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Self-Paced Timing Detects and Tracks Change in Prodromal Huntington Disease

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Abstract

Objective—This study compares self-paced timing performance (cross-sectionally and longitudinally) between participants with prodromal Huntington disease (pr-HD) and a comparison group of gene non-expanded participants from affected families (NC).

Methods—At baseline, participants in two groups (747 pr-HD: 188 NC) listened to tones presented at 550ms intervals, matched that pace by tapping response keys and continued the rhythm (self-paced) after the tone had stopped. Standardized cross-sectional and longitudinal linear models examined the relationships between self-paced timing precision and estimated proximity to diagnosis, and various other demographic factors.

Results—Pr-HD participants showed significantly less timing precision than NC. Cross-sectional comparison of pr-HD and NC participants showed a significant performance difference on two administration conditions of the task (dominant hand: $p<.0001$; alternating thumbs: $p<.0001$). Additionally, estimated proximity to diagnosis was related to timing precision in both conditions, (dominant hand: $t=-11.14$,df=920, $p<.0001$; alternating thumbs: $t=-11.32$, df=918, $p<.0001$), even

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considering demographic and experience variables. Longitudinal modeling showed that pr-HD participants worsen more quickly at the task than the NC group, and that decline rate increases with estimated proximity to diagnosis in both conditions (dominant hand: t=−2.85,df=417, p=.0045; alternating thumbs: t=−3.56, df= 445, p=.0004). Effect sizes based on adjusted mean annual change ranged from −0.34 to 0.25 in the longitudinal model.

Conclusions—The self-paced timing paradigm has potential for use as a screening tool and outcome measure in pr-HD clinical trials to gauge therapeutically-mediated improvement or maintenance of function.

Keywords

Basal Ganglia; tapping; clinical trials; cognition; isochronous serial interval production

Introduction

Huntington disease (HD) is a progressive neurodegenerative disorder of autosomal dominant inheritance which typically manifests in a triad of domains: cognitive, psychiatric, and movement (Walker, 2007). HD neuropathology is caused by a polyglutamine (CAG) expansion in the IT15 gene which leads to the production of a mutant form of the protein *huntingtin.* The polyglutamine expansion can vary in length from patient to patient; longer expansions typically confer a disease phenotype with earlier onset (Brinkman, Mezei, Theilmann, Almqvist, & Hayden, 1997). The mutant protein tends to form aggregates which are highly toxic to cells (Ramaswamy, Shannon, & Kordower, 2007). Cell death in early HD is especially prominent in the striatum, where the enkephalinergic medium spiny neurons of the indirect motor pathway are affected, ostensibly causing a lack of movement inhibition (Reiner et al., 1988). Clinical diagnosis of “manifest HD” is based on the unequivocal presence of an extrapyramidal movement disorder (oculomotor function, chorea, dysarthria, dystonia, gait and postural stability disturbance), which is operationalized for research purposes as a diagnostic confidence level above 99% on the Unified Huntington’s Disease Rating Scale (UHDRS), a standardized motor exam (Huntington Study Group, 1996).

The development of a genetic test for HD has allowed an unprecedented opportunity to study the earliest stages of neuronal dysfunction. Measurements prior to clinical diagnosis in nominally healthy research volunteers with an expanded HD gene (pr-HD) are allowing researchers to characterize functional and neurobiological correlates of very early disease development (Paulsen et al., 2006). By studying pr-HD volunteers, researchers are gaining critical insights into the earliest manifestations of HD development, which can include cognitive deficits in psychomotor speed, executive function, processing speed, and attention, often taking place years or decades before formal diagnosis (Campodonico, Codori, & Brandt, 1996; Paulsen et al., 2008).

Various neuropsychological measures have been applied to the study of pr-HD with the goal of further describing the cognitive profile of early HD and identifying whether cognition might prove a useful marker of disease for pr-HD clinical trials. Despite numerous candidates, no one cognitive measure has yet proven more robust than others in the early detection or tracking of disease. One type of impairment suggested by functional imaging studies in prodromal and early manifest HD is the perception, experience, and interval production of time. Timing is an integral cognitive function for most organisms, mediating various aspects of behavior and movement including reflexes, motor programs, action planning, and executive functions (Buonomano & Karmarkar, 2002). Timing has been used as a model system of cognitive dysfunction in neurological disease states because it involves many important mental functions; perception and encoding of temporal information, attentional shifting, storage and retrieval of

long-term memory, and comparison of the temporal memory with other perceptions stored in working memory (Balci, Meck, Moore, & Brunner, 2009). Disorders of temporal processing have been noted in a variety of neurological and psychiatric conditions including attention deficit hyperactivity disorder (Toplak, Dockstader, & Tannock, 2006), schizophrenia (Davalos, Kisley, & Freedman, 2005), mild cognitive impairment (MCI) and Alzheimer's disease (Carrasco, Guillem, & Redolat, 2000), Parkinson disease (Perbal et al., 2005), amnesia (Bangasser, Waxler, Santollo, & Shors, 2006), and HD (Hinton et al., 2007; Paulsen et al., 2004; Zimbelman et al., 2007).

