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BRIEF COMMUNICATION

Motor timing variability increases in preclinical Huntington's disease patients as estimated onset of motor symptoms approaches

SEAN C. HINTON,[1] JANE S. PAULSEN,[2] RAYMOND G. HOFFMANN,[3] NORMAN C. REYNOLDS,[1] JANICE L. ZIMBELMAN,[1] AND STEPHEN M. RAO[1]

[1]Department of Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin
[2]Departments of Psychiatry and Neurology, University of Iowa, Iowa City, Iowa
[3]Division of Biostatistics, Medical College of Wisconsin, Milwaukee, Wisconsin

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Abstract

Huntington's disease (HD) is a neurodegenerative disorder diagnosed clinically with the development of choreiform movements. However, neuropsychological studies have demonstrated cognitive and psychiatric changes during the preclinical phase (pre-HD) prior to formal diagnosis. Previous studies have demonstrated the sensitivity of time reproduction tasks to basal ganglia pathology, as seen in clinical HD and Parkinson's disease. In this study, 29 pre-HD participants, ranging from 3 to 39 years from estimated onset (YEO) of HD based on genetic testing and chronological age, were administered the paced finger-tapping task using target intervals of 600 and 1200 ms. Mean inter-response interval, a measure of timing accuracy, did not systematically deviate from the target interval as a function of YEO. In contrast, timing variability increased curvilinearly as a function of YEO, but not with chronological age alone. Motor timing variability, but not accuracy, may serve as a marker to define the earliest behavioral changes in HD. The present study is among the first to examine the relationship between behavioral measures and YEO in pre-HD. (*JINS*, 2007, *13*, 539–543.)

Keywords: Psychology, Neurodegenerative diseases, Movement disorders, Cognition disorders, Basal ganglia diseases, Psychomotor performance, Sensory motor performance, Task performance and analysis, Auditory perception, Time perception

INTRODUCTION

Huntington's disease (HD) is an autosomal-dominant, neurodegenerative disorder resulting from expansion of the trinucleotide CAG repeat in the gene encoding the protein huntingtin. The defect leads to degeneration of basal ganglia structures, primarily the caudate and putamen, although the exact pathophysiologic mechanism is not well understood. HD is diagnosed clinically with the onset of motor symptoms; however, varied and subtle neuropsychological deficits may appear a decade or more prior to diagnosis during the preclinical (pre-HD) phase (Paulsen et al., 2004). These deficits become more pronounced as individuals approach conversion to manifest HD (Paulsen et al., 2001, 2004), as determined by the participants' current age and CAG repeat length (Langbehn et al., 2004).

Measures of timing behaviors could serve as sensitive markers of neurobehavioral dysfunction in pre-HD participants. Impairments on perceptual and motor timing tasks have been noted previously in patients with Parkinson's disease (Elsinger et al., 2003; Harrington et al., 1998) and with manifest HD (Woodruff-Pak & Papka, 1996). The basal ganglia are known to play an important role in timing behaviors based on lesion studies in patients (Harrington & Haaland, 1999) as well functional neuroimaging studies involving healthy adults (Rao et al., 1997, 2001).

In the current study, we administered the paced finger-tapping task (PFT), a measure of motor timing, to pre-HD

Correspondence and reprint requests to: Stephen M. Rao, Ph.D., Medical College of Wisconsin, 8701 Watertown Plank Road, MEB 4530, Milwaukee, WI 53226, USA. E-mail: srao@mcw.edu

participants. The PFT requires that participants tap their finger to an auditory metronome and then continue tapping without the benefit of the pacing stimulus. The PFT has not been studied previously in pre-HD participants. Our goal was to correlate PFT performance with the number of estimated years to manifest HD. We hypothesized that PFT performance would show increased disruption as the number of years to manifest HD decreases.

METHODS

A total of 29 pre-HD adults (10 men; mean age = 32.1 years; range, 18–52) participated according to Medical College of Wisconsin Institutional Review Board guidelines. Years from estimated onset (YEO) of motor symptoms was calculated using a survival formula based on chronological age and CAG repeat length (Langbehn et al., 2004). Motor symptoms were assessed using the Motor Assessment portion of the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996).

