Self-Paced Timing Task Detects Subtle Changes in Prodromal Huntington Disease

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Background:

Pr-HD:

• Huntington disease (HD) is an autosomal dominant neurodegenerative disease with a triad of symptom domains: cognitive, psychiatric, and movement. HD is caused by CAG repeat expansion in the IT15 gene. CAG repeat expansion can vary in length from patient to patient; longer expansions are related to earlier onset of motor symptoms (Brinkman et al, 1997).

• Clinical diagnosis is based on unequivocal presence of extrapyramidal movement disorder (oculomotor dysfunction, chorea, dysarthria, dystonia, etc) (Huntington Study Group 1996).

• We study pr-HD participants, that is participants with a CAG repeat length of 36+ who have not yet begun showing diagnosable motor symptoms.

Timing:

• Timing has been used as a model system of cognitive dysfunction because it involves many important mental functions; perceiving and encoding temporal information, attentional shifting, storage and retrieval of long-term memory, and working memory (Balci et al, 2008).

• Brain structures affected in Huntington's disease have shown involvement with the timing circuit during functional neuroimaging studies (Witt, 2008) .

• Pr-HD participants as well as HD participants who are showing motor signs have shown impaired self-paced timing performance worsening with progression of the disease. However, these studies used smaller samples and often lacked an experimental control group. Zimbelman, 2007; Paulsen , 2004; Hinton, 2007; Michell, 2008)

Purpose:

1. To analyze self-paced timing performance in pr-HD and control participants.
2. To observe the relationship between proximity to HD diagnosis and self-paced timing performance in pr-HD individuals.
3. To characterize possible error variance in the task by considering other demographic and experience variables that could impact task performance.

Method:

The Task:

• A 550ms paced tone is presented and the participant taps in time with the tone using the response module (Figure 1). The tone stops and the participant continues tapping at the previously established pace.

• Data are collected upon pacing tone termination, and the variable of interest is tapping "precision", defined as the inverse of the standard deviation of mean inter-tap interval.

The Study:

• PREDICT-HD is a longitudinal, observational study designed to examine biomarkers (blood, urine, imaging) and clinical markers (cognitive, psychiatric, sensory, motor) of early disease in participants with the HD gene expansion.

• Pr-HD participants have a CAG repeat of 36 or more. Control participants have repeats of 30 or fewer and are from HD-affected families.

The Analysis:

• We examined baseline data from 747 pr-HD and 188 control individuals (see table 1 for demographic information).

• Probability of diagnosis within 5 years was derived from the Langbehn et al (2004) formula, which considers CAG repeat length and current age.

• Statistical analyses are based on linear models with an individual's timing precision as the outcome measure. Main predictor variables were gene expansion status and five-year diagnosis probability, nested within the pr-HD group. Other covariates, defined a priori, were gender, age, and years of education (Table 2).

• We also covaried for musical training (yes/no) and substantial typing experience (yes/no), both identified by a preliminary analysis.

• Finally, we considered history of limb injury, pain, and arthritis relative to task performance.

Response Module

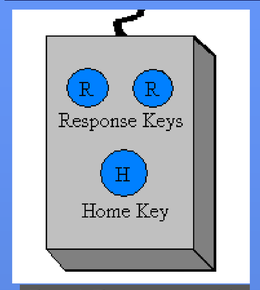

Figure 1: The response module is held in both hands and the thumbs rest on the response keys. The participant makes responses by pressing the response keys using alternating thumbs.

Self-paced Timing Relative to Probability of 5-year Diagnosis

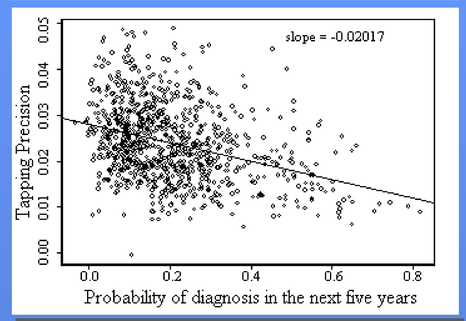

Figure 2: Precision is the inverse standard deviation of mean inter-tap interval during the self-paced tapping task. The model controlled for effects of gender, age, education, gene status. Bimanual tapping precision decreases as participants approach diagnosis. In this graph, precision is centered at its overall mean.