The current report evaluates performance on a self-paced timing task in a pr-HD group. The timing circuit is compelling to investigate in HD because many of the brain structures affected in the disease have shown evidence of involvement with timing. A recent meta-analysis of 38 published functional neuroimaging studies (Witt, Laird, & Meyerand, 2008) showed that the bilateral basal ganglia, anterior cerebellum, sensorimotor cortices, supplementary motor area, inferior parietal cortices, and left ventral premotor cortex have common and robust activation during paced finger-tapping tasks in healthy normal participants. The above constellation of activated regions includes several important brain areas which are consistently targeted by HD neuropathology (Thieben et al, 2002), suggesting that paced timing tasks may be sensitive to HD-related dysfunction.

Investigation of self-paced timing tasks in the context of manifest HD (Michell et al., 2008) and Parkinson disease (Harrington, Haaland, & Hermanowicz, 1998) has shown impaired performance worsening with progressive degeneration of the basal ganglia and other disease-associated structures. Two recent functional neuroimaging studies using timing tasks (Paulsen et al., 2004; Zimbelman et al., 2007) reported significant changes in brain activation of pr-HD participants as they approach estimated diagnosis. The study by Paulsen et al. (2004) used a time discrimination task during functional imaging and required that participants indicate whether a stimulus interval was shorter or longer than a target interval (1200ms). Participants with higher estimated probability of diagnosis (based on age and CAG repeat length, Langbehn et al., 2004) performed less accurately and had different patterns of activation than participants estimated further from diagnosis. The paced timing task used by Zimbelman et al (2006) required participants to reproduce a time interval using right index finger key presses, and again revealed different patterns of activation across prognostic groups. The study further showed that participants with higher estimated probability of diagnosis had more variability in timing than participants with lower probability of diagnosis and comparison participants. An additional study emphasizing the behavioral component of timing (Hinton et al., 2007) reported a significant curvilinear relationship between estimated "years to HD diagnosis" (Langbehn et al., 2004) and variability on a self-paced finger tapping task in a group of 29 pr-HD participants. The cross-sectional analysis found that individuals with higher estimated probability of HD diagnosis had more variability (less precision) in self-paced timing. Finally, a report using an earlier subset of the data reported in the current paper (Paulsen et al., 2008) showed a significant relationship between "years to HD diagnosis" and decreased timing precision on part of this task using a nonlinear model that controlled for age, gender, and education.

The goals of the current project were to replicate and extend findings previously reported in pr-HD with a much larger sample size. Consistent with previous publications, we anticipated that performance would diminish in pr-HD participants who were estimated by CAG length and age to be more likely to receive diagnoses of manifest motor disease in the following five years. The current work is expanded and distinct from previous studies in that we compared pr-HD participants with a demographically comparable at-risk comparison group and we made every effort to reduce possible error variance in this task through consideration of other demographic and experience variables that could impact performance. Additionally, we have

included longitudinal analyses of this task which have never before been reported in any pr-HD sample.

Methods

Data were collected from participants in PREDICT-HD, a 32-site longitudinal observational study designed to examine biomarkers (i.e., blood, urine, and imaging) as well as refined clinical markers (cognitive, psychiatric, sensory, and motor) of early disease in persons with the gene expansion for HD (Paulsen et al., 2006). PREDICT-HD recruited two groups of individuals from affected families: 1) those with the gene expansion (CAG ≥36) but without motor signs sufficient for clinical HD diagnosis, hereafter referred to as the prodrome HD group (pr-HD) and 2) those without the gene expansion (CAG<30), hereafter referred to as the normal comparison group (NC). PREDICT-HD exclusion criteria include history of other CNS disease or events (e.g., seizures or head trauma), pacemaker, metallic implants, prescribed antipsychotic or phenothiazine derivative antiemetic medication in the past 6 months, and clinical evidence of unstable medical or psychiatric illness. Additionally, individuals with developmental cognitive disorders (e.g. mental retardation, special education for reading or math) are excluded. No restrictions are imposed regarding over-the-counter and natural remedies. All participants are 18 years or older and have had voluntary independent genetic testing prior to enrollment in the study. The study was approved by institutional review boards at all study and data-processing sites. Participants provided informed consent for participation.