The PFT began with a 30-s synchronization phase (Sync), in which participants pressed a key with their index finger in synchrony with an auditory pacing tone (50 ms, 380 Hz). This phase was immediately followed by a 30-s continuation phase (Cont), in which they were asked to continue tapping at the same rate without the pacing tone. Sync and Cont phases were followed by an 18-s Rest phase, each of which was designated using visual cues and together composed a single trial. In a block consisting of five trials, participants performed one of two isochronous pacing intervals (600- or 1200-ms stimulus onset asynchrony; SOA). Each participant performed each pacing interval with each hand, starting with the right (dominant) hand for the first two blocks and with order of pacing interval randomized across participants. The data we report here include only those performed with the right hand. Auditory stimuli were presented and response times collected using custom software. A key-press device recorded participants' responses.

Accuracy was defined as the deviation in the mean interresponse interval (IRI) from the target tapping interval (600 or 1200 ms); variability was defined as the standard deviation (*SD*) of the IRI. IRIs more than 50% shorter or longer than the target duration were excluded from further analyses. Such exclusions occurred on approximately 3.6% of key presses; however, 91% were explainable by subjects not fully depressing the response key.

A multiple regression analysis was performed between the eight behavioral indices (accuracy and variability for the 600- and 1200-ms Sync and Cont conditions) *versus* chronological age and YEO. A p value of .05 was used to define statistically significant linear and quadratic relationships. The data had a strong curvilinear effect with years of onset when originally graphed. This effect was modeled with a linear term and a quadratic term that was orthogonal to the linear term; thus, the quadratic term only tested whether there was curvature in addition to the linear trend. The tests of whether age or motor score added to or explained the relationship used a single multiple regression model; this strategy not only tested whether age and motor score added to the factor of YEO, but simultaneously tested whether the linear and quadratic terms of YEO were explained by age or motor score. In addition, a multivariate analyses of the variance (MANCOVA) was used to validate the models taking into account the correlation among the timing outcomes. In every case, the linear and quadratic YEO terms were statistically significant (at p values from .033 to .002). Multiple-testing corrections are sometimes made when large numbers of factors, interactions, and so on are used in a model-building process; however, they are not used when testing hypothesis-driven analyses, such as whether poor motor scores explain the increased motor variability as a function of YEO. Residual analysis was used to evaluate any abnormalities in the modeling of the data.

RESULTS

UHDRS motor scores were obtained for 28 of the 29 participants and are listed in Table 1 with YEO and age for

Table 1. YEO, age, and UHDRS motor score for each of the 28 pre-HD participants

YEO	Age (years)	Motor score
3.2	28	4
5.2	28	11
5.3	41	0
7.2	22	0
9.0	25	1
9.4	25	0
9.4	36	2
10.1	35	1
10.4	37	2
10.4	52	3
14.1	51	1
14.7	24	0
15.2	21	2
16.3	32	0
17.3	33	2
19.5	44	5
19.6	26	0
22.2	36	0
23.0	31	2
23.7	20	1
25.2	38	0
25.4	28	0
25.6	18	0
26.4	26	0
27.1	21	0
30.2	32	0
31.3	39	0
39.9	38	1
17.72 +/− 9.24	31.7 +/− 8.9	1.4 +/− 2.3

Note. The maximum possible UHDRS motor score is 128. The last row shows means for each variable plus or minus standard deviation. YEO = years from estimated onset; UHDRS = Unified Huntington's Disease Rating Scale; HD = Huntington's disease.

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Table 2. Adding motor score as a factor in the regression model

	600-ms Sync	600-ms Cont	1200-ms Sync	1200-ms Cont
R^2 for age (p value)	.033 (.35)	.07 (.17)	.027 (.41)	.076 (.19)
R^2 for YEO (p value)	.672 (<.0001)	.586 (<.0001)	.720 (<.0001)	.658 (<.0001)
R^2 for YEO adj. age (p value)	.619 (<.0001)	.624 (<.0001)	.682 (<.0001)	.565 (<.0001)

Note. A model including age and age-squared is not significantly different from the model that only includes age (all $p > 0.05$). Sync = synchronization phase; Cont = continuation phase; YEO = years from estimated onset.

each individual. Motor scores were not correlated with chronological age ($y = 0.54x + 30.95$, $r^2 = .02$), but they were negatively correlated with YEO ($y = -1.58x + 19.86$, $r^2 = .16$). Motor scores positively correlated with performance on the 600-ms Sync and 1200-ms Sync conditions ($y = 3.47x + 40.08$, $r^2 = .28$; and $y = 10.78x + 71.86$, $r^2 = .36$, respectively), but not with the 600-ms or 1200-ms Cont conditions ($r^2 = .11$ and .08, respectively).

