demonstrated good discrimination between groups (Hinton et al., 2007; Paulsen et al., 2008; Rowe et al., 2010). A second measure of IIV, the coefficient of variation, was calculated for paced timing [paced timing coefficient of variation (CV)] by dividing the standard deviation of inter-tap intervals by the mean inter-tap interval for each participant.

In addition, the Beck Depression Inventory–II (BDI-II) was administered as a measure of cognitive, affective, and physiological symptoms of depression. Severity of depressive symptoms has been associated with significantly poorer performance on cognitive measures in individuals with prodromal HD (Smith, Mills, Epping, Westervelt, &

Table 2. Neuropsychological tasks administered to participants in the current study

Task	Reference	Variable	Cognitive factor[a]
Stroop Color and Word Test (Stroop)	Stroop, 1935	Color naming total score	Speed and inhibition
Controlled Oral Word Association Test (COWAT)	Benton et al., 1983	Total number of correct words across three trials	Verbal working memory
Trail Making Test, Part A (TMTA)	Reitan, 1958	Number of seconds to complete Trails A	Attention and information integration
Trail Making Test, Part B (TMTB)	Reitan, 1958	Number of seconds to complete Trails B	Attention and information integration
Symbol Digit Modalities Test (SDMT)	Smith, 1991	Total number of correct responses in 90 seconds	Attention and information integration
Wechsler Adult Intelligence Scale (WAIS)-III: Letter-Number Sequencing (LNS)	Wechsler, 1997	Total number of correct trials	Verbal working memory
Hopkins Verbal Learning Test-Revised (HVLT)	Brandt & Benedict, 2001	Total number of words learned over the learning trials	Verbal learning and memory
Benton Facial Recognition Test	Benton et al., 1983	Total number of correct responses	Not included
Emotion Recognition Task	Johnson et al., 2007	Total number of correctly identified negative emotions	Sensory and perceptual processing
Towers 4	Similar to Saint-Cyr et al., 1988; Papp et al., 2013	Difference in mean number of moves from the first to fourth trial	Not included
Cued Movement Sequencing: Buttons	Based on Georgiou et al., 1995	Mean movement standard deviation (within-task IIV)	Motor planning and speed
Two-Choice Reaction Time: Chooser	See Stout et al., 2011	Mean movement time	Motor planning and speed
Speeded Tapping	Hinton et al., 2007; Paulsen et al., 2004	The standard deviation of inter-tap intervals for the nondominant hand (within-task IIV)	Motor planning and speed
Paced Timing	Hinton et al., 2007; Paulsen et al., 2004	Reciprocal of the standard deviation (within-task IIV)	Motor planning, speed and sensory and perceptual processing
Serial Reaction Time Task	Willingham et al., 1989	Difference in response times for random sequence (fifth block) compared to the fourth presentation of the set sequence	Not included

[a]Based on Harrington et al.'s 2012 factor analysis.

Paulsen, 2012). The BDI-II was used as a covariate to control for effects of mood symptoms on cognition in the current study.

Statistical Analyses

The analysis focused on the ability of the across- and within-task variability to discriminate among the CAP groups and controls, adjusting for age, gender, and years of education. As mentioned previously, within-task variability measures included the paced timing proficiency and paced timing CV. Across-task variability (dispersion) among the 15 cognitive measures previously described was computed as both the intra-individual standard deviation (ISD) and the intra-individual coefficient of variation (ICV). The coefficient of variation was used because some researchers recommend correcting IIV to allow for the adjustment of scores to mean level of performance (Duchek et al., 2009).

The following procedure was used to compute across-task IIV. First, adjusting for age, gender, and years of education, we used a general linear model (SAS PROC GLM) to obtain residual values for each participant, which can be regarded as demographically adjusted scores to be used in place of raw scores. Seven of the cognitive measures (Trail Making Test, Part A, Trail Making, Part B, Towers 4 Task, Cued Movement Sequencing: Buttons, two-choice reaction time: Chooser, speeded tapping, and serial reaction time task) increased as disease progressed, the opposite direction of the other cognitive measures. To address the difference in scoring, we reversed the sign on the residuals for these seven cognitive values. Consistent with previous research, we scaled each demographically adjusted score to have a mean $= 50$ and a standard deviation $(SD) = 10$ (Christensen et al., 1999; Hilborn et al., 2009; Morgan et al., 2012a, 2012b). Finally, we computed the mean and SD among the T-scores. Intra-individual standard deviation was the SD among the T-scores for the 15 measures. The coefficient of variation was computed as the ratio of the SD to the mean of the 15 tasks (ISD/mean T-score).