The current analysis examined the baseline and follow-up visits of pr-HD and NC participants who enrolled between September 2002 and April 2008. Confirmation of polyglutamine (CAG) repeat length was determined from baseline blood draws, and estimated probability of diagnosis within 5 years of study entry was derived using the Langbehn et al. formula (2004). The formula, derived from survival analysis of lifetime diagnosis-age distributions, considers CAG repeat length and current age to estimate the probability of receiving a clinical diagnosis in the next five years. In the current sample, pr-HD participants had five-year diagnostic probabilities ranging from 0.32% to 76.1%, and all gene NC participants had probabilities of 0 (by definition).

The self-paced finger-tapping task is one of more than 20 cognitive tasks administered by trained study personnel at annual PREDICT-HD visits (see Paulsen et al., 2006 for details). Two conditions are tested, one using the dominant hand index finger, and the other using both thumbs tapping in an alternating pattern to produce the target rhythm. These measures were selected for use in the PREDICT-HD battery at the time of its inception because of their demonstrated sensitivity to timing changes in Parkinson Disease. It was hypothesized that the alternating-thumbs condition would be more sensitive than the dominant hand condition because it relies on interhemispheric components of processing which could add complexity to the task.

As with several other tasks in the cognitive assessment, the self-paced tapping task uses an external input device connected to a computer. The input device is a small platform on which there are three mounted switches. For the “dominant hand” condition, the participant rests the arm on a computer stand and is instructed to hold the hand flat with the index finger resting on a specified switch. For the “alternating-thumbs” condition the participant places the switch platform on her/his lap with the thumbs each resting on separate horizontally placed switches and the remaining fingers placed beneath the platform to provide stability during tapping. Each condition is tested for five blocks, with the index finger used for the first condition, and alternating thumbs for the second condition. All blocks have an identical sequence. First, a pacing tone is presented at a rate of one tone per 550 ms (1.82 Hz). Participants are asked to listen to the tone, and once ready, to begin tapping the specified switch(es) in time with the

tone, and then to continue tapping at that same rate after the tone stops. The tone signal is presented eleven more times once the participant begins tapping (for a total of 12 tone paced taps). Then the tone is discontinued, and the participant continues tapping until 31 additional taps have been completed. To signal the end of the block, an alternate tone is presented, indicating to the participant that he/she can stop tapping. Self-paced timing is assessed using the 31 taps per block that occur once the pacing tone has been discontinued. Over all 5 blocks administered at the baseline visit, 155 total self-paced taps are recorded. The precision of all taps taken together is directly estimated. Precision (rather than rate) has been the variable of interest in past studies of paced timing in pr-HD (Hinton et al., 2007; Paulsen et al., 2008; Zimbelman et al., 2007). Timing precision is calculated as 1/standard deviation (SD) of the inter-tap interval. Compared to a direct analysis of the SD, its reciprocal is preferred for data analysis because it more closely satisfies statistical modeling assumptions of linear relationships to covariates of interest, approximates normality, and maintains constant variance of the differences between observed and predicted values.

As a part of the PREDICT-HD annual visit, demographic variables were recorded. The total baseline sample was predominantly right-handed (91.4%), Caucasian (80.6%), and married (67.4%). Pe-HD participants' average age was 40.9 (18.1–75.9), 62.9% of them were women (277m: 470f), and the group had an average 14.3 years of education (8–20). At the baseline visit, NC participants' average age was 43.9 (19.2–72.2), 66.3% were women (65m: 123f), and this group had an average 14.7 years of education (8–20). Participants were also asked about events that could potentially moderate paced timing performance, such as musical training, experience as a typist, and pain in the wrist or hand. Of pr-HD participants, 11.8% had musical training, 30.6% had experience as a typist, 7.2% had experienced hand or wrist injury, 13.3% identified having hand or wrist pain, and 11.3% had a history of arthritis. In the NC participant group, 13.2% had extensive musical training, 32.8% had experience as a typist, 3.7% had hand or wrist injury, 12.6% identified hand or wrist pain, and 17.6% had a history of arthritis. Pr-HD and NC participants did not differ significantly on years of education, gender, history of limb pain or injury, musical or typing experience (education independent samples t-test $t = -1.56$; gender df = 1, $X^2 = 0.66$; hand injury df = 1, $X^2 = 3.08$; hand pain df = 1, $X^2 = 0.06$; music experience df = 1, $X^2 = 0.30$; typing experience df = 1, $X^2 = 0.34$; $p > .05$ for all). The pr-HD individuals were slightly but significantly younger and had less incidence of arthritis than their NC counterparts (age df = 263, $t = -3.41$, $p < .001$; arthritis df = 1, $X^2 = 5.44$, $p < .02$). *T*-test on age uses Satterthwaite approximation for unequal variances.