Adding motor score as a factor in the regression model only significantly improved the fit for the 1200-ms Sync condition ($p < .01$). This effect was carried by the two participants with high motor scores (motor score = 11, YEO = 5.2; motor score = 5, YEO = 19.5; Table 2).

Scatterplots in Figure 1 demonstrate that chronological age did not correlate with measures of variability for the 600-ms Sync, 600-ms Cont, 1200-ms Sync, or 1200-ms Cont conditions. In contrast, Figure 2 demonstrates that variability generally increased as YEO decreased ($p < .05$). The increases were curvilinear except for the 600-ms Cont condition, in which the increase was linear.

With one exception, no statistically significant correlations were observed between accuracy and either chronological age or YEO. For the 1200-ms Sync condition, participants closer to diagnosis were less accurate, characterized by longer mean IRI, than those farther from diagnosis ($r = -0.32$, $p < .05$).

Because the timing outcomes are correlated, a MANCOVA on the variability in the four timing outcomes with YEO was used to test the overall relationship. The MANCOVA was significant both for the linear term ($p < .0065$) and the quadratic term ($p < .016$). After adjusting for motor score, both terms were still significant ($p < .029$ and $p < .034$, respectively). Residual analysis confirmed the choice of the models as being appropriate because neither abnormal residuals nor abnormal patterns in the residuals were observed.

DISCUSSION

Our data confirmed that chronological age alone is not a strong predictor of PFT performance in pre-HD participants. In contrast, YEO, which incorporates both CAG trinucleotide repeat length and chronological age as predictors (Langbehn et al., 2004), was significantly related to PFT

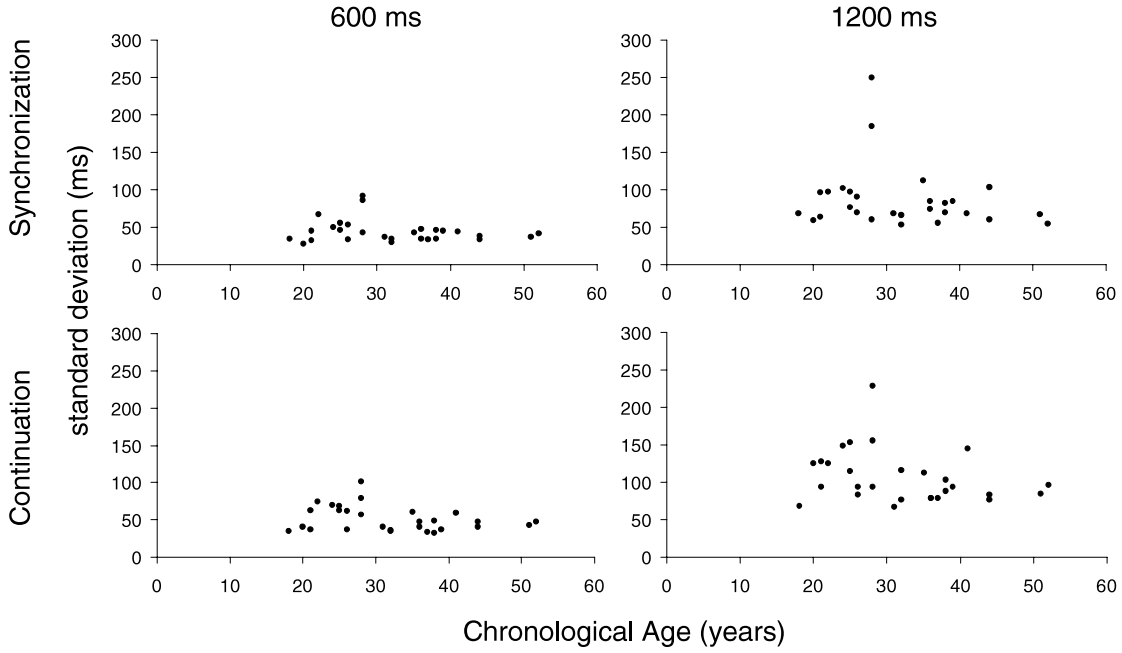

Fig. 1. Motor timing variability [standard deviation of the inter-response interval (IRI)] plotted as a function of age. Data are presented for the synchronization and continuation phases for the 600- and 1200-ms interstimulus intervals (ISIs).