After computing IIV across T-scores for each participant, we used analysis of variance (ANOVA) to examine omnibus CAP group differences, unadjusted paired comparisons to assess inequalities among group means, and Cohen's d to evaluate the effect sizes of the pairwise comparisons. Relative sensitivity was evaluated by comparing intra-individual standard deviation and coefficient of variation with ANOVA using SDMT, paced timing proficiency, and paced timing CV. A second analysis using analysis of covariance (ANCOVA) was conducted for all outcomes (intra-individual standard deviation, coefficient of variation, SDMT, paced timing proficiency, paced tapping CV) to adjust for BDI-II (Smith et al., 2012) and total motor score (TMS).

RESULTS

Means and SDs of the standardized T-scores by CAP group are presented in Table 3. Participants in the medium and high CAP groups had poorer cognitive performance (mean T-scores ≤ 50) than those in the Control and Low CAP groups (mean T-scores > 50).

Across-task Variability

Table 4 shows the ANOVA and ANCOVA results. The ANOVA results show mean intra-individual standard deviation ($F_{(3,880)} = 8.48$; $p < .0001$) varied by CAP group. Pairwise comparisons suggested that the intra-individual standard deviation was significantly greater for the High group, but there was no evidence of a difference among the Control, Low, and Medium groups. After adjusting for BDI-II and TMS in the ANCOVA model, there was still an effect for CAP group ($F_{(3,877)} = 4.41$; $p < .001$) for intra-individual standard deviation. However, pairwise comparisons revealed the High and Control CAP group differences were no longer statistically significant for intra-individual standard deviation.

In terms of intra-individual coefficient of variation, the ANOVA results (Table 4) show the mean coefficient of variation ($F_{(3,880)} = 24.48$; $p < .0001$) varied by CAP group. Pairwise comparisons showed the coefficient of variation had significantly larger means for the High group, but there was no evidence of a difference among the Control, Low, and Medium groups. After adjusting for BDI-II and TMS in the ANCOVA model, there was still an effect for the CAP group for intra-individual coefficient of variation ($F_{(3,877)} = 11.25$; $p < .0001$). Pairwise comparisons revealed the difference between the High group and Control group remained statistically significant for coefficient of variation.

Within-Task IIV

ANOVA results revealed significant main effects for the paced timing proficiency score (Table 4), suggesting it was strongly associated with CAP group ($F_{(3,880)} = 42.19$; $p < .0001$). Pairwise comparisons revealed that the High and Medium CAP groups obtained significantly lower scores on paced timing proficiency compared to the Control group. There were no significant differences between the Low CAP group and the Control group. After adjusting for BDI-II and TMS (ANCOVA analysis), the strength of the CAP group effect was diminished ($F_{(3,877)} = 22.89$; $p < .0001$) but still significant. Paced tapping was significantly but modestly correlated with across-task variability (see Table 5: ISD, $r = -0.15$; $p < .0001$; ICV; $r = -0.33$; $p < .0001$).

ANOVA results revealed significant main effects for the paced timing CV score (Table 4), suggesting it was strongly associated with CAP group ($F_{(3,880)} = 34.64$; $p < .0001$). Pairwise comparisons revealed the High and Medium groups obtained significantly lower scores on paced timing compared to the Control group, and the High group obtained significantly lower scores than the Low group. After adjusting for BDI-II and motor score with ANCOVA models, the main effect of the CAP group remained significant