The primary statistical analyses were based on linear models separately examining precision for the two conditions (index finger and thumbs) as the outcome measures. Both longitudinal and cross-sectional measures are reported here. The main predictor variables of interest for the cross-sectional analyses were gene expansion status and five-year diagnosis probability, nested within the pr-HD group (NC have a diagnostic probability of 0 by definition). We model "probability of diagnosis" rather than alternative concepts like "estimated years to diagnosis" in the cross-sectional model for the empirical reason that the regression relationships are approximately linear in the former and highly nonlinear in the latter (Hinton et. al, 2007; Paulsen et. al, 2008). Other covariates, defined a priori, were gender, age, and years of education. We also covaried for musical training (yes or no), and substantial typing experience (yes or no), both identified by the above-described preliminary analyses. Finally, for the alternating-thumbs baseline measurement, there was some evidence ($p = .01$) of systematic variation at a single site. When subjects from this site were removed from analysis, however, fixed effect estimates only differed trivially from those obtained from the full data. Further, this site did not show differences for dominant hand baseline analysis or any longitudinal analysis. Thus, we did not exclude the site in question from analysis.

Among the pr-HD participants, age implicitly enters the above statistical models in a nonlinear fashion due to its role in estimating proximity to diagnosis. Ideally then, the explicit additional inclusion of age in the model accounts for possible normal aging effects that are common to both pr-HD and NC participants. This is a strong and potentially inaccurate modeling assumption however, and we checked its plausibility by testing for interactions of age and gene status in the cross-sectional linear model.

For the longitudinal analyses, we considered performance across groups defined by estimated time to diagnosis broken down into participants far from diagnosis (15 + years), midway to diagnosis (9–15 years), near to diagnosis (< 9 years), and those who have received a formal HD diagnosis by UHDRS diagnostic confidence rating of >99%. We use this grouping rather than estimated probability of diagnosis to incorporate those with prospectively observed diagnoses as a separate, well-defined ordinal category. The main variable of interest was the mean annual change in tapping performance between pr-HD participants and NC participants. The self-paced timing task was administered every two years and sample sizes include all pr-HD participants without baseline diagnosis who had at least one follow-up visit. For the dominant hand index finger condition, data from 464 pr-HD and 75 NC participants were analyzed, including 336 participants with two-year follow-up, and 203 with four-year follow-up. For the alternating thumbs condition, data from 472 pr-HD and 75 NC participants were analyzed, which included 342 participants at two-year follow-up and 205 at four-year follow-up. Other covariates included age, education, and gender, as well as prior musical and typing experience. Two-year changes in tapping precision were directly analyzed as the outcome variable. HD group membership was time-dependant. For example, if a participant is classified in the “near” group at visit 3 and then receives a research diagnosis of manifest HD at visit 5, this is reflected in the analysis. A Toeplitz covariance structure was used to model within-subjects dependencies of change scores. Satterthwaite approximation was used to estimate degrees of freedom in all F- and *t*-tests on the longitudinal analysis (Brown & Prescott, 1999). Additionally, longitudinal random effects of data collection site were tested and found to be non-significant ($p > .05$) on both conditions of the task and so were not included in the model presented here.

Results

On cross-sectional analysis, significant performance differences between the 747 pr-HD and 188 NC participants were observed on timing precision on both conditions of the finger-tapping task (dominant hand: df = 920, $t = -6.27$, $p < .0001$; alternating-thumbs: df = 918, $t = -7.43$, $p < .0001$). Conversely, analysis of mean inter-tap intervals, completed to verify that there were no differences between pr-HD and NC participants on overall timing accuracy (speed), yielded no significant difference on either condition (dominant hand: $p = .53$, alternating thumbs: $p = .41$). Pr-HD participants exhibited less timing precision than NC participants in both conditions. Within the pr-HD group, individuals who were closer to estimated diagnosis (expressed as higher probability of diagnosis in the statistical model) tended to show less timing precision than their further-from-diagnosis counterparts ($p < .0001$ for both conditions, Table 1). Further analysis revealed that even pr-HD participants with very low likelihoods of developing HD during the next 5 years were significantly less precise than NC; the difference in tapping precision was statistically significant at the $p = .05$ level for pr-HD participants with probability of five-year diagnosis as low as 4.3%. This finding emphasizes the sensitivity of the task to very early changes during prodromal HD.