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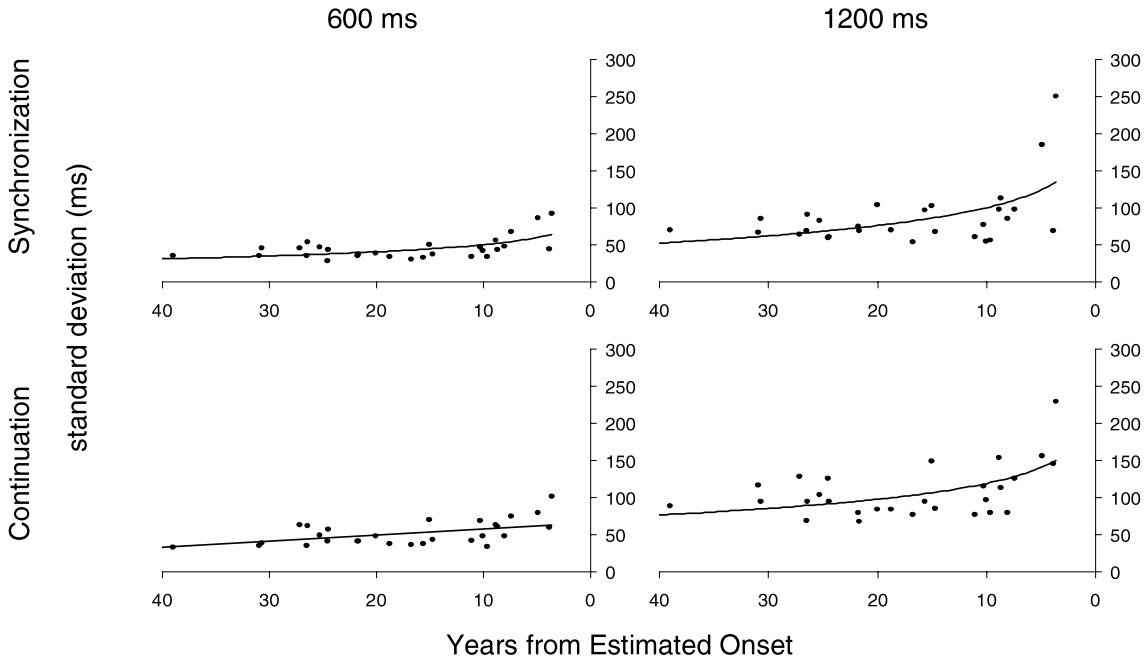

Fig. 2. Motor timing variability [standard deviation of the inter-response interval (IRI)] plotted as a function of years from estimated onset (YEO) of motor symptoms. Data are presented for the synchronization and continuation phases for the 600- and 1200-ms interstimulus intervals (ISIs). Significant linear and nonlinear regressions are indicated with trend lines ($p < .05$).

performance. Specifically, we observed increased PFT variability as YEO decreased. This pattern was found for the Sync and Cont phases at both the 600- and 1200-ms tapping intervals. The relationships were mostly curvilinear, suggesting that PFT variability increases at an accelerating rate as YEO decreases. In contrast, PFT accuracy was not strongly related to age or YEO. Motor score was added as a factor to the curvilinear model of performance as a function of YEO. This modification only improved the fit for the 1200-ms Sync condition, suggesting that these effects are more properly characterized as specific timing deficits rather than being attributable to motor difficulties.

Various other studies have examined presymptomatic gene carriers as a group or have examined structural measures as a function of YEO (e.g., Aylward et al., 1996, 2000, 2004; Campodonico et al., 1998). However, to our knowledge, this report is among the first studies to examine behavioral measures in pre-HD as a function of YEO, although another study's findings have suggested this relationship (Paulsen et al., 2001). This study contributes additional evidence that PFT variability can be a sensitive gauge of impaired basal ganglia function. These findings complement our previous study in patients with Parkinson's disease (Elsinger et al., 2003), in which PFT variability was significantly greater than in controls. Our results also provide support for the view that timing behaviors are more generally disrupted in pre-HD participants. In a previous study, we demonstrated that a similar group of pre-HD participants less than 12 YEO were impaired on a time-discrimination task relative to healthy controls (Paulsen et al., 2004).

While the present cross-sectional study has demonstrated that increased PFT variability may serve as a sensitive index of basal ganglia dysfunction, future studies are needed to determine whether PFT variability is also sensitive to longitudinal changes in pre-HD participants. If this connection were to be established, PFT variability could serve as a reliable preclinical marker for determining the optimal time for initiating neuroprotective treatment meant to forestall or prevent clinical HD onset (Hersch & Rosas, 2001) and for measuring therapeutic efficacy in the context of a clinical trial (Paulsen et al., 2006).