Table 3. Mean T-scores by CAG-age product (CAP) group

CAP group	T-score	Mean	*SD*	Minimum	Maximum
Control (*n* = 191)	Stroop Color and Word Test	52.56	9.63	24.36	95.19
	Controlled Oral Word	52.01	10.64	27.96	87.30
	Trail Making Test, Part A	51.98	8.37	17.43	66.69
	Trail Making Test, Part B	52.60	8.03	3.47	64.81
	Symbol Digit Modalities Test	53.07	8.48	26.48	81.36
	Benton Facial Recognition Test	52.14	9.56	21.12	73.54
	Emotion Recognition Task	53.69	8.53	32.82	73.74
	Letter-Number Sequencing	52.82	11.41	25.26	83.11
	Hopkins Verbal Learning Test	53.27	8.74	25.47	73.30
	Towers 4	51.24	10.48	20.23	70.73
	Speeded Tapping	53.31	6.30	20.72	68.99
	Paced Timing Precision	54.29	9.91	33.21	79.33
	Paced Timing CV	53.52	6.72	14.57	62.59
	Cued Movement Sequencing	51.66	9.70	−7.54	65.33
	Two-Choice Reaction Time	52.53	8.28	28.86	69.24
	Serial Reaction Time Task	49.85	10.05	0.56	76.35
Low (*n* = 186)	Stroop Color and Word Test	52.11	9.04	27.12	84.81
	Controlled Oral Word	51.78	9.37	30.68	91.56
	Trail Making Test, Part A	51.57	9.76	−6.98	65.37
	Trail Making Test, Part B	52.31	5.95	33.16	66.12
	Symbol Digit Modalities Test	53.13	10.10	25.70	82.51
	Benton Facial Recognition Test	51.43	10.86	−13.23	72.00
	Emotion Recognition	52.77	9.24	20.90	72.69
	Letter-Number Sequencing	51.48	8.95	34.15	83.45
	Hopkins Verbal Learning Test	52.31	8.12	28.74	70.16
	Towers 4	50.16	10.60	20.42	68.75
	Speeded Tapping	52.91	5.93	25.69	64.84
	Paced Timing Precision	52.40	9.39	26.98	80.75
	Paced Timing CV	52.03	8.42	6.03	61.07
	Cued Movement Sequencing	52.18	7.72	16.89	64.38
	Two-Choice Reaction Time	53.35	7.82	24.55	69.64
	Serial Reaction Time Task	50.22	9.89	10.85	70.79
Medium (*n* = 246)	Stroop Color and Word Test	50.24	10.09	23.78	77.89
	Controlled Oral Word	49.77	9.48	29.42	76.06
	Trail Making Test, Part A	50.54	9.16	12.85	65.95
	Trail Making Test, Part B	49.93	9.67	−5.71	64.04
	Symbol Digit Modalities Test	49.62	9.47	27.14	86.15
	Benton Facial Recognition Test	49.20	9.49	18.28	71.88
	Emotion Recognition	49.30	9.44	17.63	72.81
	Letter-Number Sequencing	49.10	9.11	19.59	77.61
	Hopkins Verbal Learning Test	49.84	9.55	21.86	68.07
	Towers 4	50.39	9.23	22.05	67.15
	Speeded Tapping	50.87	7.91	1.85	65.42
	Paced Timing Precision	50.16	9.03	32.08	76.39
	Paced Timing CV	50.83	7.44	14.81	62.44
	Cued Movement Sequencing	50.03	9.47	−6.48	62.47
	Two-Choice Reaction Time	49.49	10.01	13.78	69.53
	Serial Reaction Time Task	50.47	9.43	8.94	73.70
High (*n* = 261)	Stroop Color and Word Test	46.40	9.83	19.96	90.48
	Controlled Oral Word	47.48	9.90	23.63	79.21
	Trail Making Test, Part A	46.92	11.28	−5.25	65.05
	Trail Making Test, Part B	46.51	12.57	−27.10	64.78
	Symbol Digit Modalities Test	45.88	9.95	17.53	70.02
	Benton Facial Recognition Test	48.17	9.75	17.62	73.85
	Emotion Recognition	45.98	10.47	16.43	73.27
	Letter-Number Sequencing	47.73	9.80	25.04	77.03
	Hopkins Verbal Learning Test	46.11	11.14	13.41	67.73
	Towers 4	48.61	9.80	20.00	69.13

Table 3: (*Continued*)

CAP group	T-score	Mean	*SD*	Minimum	Maximum
	Speeded Tapping	44.68	13.54	−19.15	71.40
	Paced Timing Precision	45.00	9.25	25.92	75.03
	Paced Timing CV	45.20	12.96	−18.30	61.42
	Cued Movement Sequencing	47.20	11.43	−21.95	64.87
	Two-Choice Reaction Time	46.24	11.15	5.89	70.80
	Serial Reaction Time Task	49.51	10.58	7.73	75.25

Note. SD = standard deviation; CV = coefficient of variation.