Demographic Information

	Pr-HD	Control	P-value
N	747	188	
Age	40.86* (18.1-75.9)	43.92* (19.2-72.2)	$P < .001$
Gender	62.9% F (277M, 470F)	66.3% F (63M, 123F)	$P = .42$
Education (years)	14.33 (8-20)	14.67 (8-20)	$P = .12$
Music Experience	11.76%	13.23%	$P = .58$
Typing Experience	30.61%	32.80%	$P = .56$
Hand or Wrist Injury	7.19%	3.68%	$P = .08$
Hand or Wrist Pain	13.32%	12.63%	$P = .8$
History of Arthritis	11.25%	17.55%	$P = .02$

Table 1: T-test on age uses Satterthwaite approximation for unequal variances.

Significant Predictors in Mixed Linear Model of Self-paced Timing Performance

Predictor Variable	Estimate	S.E.	T-statistic	P-value	Comment
Probability of 5-year diagnosis	-.02	.002	-11.32	<.0001	Less precision when 5-year diagnosis is more likely.
Gender	-.0020	.0005	-3.76	.0002	Women less precise than men.
Age (years)	.00008	.00003	3.12	.0019	Less precision with increased age.
Education (years)	.0006	.0001	5.91	<.0001	Less precision with lower education.
Music Experience	.0049	.0008	6.07	.0001	More precision with more musical experience.
Typing Experience	.0013	.0006	2.28	.0228	More precision with more typing experience.

Table 2: Total model R-square = 0.260. Comparison of case vs. control: $t = -7.43$, $p < .0001$, based on definition of pr-HD probability of 5-year diagnosis = 0.207. Probability of diagnosis (scale 0-1) calculated based on CAG repeat length and current age using Langbehn 2004 formula. Model outcome variable "precision" is defined as the inverse standard deviation of mean inter-tap interval.

Results:

• Groups did not differ significantly on years of education, gender, history of limb pain or injury, musical or typing experience, though pr-HD participants were slightly but significantly younger and had less incidence of arthritis than their non-expanded counterparts (Table 1).

• Significant timing performance differences were noted between pr-HD and control participants (df=918, t= -7.43, p <.0001).

• Within the pr-HD group, participants who were closer to estimated time of diagnosis tended to show less timing precision than their further-from-diagnosis counterparts (p<.0001) (figure 2, table 2).

• The task showed significant imprecision (p = .05) in pr-HD participants with a diagnostic probability of 4.3% or higher.

• There were significant effects of gender, age, and education (male, younger, highly educated: more precise), as well as prior music and typing experience (more experience: more precision).

• However, the adjustment for demographic and experience covariates did not substantially alter the strength of association between estimated probability of diagnosis and timing precision, nor did they suggest group-level confounding.

Discussion

• Self-paced timing precision was observed to be significantly poorer in pr-HD participants compared with controls, which is consistent with previous work (Hinton et al., 2007; Paulsen et al., 2008, Zimbelman et al., 2007).

• Pr-HD participants with poorer timing precision had a greater probability of diagnosis in the next five years. Importantly, this robust association remains even after considering demographic (age, gender, education) and experience (music, typing) variables (Figure 2, Table 2) .

• This relationship is important to clinical trials in pr-HD for three reasons:

1. Self-paced timing could be used as an effective screening tool for clinical trials in order to enroll participants with measurable deficits.
2. The task could also work as a salient outcome measure, even in the earliest stages of the disease.
3. It may be possible, given significant further research, to construct therapeutics targeted to specific phases of the pre-diagnostic syndrome. In that case, it will become critical to take into account the potentially varying degrees of dysfunction that may exist prior to neurological (motor) diagnosis.

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