There were significant effects of gender (women associated with less precision), age (older age associated with less precision), and education (lower education associated with less precision) on timing precision on cross-sectional analysis (see Table 1). Further analyses of possible interaction effects (age-by-gene status and education-by-gene status) were non-

significant, suggesting that age and education contribute approximately equally to timing precision in pr-HD and NC participants. History of limb pain, injury, and arthritis were not significantly associated with timing performance for either pr-HD or NC participants (although the incidence of these was low). In contrast, prior musical and typing experience were strongly related to timing ($p < .0001$, and $p = .02$ respectively) after controlling for all other covariates. We emphasize, however, that the adjustment for these demographic and experience covariates did not substantially alter the strength of association between estimated probability of diagnosis and timing precision. The incidence of these covariates was evenly spread among the various stages of disease progression and our ability to detect the relationship between estimated proximity to diagnosis and cognitive performance was not diminished by a confounding of covariates with disease progression.

The longitudinal analysis of these participants revealed a similar pattern of results. As pr-HD participants approached their estimated time of diagnosis, their timing precision was decreased. This may be noted in a simple comparison of mean annual change between pr-HD and NC participants (dominant hand: df = 417, $t = -2.85$, $p < .01$; alternating thumbs: df = 445, $t = -3.56$, $p < .001$). Pr-HD participants worsened at the task annually while the NC group did not.

Longitudinal analysis comparing performance of various pr-HD groups over time revealed some interesting patterns. First, analysis of the overall effect of groups yielded a significant result (dominant hand condition: $F_{(4,424)} = 4.25$, $p < .01$; alternating-thumbs condition: $F_{(4,434)} = 8.79$, $p = <.0001$). Next, analyzing the trends within different groups, it was noted that pr-HD participants' task performance tended to deteriorate at a faster rate as they approached diagnosis (dominant hand condition: $F_{(1,359)} = 6.15$, $p = .01$; alternating thumbs condition: $F_{(1,375)} = 14.31$, $p = .0002$). For an in-depth breakdown of change scores and effect sizes across groups see Table 2. Effect sizes were calculated based on adjusted mean annual change, and they reveal slightly greater sensitivity in the alternating thumbs condition as compared with the dominant hand condition. It was noted that NC and far-from-diagnosis pr-HD participants tended to improve slightly on the task annually, while the midway-to-diagnosis, near-to-diagnosis, and diagnosed participants tended to worsen annually. The improvement in the NC and pr-HD far groups may reflect a practice effect on the task which is not observed in participants with higher estimated probability of diagnosis. Analysis comparing groups reveals significant performance difference in NC participants compared to pr-HD mid (dominant hand: $p = .02$, alternating thumbs: $p = <.0001$), pr-HD near (dominant hand: $p < .001$, alternating thumbs: $p < .0001$), and diagnosed HD groups (dominant hand: $p < .001$, alternating thumbs: $p = <.0001$), though NC participants do not differ from pr-HD far group (dominant hand: $p = .12$, alternating thumbs: $p = .25$).

Analysis of covariates showed fewer significant effects than in the cross-sectional analysis. In the dominant hand index finger tapping condition, there were significant effects of gender ($t = 2.3$, $p = .02$) and prior musical experience ($t = 2.02$, $p = .04$), though these effects were non-significant in the alternating-thumbs tapping condition. This finding may suggest that longitudinal change in the alternating-thumbs condition is more robust to individual variation than the dominant hand index finger tapping condition. Alternatively, the advantage of the alternating thumbs over the dominant index finger condition could reflect components of the order of task completion since alternating thumbs was administered after the dominant hand index finger condition and performances may have been impacted by fatigue and/or practice. However, when controlling for all above-mentioned covariates, the effect of group (proximity to diagnosis) is still significant in both conditions.

In addition, there is some literature to suggest a significant effect of drift in self-paced tapping tasks. That is, the overall speed of tapping might change systematically over the self-paced

portion of the individual tapping blocks. In additional analyses, not presented here in detail, we found no evidence of systematic differences among pr-HD groups and NC participants with respect to drift.

Discussion

Consistent with previous work (Hinton et al., 2007; Paulsen et al., 2008; Zimbelman et al., 2007), precision of self-paced timing was significantly poorer in pr-HD individuals compared to NC individuals. In addition, findings suggest that precision on the self-paced timing task is associated with increased proximity to manifest motor disease in pr-HD. That is, participants with poorer timing precision had a greater probability of diagnosis over the next five years. Importantly, the robust association between timing precision and probability of HD diagnosis remains after considering demographic variables (age, education, gender) and experience variables (music, typing), which were not considered in the previous studies. Furthermore, this finding remains robust when examined longitudinally and comparing mean annual change in self paced timing performance.