Table 4. Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) results for CAG-Age Product (CAP) group effect

Measure	ANOVA *F*-value (*p*-value)	Pairwise comparisons[a]	ANCOVA *F*-value (*p*-value)	Pairwise comparisons
IIV	8.48 (<.0001)	C, L, M < H	4.41 (0.0044)	L, M < H
CV	24.48 (<.0001)	C, L, M < H	11.25 (<.0001)	C, L, M < H
SDMT	29.59 (<.0001)	C, L > M > H	13.92 (<.0001)	C, L > M > H
Paced timing precision	42.19 (<.0001)	C, L > M > H	22.89 (<.0001)	C > M > H L > H
Paced timing CV	34.64 (<.0001)	C > M > H L > H	15.67 (<.0001)	C, L, M > H

Note. IIV = intra-individual variability; CV = coefficient of variation; SDMT = Symbol Digit Modalities Test; C = Control CAP group; L = Low CAP group; M = Medium CAP group; H = High CAP group.
[a]Classification of participants into low, medium, and high is based on the CAG-age product (CAP) (see "Method" section). Low: low probability (>15 years from diagnosis); Medium: medium probability (9–15 years from diagnosis); High: high probability of near-future diagnosis (estimated to be <9 years from diagnosis).

($F_{(3,877)} = 15.67$; $p < .0001$), and the High group obtained significantly lower scores compared to other CAP groups.

SDMT

The ANOVA results (Table 4) revealed a significant main effect for the SDMT score ($F_{(3,880)} = 29.59$; $p < .0001$). Pairwise comparisons showed differences among all groups with the exception of the Low CAP group *versus* Control group. After adjusting for BDI-II and motor score with ANCOVA models, the strength of the CAP group effect was also diminished ($F_{(3,877)} = 13.92$; $p < .0001$) but was still significant. Pairwise comparisons remained the same.

Effect Size

The ANOVA/ANCOVA results indicate paced timing proficiency, paced timing CV, and SDMT were more strongly associated with CAP group than the across-measures of IIV. Cohen's *d* values (Table 6) confirmed these results. Effect sizes for paced timing proficiency, paced timing CV, and SDMT, comparing the High CAP group to controls, were larger in magnitude than those for the across-task measures of IIV.

DISCUSSION

The purpose of the present study was to determine whether individuals with prodromal HD displayed larger neuropsychological test variability than healthy controls.

It was hypothesized that, because IIV has demonstrated utility in predicting progression of cognitive decline in MCI and Alzheimer dementia, it may be sensitive to cognitive decline in other degenerative conditions, such as prodromal HD. This hypothesis was partially supported in the current study in that mean IIV, as measured by within- and across-task variability, was elevated in individuals with prodromal HD who were estimated to be relatively close to diagnosis, even when adjusting for depression and motor symptoms. The largest effect sizes were found for the measure of within-task variability (paced timing). It is also noteworthy that an individual measure of processing speed (SDMT) produced larger effect sizes between CAP groups than across-task IIV, but did not perform as well as paced timing proficiency.

Using the coefficient of variation corrects the scores for mean performance and provides a signal that is less confounded by overall ability level, and thus, is hypothesized to provide a purer signal of IIV variability. This is further supported by the finding that the coefficient of variation discriminated the High CAP group from controls even after controlling for depression and motor performance, but intra-individual standard deviation did not. Using coefficient of variation as a measure of across-task variability also resulted in larger effect sizes compared to using the simpler intra-individual standard deviation variable. On the other hand, when intra-individual standard deviation and the coefficient of variation were examined as a measure of within-task variability, the intra-individual standard deviation (paced timing proficiency) produced larger effect sizes compared to the coefficient of variation (paced timing CV).

Table 5. Correlations among neuropsychological variables

| | Pearson correlation coefficients, $N = 884$ | | | | | | | | | | | | | | | |
| | Prob > |r| under H0: Rho = 0 | | | | | | | | | | | | | | | |

