Background:

Pr-HD:
- Huntington disease (HD) is an autosomal dominant neurodegenerative disease with a triad of symptoms: 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, dystonia, dysarthria, 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 diagnostically 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 (Alloway et al., 2003).
- Brain structures affected in Huntington’s disease have shown involvement with the timing circuit during functional neuroimaging studies (Cohen et al., 2006).
- Pr-HD participants as well as HD participants who age 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.

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 500ms 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.

The Study:
- PREDICT-HD is a longitudinal, observational study designed to examine biomarkers (blood, urine, imaging) and clinical traits (cognitive, sensory, motor) of early disease in participants with 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. Additional predictors included age, gender, 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.

Demographic Information

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Estimate</th>
<th>S.E.</th>
<th>t-Statistic</th>
<th>p-Value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of 5-year diagnosis</td>
<td>-0.02</td>
<td>0.05</td>
<td>-1.13</td>
<td>.001</td>
<td>Less precision when 5-year diagnosis is more likely.</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.020</td>
<td>0.005</td>
<td>-3.74</td>
<td>.002</td>
<td>Women less precise than men.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.0008</td>
<td>0.0003</td>
<td>3.12</td>
<td>.019</td>
<td>Less precision with increased age.</td>
</tr>
<tr>
<td>Education (years)</td>
<td>0.0006</td>
<td>0.0001</td>
<td>3.91</td>
<td>.001</td>
<td>Less precision with lower education.</td>
</tr>
<tr>
<td>Music Experience</td>
<td>0.0049</td>
<td>0.0008</td>
<td>6.07</td>
<td>.0001</td>
<td>More precision with more musical experience.</td>
</tr>
<tr>
<td>Typing Experience</td>
<td>0.0013</td>
<td>0.0006</td>
<td>2.28</td>
<td>.022</td>
<td>More precision with more typing experience.</td>
</tr>
</tbody>
</table>

Table 1: Predictor Variable in Mixed Linear Model of Self-paced Timing Performance

Table 2: Model Predictors

References:

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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.