The association between increased five-year diagnostic probability and decreased precision in self-paced timing (manifested as increased variability in inter-tap intervals) demonstrates the sensitivity of self-paced tapping to subtle pre-diagnostic changes in function (see Figure 1). This finding is important to clinical trials in pr-HD for several reasons. First, the self-paced timing task may be an effective screening tool for clinical trials in order to enroll participants who have measurable deviation from expected performance. Identification of measurable changes prior to diagnosis may be prerequisite for detecting any slowing or halting of HD-related deterioration that could potentially result from treatment. Second, given the task's sensitivity (e.g. participants with relatively low probabilities of diagnosis demonstrate differences in timing performance compared to NC participants), self-paced timing could serve as a salient outcome measure in the many stages of pr-HD. Third, it may be possible (with further research) to construct therapeutics targeted to a particular phase of the prodromal syndrome. In that case, it will be critical that comparisons across groups of prodromal participants take into account the potentially varying degrees of dysfunction that may exist prior to neurological (motor) diagnosis. The self-paced timing task may prove useful in quantifying that dysfunction.

Another factor considered in previous studies of timing tasks is the effect of aging. Prior reports have failed to reveal statistically significant differences among adults at various stages of normal aging on timing tasks, though a trend of increasing variability has been observed in some studies (Duchek, Balota, & Ferraro, 1994; Greene & Williams, 1993). While it is notable that our findings suggest a weak but statistically significant effect of age on self-paced timing precision, it remains unclear whether the effect accurately reflects "normal aging" or rather some remnant of HD progression not perfectly controlled by the role assigned to age in estimating "probability of diagnosis." Though inconclusive, the finding of an age trend on self-paced timing precision may be important to bear in mind when planning comparisons of neurological disease cohorts of different ages.

The root cause of impaired timing precision (variability of inter-tap interval) in the face of intact timing accuracy (mean inter-tap interval) remains unclear. It may be that timing precision requires more complex feedback between the basal ganglia and the motor cortices involved in producing the required movements, whereas the mere maintenance of a given mean inter-tap interval may be somewhat more simple and resilient to the subtle impairments noted at the very earliest stages of Huntington disease. Impairment of both timing precision and accuracy has been reported in individuals with diagnosed Parkinson disease (O'Boyle, Freeman & Cody, 1996). Given that finding and the significant effect of aging observed in the current study, it

is possible that the pr-HD sample in the current study was too young and/or not yet severely affected enough as a group to show impaired timing accuracy.

While this study includes the largest sample of pr-HD participants ever tested, it has some limitations associated with the demographics of the sample. The PREDICT-HD study recruits participants heavily from the United States, Canada, Europe, and Australia, resulting in a Caucasian bias in sampling. The participants recruited are predominantly women, married, and middle-aged. This demographic combination could have a relationship with task performance, so further study in a sub-population of participants with varying backgrounds could potentially reveal a slightly different performance pattern. Systematic differences between HD-expanded gene carriers who do and do not elect to undergo genetic testing and volunteer for research may also limit generalizability to the HD gene carrier population as a whole. In addition, there was a technical constraint on the order of administration of the two conditions of the self-paced timing task. The dominant hand index finger condition always preceded the alternating-thumbs condition, suggesting the possibility that the slightly poorer performance of the pr-HD participants on the later condition reflected poorer procedural learning, rather than reflecting greater sensitivity of that condition to HD-related deficits in timing.