	IIV	CV	Stroop Color	COWAT	Trails A	Trails B	SDMT	Face	Emotion	Letter-Number	HVLT	Towers 4	Speeded tapping	Paced tapping	Buttons	Chooser
IIV	1															
CV	0.92***	1														
Stroop Color	−0.08*	−0.28***	1													
COWAT	−0.08*	−0.25***	0.35***	1												
Trails A	−0.33***	−0.47***	0.32***	0.27***	1											
Trails B	−0.34***	−0.5***	0.40***	0.33***	0.47***	1										
SDMT	−0.22***	−0.44***	0.48***	0.36***	0.44***	0.52***	1									
Face	−0.11**	−0.2***	0.11***	0.14***	0.09**	0.15***	0.15***	1								
Emotion	−0.18***	−0.3***	0.26***	0.31***	0.19***	0.27***	0.33***	0.23***	1							
Letter-Number	−0.06	−0.2***	0.35***	0.36***	0.23***	0.40***	0.36***	0.16***	0.26***	1						
HVLT	−0.19***	−0.3***	0.26***	0.31***	0.24***	0.36***	0.42***	0.16***	0.31***	0.35***	1					
Towers 4	−0.12***	−0.2***	0.15***	0.08**	0.14***	0.22***	0.26***	0.03	0.10**	0.14***	0.18***	1				
Speeded tapping	−0.32***	−0.4***	0.32***	0.22***	0.26***	0.23***	0.36***	0.18***	0.27***	0.16***	0.23***	0.10**	1			
Paced tapping	−0.15***	−0.3***	0.36***	0.25***	0.22***	0.28***	0.37***	0.20***	0.34***	0.27***	0.23***	0.14***	0.43***	1		
Buttons	−0.4***	−0.5***	0.20***	0.16***	0.23***	0.20***	0.28***	0.09**	0.16***	0.16***	0.24***	0.10**	0.30***	0.33***	1	
Chooser	−0.27***	−0.4***	0.26***	0.23***	0.28***	0.28***	0.37***	0.13***	0.28***	0.20***	0.31***	0.09**	0.38***	0.33***	0.32***	1
Serial	−0.11***	−0.12***	0.01	0.08**	0.01	0.01	0.06	0.05	−0.01	0.05	0.05	−0.01	0.02	0.02	0.04	−0.01

Note. IIV = intra-individual variability; CV = coefficient of variation; Stroop Color = Stroop Color and Word Test; COWAT = Controlled Oral Word Association Test; Trails A = Trail Making Test, Part A; Trails B = Trail Making Test, Part B; SDMT = Symbol Digit Modalities Test; Face = Benton Facial Recognition Test; Emotion = Emotion Recognition Task; Letter-Number = Wechsler Adult Intelligence Scale-III: Letter-Number Sequencing; HVLT = Hopkins Verbal Learning Test-Revised; Buttons = Cued Movement Sequencing: Buttons; Chooser = Two-Choice Reaction Time: Chooser.
*$p < .05$.
**$p < .01$.
***$p < .001$.

Table 6. Cohen's *d* effect sizes

Groups	Intra-individual SD	CV	SDMT	Paced Timing Precision	Paced Timing CV
Control vs. High	0.26	0.55	−0.79	−1.01	−0.79
Control vs. Medium	−0.07	0.13	−0.39	−0.44	−0.37
Control vs. Low	−0.14	−0.09	0.004	−0.19	−0.20
Low vs. High	0.40	0.61	−0.72	−0.80	−0.61
Low vs. Medium	0.09	0.23	−0.36	−0.24	−0.15
High vs. Medium	0.33	0.45	−0.39	−0.57	−0.53

Note. SD = standard deviation; CV = coefficient of variation; SDMT = Symbol Digit Modalities Test; Control = Control CAG-age product (CAP) group; Low = Low CAP group; Medium = Medium CAP group; High = High CAP group.

Some researchers have found no significant differences in results when comparing these two methods (Morgan et al., 2012a). However, others report decreased significance when controlling for mean performance of the individual (Stuss et al., 2003). The results of the current study suggest that using coefficient of variation provides a stronger signal in individuals with prodromal HD compared to the uncorrected intra-individual standard deviation for across-task variability, but not for the measure of within-task variability.

Increased IIV for individuals with prodromal HD may have implications for clinical practice. Our finding that individuals with prodromal HD, who are estimated to be within a decade of clinically definitive diagnosis, have increased across-task coefficient of variation and within-task IIV is consistent with MacDonald et al. (2009), who hypothesize that IIV may be an early marker of cognitive decline. This finding suggests that increased across-task and within-task IIV may be markers for increased frontal lobe involvement and poorer top-down executive control in individuals with prodromal HD who are estimated to be within nine years of diagnosis. However, this study did not explicitly examine imaging data, and further research is needed to determine whether IIV is a marker of frontal lobe involvement in prodromal HD. In addition, no normative data are available at this time to guide decisions about normal *versus* pathological levels of IIV, and future research is needed to investigate the ecological validity of IIV and its relationship to functional outcomes in prodromal HD.