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REFERENCES

Aylward, E.H., Codori, A.M., Rosenblatt, A., Sherr, M., Brandt, J., Stine, O.C., Barta, P.E., Pearlson, G.D., & Ross, C.A. (2000). Rate of caudate atrophy in presymptomatic and symptomatic stages of Huntington's disease. *Movement Disorders*, *15*, 552–560.

Aylward, E.H., Reiss, A.L., Reader, M.J., Singer, H.S., Brown, J.E., & Denckla, M.B. (1996). Basal ganglia volumes in chil-

https://doi.org/10.1017/S1355617707070671 Published online by Cambridge University Press

dren with attention-deficit hyperactivity disorder. *Journal of Child Neurology*, *11*, 112–115.

Aylward, E.H., Sparks, B.F., Field, K.M., Yallapragada, V., Shpritz, B.D., Rosenblatt, A., Brandt, J., Gourley, L.M., Liang, K., Zhou, H., Margolis, R.L., & Ross, C.A. (2004). Onset and rate of striatal atrophy in preclinical Huntington disease. *Neurology*, *63*, 66–72.

Campodonico, J.R., Aylward, E., Codori, A.M., Young, C., Krafft, L., Magdalinski, M., Ranen, N., Slavney, P.R., & Brandt, J. (1998). When does Huntington's disease begin? *Journal of the International Neuropsychological Society*, *4*, 467–473.

Elsinger, C.L., Rao, S.M., Zimbelman, J.L., Reynolds, N.C., Blindauer, K.A., & Hoffmann, R.G. (2003). Neural basis for impaired time reproduction in Parkinson's disease: An fMRI study. *Journal of the International Neuropsychological Society*, *9*, 1088–1098.

Harrington, D.L. & Haaland, K.Y. (1999). Neural underpinnings of temporal processing: A review of focal lesion, pharmacological, and functional imaging research. *Reviews in the Neurosciences*, *10*, 91–116.

Harrington, D.L., Haaland, K.Y., & Hermanowicz, N. (1998). Temporal processing in the basal ganglia. *Neuropsychology*, *12*, 3–12.

Hersch, S.M. & Rosas, H.D. (2001). Neuroprotective therapy for Huntington's disease: New prospects and challenges. *Expert Review of Neurotherapeutics*, *1*, 111–118.

Huntington Study Group (1996). Unified Huntington's Disease Rating Scale: Reliability and consistency. *Movement Disorders*, *11*, 136–142.

Langbehn, D.R., Brinkman, R.R., Falush, D., Paulsen, J.S., Hayden, M.R., & International Huntington's Disease Collaborative Group. (2004). A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clinical Genetics*, *65*, 267–277.

Paulsen, J.S., Hayden, M., Stout, J.C., Langbehn, D.R., Aylward, E., Ross, C.A., Guttman, M., Nance, M., Kieburtz, K., Oakes, D., Shoulson, I., Kayson, E., Johnson, S., Penziner, E., & the Predict-HD Investigators of the Huntington Study Group (2006). Preparing for preventive clinical trials: The Predict-HD study. *Archives of Neurology*, *63*, 883–890.

Paulsen, J.S., Zhao, H., Stout, J.C., Brinkman, R.R., Guttman, M., Ross, C.A., Como, P., Manning, C., Hayden, M.R., & Shoulson, I. (2001). Clinical markers of early disease in persons near onset of Huntington's disease. *Neurology*, *57*, 658–662.

Paulsen, J.S., Zimbelman, J.L., Hinton, S.C., Langbehn, D.R., Leveroni, C.L., Benjamin, M.L., Reynolds, N.C., & Rao, S.M. (2004). fMRI biomarker of early neuronal dysfunction in presymptomatic Huntington's disease. *American Journal of Neuroradiology*, *25*, 1715–1721.

Rao, S.M., Harrington, D.L., Haaland, K.Y., Bobholz, J.A., Cox, R.W., & Binder, J.R. (1997). Distributed neural systems underlying the timing of movements. *Journal of Neuroscience*, *17*, 5528–5535.

Rao, S.M., Mayer, A.R., & Harrington, D.L. (2001). The evolution of brain activation during temporal processing. *Nature Neuroscience*, *4*, 317–323.

Woodruff-Pak, D.S. & Papka, M. (1996). Huntington's disease and eyeblink classical conditioning: Normal learning but abnormal timing. *Journal of the International Neuropsychological Society*, *2*, 323–334.