Further analysis of the self-paced timing portion of the finger tapping task is warranted as theoretical modeling has suggested disparate roles of a central timekeeping mechanism and a motor execution mechanism. For example, Wing and Kristofferson (1973) posit that these mechanisms can be separate sources of variability in timing tasks and can be related to dysfunction in different brain regions. The model has been applied to some studies of Parkinson's disease (Duchek et al., 1994; Harrington & Haaland, 1998; Harrington, Haaland, & Hermanowicz, 1998; O'Boyle, Freeman, & Cody, 1996) and cerebellar lesions patients (Ivry, Keele, & Diener, 1988). These analyses have suggested separate roles of the affected areas; erroneous central timekeeping was observed in the patients with dysfunctional basal ganglia and greater motor implementation error was noted in the patients with cerebellar atrophy. The study of central timekeeping will benefit from a forthcoming detailed analysis of PREDICT-HD data, tracking central timekeeper performance in relation to basal ganglia degeneration as patients approach motor diagnosis. Additionally, consideration of structural imaging data in pr-HD participants would shed further light on how self-paced timing performance in HD is related to the integrity of the basal ganglia and other disease-associated structures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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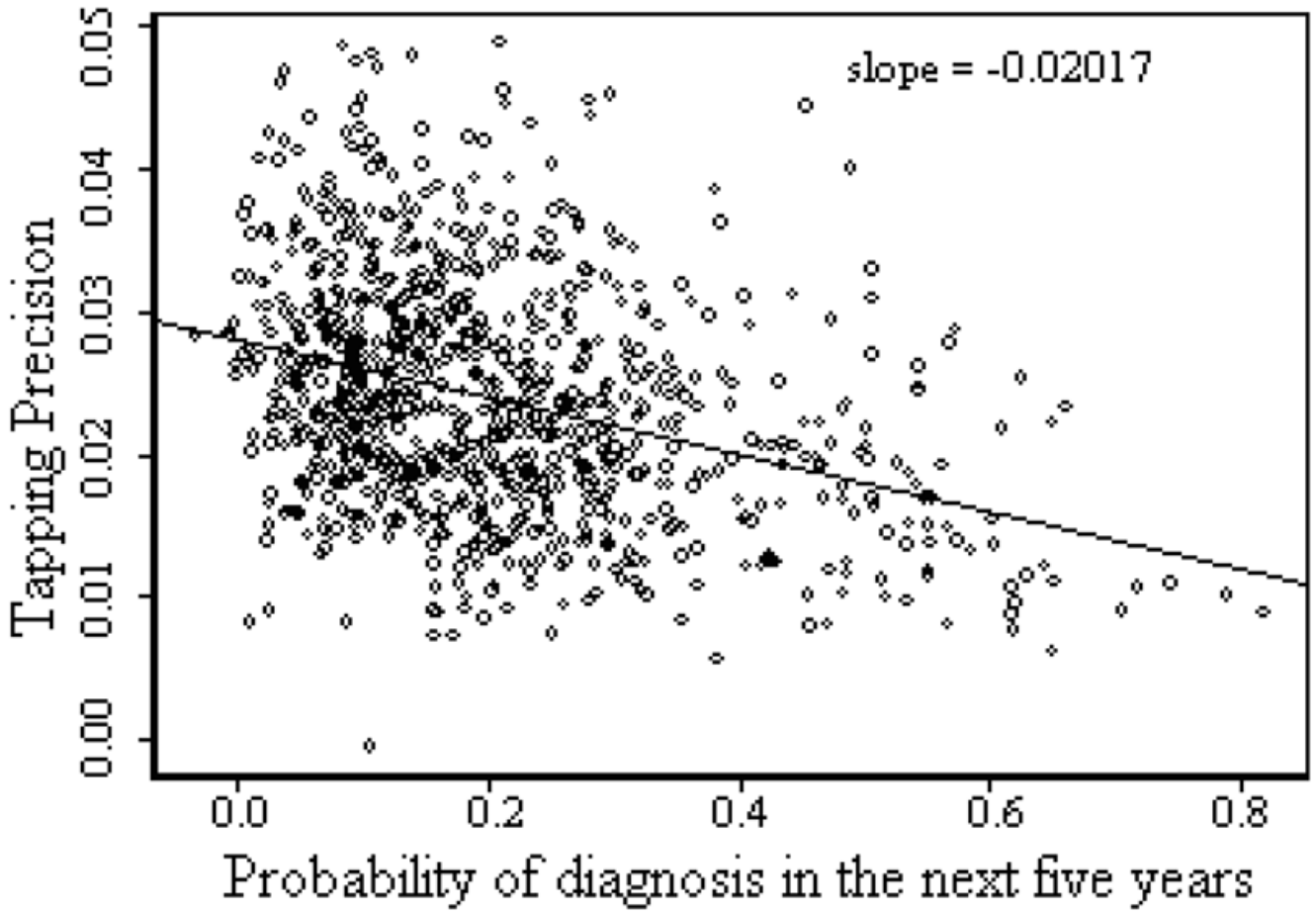

Figure 1.
Effect of probability of 5-year diagnosis vs. timing precision
Note. Precision is the reciprocal of standard deviation of mean inter-tap interval during the alternating thumbs self-paced tapping task in pr-HD participants. The model controlled for effects of gender, age, education, gene status, music, and typing experience. Table shows decreasing self-paced tapping precision as pr-HD participants approach diagnosis. In this graph, precision is centered at the group mean.

Table 1

Predictors in standardized cross-sectional linear model comparing "alternating-thumbs" self-paced timing precision between pr-HD and NC participants.