While across-task coefficient of variation may offer clinical utility for measuring cognitive integrity in patients with prodromal HD, this study suggests it may not be sensitive enough for clinical trials. The findings of the current study suggest across-task variability is not as sensitive to initial declines in cognition as the group means of some individual cognitive measures. Specifically, paced timing and SDMT better discriminated between CAP groups compared to across-task variability. It is also important to note paced timing proficiency has been shown to be more sensitive compared to other measures of within-task IIV in the PREDICT-HD battery (Stout et al., 2011), suggesting not all measures of within-task IIV are as sensitive to cognitive

changes in prodromal HD as paced timing. In the current study, paced timing CV, a purer signal of IIV, did not produce larger effect sizes in the discriminating groups, suggesting the current finding may be a result of the specificity of the paced timing task to normal striatal function, rather than top-down attentional control. Harrington et al. (2012) found the factors they labeled as motor planning/speed and sensory-perceptual processing were the best indicators of estimated time to diagnosis in PREDICT-HD. Paced timing loaded on both of these factors, and the authors concluded that paced timing proficiency may be exquisitely sensitive to striatal functioning.

One explanation for the fact that individuals estimated to be more than 15 years from diagnosis do not show increased IIV could be that few measurable cognitive changes occur at this point in the disease process (Paulsen et al., 2008; Stout et al., 2011). Paced timing proficiency and SDMT differentiated individuals estimated to be 9–15 years from diagnosis and controls, while measures of across-task IIV and paced timing CV did not. Stout et al. (2011) suggest individuals estimated to be 9–15 years from clinical diagnosis demonstrated lower performance on approximately half of the variables measured, including small effect sizes for some measures of working memory, processing speed, and executive functioning. However, several measures of executive functioning were not significantly affected in these same individuals (e.g., n-back task and Tower Tasks) in the study by Stout et al. (2011). It is possible that individuals who are more than nine years from diagnosis do not experience deficits in the executive construct of efficiency in sustaining cognitive control and coordinating behavior across a neuropsychological test battery. As noted above, poorer discrimination, as demonstrated by paced timing CV, suggests the effectiveness of the paced timing task may not be related to attentional vigilance and may reflect significant difficulty with motor demands and time perception in prodromal HD (Scahill et al., 2013). Harrington et al. (2012) hypothesized the tasks involving psychomotor planning/speed and sensory-perceptual factors may measure core networks that are particularly affected in prodromal HD, while individuals are able to compensate for deficits in other cognitive domains.

One of the limitations of the current study is that PREDICT-HD participants are self-selected. This sample was relatively well educated and dedicated to research involving improved outcomes for individuals with prodromal HD. These considerations should be taken into account, as they may not reflect other individuals with prodromal HD who do not chose to have genetic testing or become involved in this type of longitudinal study. One of the strengths of the current study is the large sample size. Such large samples of individuals with prodromal HD enabled the authors to examine IIV within stratified groups of individuals at various stages relative to the estimated time to diagnosis. Another strength of the current study is that individuals underwent extensive neuropsychological testing that surveyed most cognitive domains. However, these tasks were selected based on the assumption they would be sensitive to the brain

changes of HD, and it is possible a battery including a broader mix of tasks (in regards to HD sensitivity) may result in a larger dispersion index in prodromal HD. Furthermore, this study uses some tests that have been developed specifically for this study and have demonstrated sensitivity to impairment in prodromal HD. As such, they are not available to clinicians, limiting the ability to apply the results of the current study to clinical practice in general.

To the best of our knowledge, this is the first study to examine IIV in prodromal HD. Although future research is needed to understand the potential value of across-task and within-task IIV, individuals in this study, who were estimated to be fewer than nine years from diagnosis, demonstrated increased IIV, suggesting IIV may be a marker for frontostriatal dysfunction in prodromal HD. The current study suggests that across-task IIV may not be the most sensitive marker of cognitive dysfunction, as paced timing proficiency and a commercially available brief measure of processing speed (SDMT) were sensitive to cognitive decline in individuals estimated to be fewer than 15 years from diagnosis. However, this needs to be examined longitudinally using the PREDICT-HD data.

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