Dominant Hand Index Finger Tapping Condition					
Predictor Variable	**Estimate**	**SE**	***t***	***p***	**Comment**
Probability of 5- year diagnosis	*−23.12	*2.07	−11.14	<.0001	Less precision when 5-year diagnosis is more likely.
Gender	*−4.19	*0.63	−6.68	<.0001	Less precision in women than men
Age (decades)	*1.64	*0.31	5.22	<.0001	Less precision with increased age.
Education (years)	*0.25	*0.11	2.28	.02	Less precision with lower education.
Music Experience	*4.57	*0.93	4.92	<.0001	More precision with more musical experience.
Typing Experience	*0.62	*0.66	0.95	.34	Non-significant trend
Gene Status (pr-HD vs. NC)	*0.13	*0.87	0.15	.88	No fundamental performance difference between pr-HD very far from onset (prob 5-year ≈ 0) and NC participants.
Alternating-Thumbs Tapping Condition					
Predictor Variable	**Estimate**	**SE**	***t***	***p***	**Comment**
Probability of 5- year diagnosis	*−20.33	*1.80	−11.32	<.0001	Less precision when 5-year diagnosis is more likely.
Gender	*−2.04	* 0.54	−3.76	<.001	Less precision in women than men
Age (decades)	*0.85	*0.27	3.12	<.01	Less precision with increased age.
Education (years)	*0.57	*0.10	5.91	<.0001	Less precision with lower education.
Music Experience	*4.86	*0.80	6.07	<.0001	More precision with more musical experience.
Typing Experience	*1.30	*0.06	2.28	.02	More precision with more typing experience.
Gene Status (pr- HD vs. NC)	*−0.55	*0.75	−0.73	.47	No fundamental performance difference between pr-HD very far from onset (prob 5-year ≈ 0) and NC participants.

*All Estimates and Standard Errors × 10^{-3}

Note. Total model: dominant hand condition R^2 = .22, alternating-thumbs condition R^2 = .26. Comparison of pr-HD vs NC participant: dominant hand: $t = -6.24$, p = <.0001; alternating-thumbs: $t = -7.42$, p < .0001, based on definition of gene-expanded 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, music experience defined as "extensive musical training or performance experience," typing experience defined as "experience as a typist." Model outcome variable "precision" is defined as the reciprocal of standard deviation of mean inter-tap interval. These models controlled for fixed effects (music and typing). Effect of collecting data at various sites is non-significant and so is not included in the model. Degrees of freedom = 889 for dominant hand index finger block, 887 for alternating thumbs block.

Table 2

Longitudinal Analysis:

Dominant Hand Condition Least Squares Means				Alternating-Thumbs Condition Least Squares Means			
Group	**Estimate**	**Standard Error**	**Effect Size**	**Group**	**Estimate**	**Standard Error**	**Effect Size**
NC	*0.95	*0.36	0.25	NC	*0.60	*0.24	0.22
Pr-HD Far	*0.25	*0.28	0.07	Pr-HD Far	*0.25	*0.19	0.09
Pr-HD Mid	*−0.08	*0.26	−0.02	Pr-HD Mid	*−0.57	*0.17	−0.21
Pr-HD Near	*−0.63	*0.29	−0.17	Pr-HD Near	*−0.70	*0.20	−0.26
HD Diagnosed	*−0.75	*0.36	−0.20	HD Diagnosed	*−0.92	*0.24	−0.34

*All Estimates and Standard Errors × 10^{-3}

Note: In Dominant Hand condition, Group $F_{(4,424)} = 4.25$, $p < .01$. Trend test excluding NC participants F = 6.15, $p = .01$. In Alternating-Thumbs Condition, Group F = 8.79, $p = <.0001$. Trend test excluding NC participants $F_{(1,359)} = 14.31$, $p < .001$. Analyses comparing groups reveals a significant performance difference in NC participants compared to pr-HD mid, pr-HD near, and HD diagnosed groups, though comparisons do not significantly differ from pr-HD far group. Effect of collecting data at various sites is non-significant and so is not included in the model. Model controls for baseline age, gender, education, music and typing experience. Groups defined based on Langbehn (2004) formula using CAG repeat length and current age to estimate proximity to diagnosis as follows: pr-HD far from diagnosis = 15+ years, pr-HD midway from diagnosis = 9–15 years, pr-HD near to diagnosis = <9 years. Age and education measured in years. Music experience defined as “extensive musical training or performance experience,” typing experience defined as “experience as a typist.” Model outcome variable is mean annual change in precision, where precision is modeled as reciprocal of standard deviation of mean inter-tap interval on the self-paced timing tasks. Effect size reflects longitudinal change based on adjusted mean annual change.