Published in final edited form as:

Mov Disord. 2009 March 15; 24(4): 533–540. doi:10.1002/mds.22329.

Visual Scanning and Cognitive Performance in Prediagnostic and Early-Stage Huntington's Disease

Tanya Blekher, PhD^{1,*}, Marjorie R. Weaver, MS², Jeanine Marshall, BS², Siu Hui, PhD³, Jacqueline Gray Jackson, BS², Julie C. Stout, PhD^{4,5}, Xabier Beristain, MD⁶, Joanne Wojcieszek, MD⁶, Robert D. Yee, MD¹, and Tatiana M. Foroud, PhD²

¹Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana, USA

²Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA

³Department of Medicine, Division of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana, USA

⁴Department of Psychological and Brain Sciences, Indiana University, Bloomington, Indiana, USA

⁵School of Psychology, Psychiatry, and Psychological Medicine, Monash University, Clayton, Victoria, Australia

⁶Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA

Abstract

The objective of this study was to evaluate visual scanning strategies in carriers of the Huntington disease (HD) gene expansion and to test whether there is an association between measures of visual scanning and cognitive performance. The study sample included control (NC, n = 23), prediagnostic (PDHD, n = 21), and subjects recently diagnosed with HD (HD, n = 19). All participants completed a uniform clinical evaluation that included examination by neurologist and molecular testing. Eye movements were recorded during completion of the Digit Symbol Subscale (DS) test. Quantitative measures of the subject's visual scanning were evaluated using joint analysis of eye movements and performance on the DS test. All participants employed a simple visual scanning strategy when completing the DS test. There was a significant group effect and a linear trend of decreasing frequency and regularity of visual scanning from NC to PDHD to HD. The performance of all groups improved slightly and in a parallel fashion across the duration of the DS test. There was a strong correlation between visual scanning measures and the DS cognitive scores. While all individuals employed a similar visual scanning strategy, the visual scanning measures grew progressively worse from NC to PDHD to HD. The deficits in visual scanning accounted, at least in part, for the decrease in the DS score. © 2008 Movement Disorder Society

Keywords

eye movement; Huntington's disease; digit symbol subscale; visual scanning; cognitive performance

Huntington's disease (HD) is a neurodegenerative disorder resulting from an increased number of triplet (CAG) repeats in the *huntingtin* gene.¹ The disease manifests typically in middle age

with a triad of progressive motor, cognitive, and psychological symptoms. Neurodegeneration in the striatum has historically been the focus of neuropathological² and neuro-imaging^{3,4} studies; however, recent reports show the presence of abnormalities throughout the cerebrum, including cortical thinning⁵ and decreased white matter volumes^{6–8} especially in the prefrontal cortex.⁹

Although many studies have demonstrated unequivocally that both cognitive^{10–14} and oculomotor control^{15,16} declines occur prior to the clinical diagnosis of HD, there has been little direct investigation of the potential interactions of these changes. Because volitional saccades show deficits in prediagnostic HD, the decline in performance on cognitive tests may be due, at least in part, to the impairment of eye movements. The converse, i.e. the impairment of eye movement due to the decline in cognitive performance, is also possible.

A number of studies that have recorded eye movements during cognitively demanding tasks have found that particular activities are associated with specialized gaze-shifting patterns.^{17–19} We previously reported results from a small sample of prediagnostic and early HD individuals²⁰ that demonstrated a consistent eye-shifting pattern which occurred while the subjects completed the Digit Symbol Subscale of the Wechsler Adult Intelligence Survey-Revised (DS).²¹ The DS test is a widely used neuropsychological test employed to assess cognitive performance in individuals with Alzheimer's disease, Attention-Deficit/Hyperactivity Disorder, stroke, and other neurological disorders. The DS test also has high sensitivity in prediagnostic and early-stage HD.^{11,12}

We designed the current study to dissect the visual scanning strategy employed by individuals when they completed the DS test and to quantify measures of the strategy. We developed a novel approach, in which we recorded eye movements while the subjects completed the DS test, used the Fourier analysis method to analyze the visual scanning, and correlated the measures of scanning with cognitive scores on the DS test. We applied this approach to evaluate the relationship between oculomotor control and cognitive impairments in prediagnostic and early HD subjects. The results of our study show that this novel approach can be used successfully to dissect areas of deficit in the CAG-expanded individuals.

SUBJECTS AND METHODS

Participants were part of ongoing studies of individuals at-risk for HD being completed at Indiana University. Inclusion criteria included the following: (1) a parent affected with HD; (2) not diagnosed, or having received a diagnosis of HD within the past 2 years; (3) normal or corrected visual acuity; (4) no history of eye surgery; and (5) no current significant eye-related complaints. The study included questionnaires designed to collect medical history, current medications, substance use history, and visual health information. Potential subjects were excluded if they had a neurological illness other than HD and/or self-reported current alcohol or drug abuse. For CAG determination, DNA was extracted from either a blood sample or a buccal swab using standard inorganic methods.²² A polymerase chain reaction-based test was performed to determine the number of CAG repeats in the *huntingtin* gene.²³

The participants were asked not to disclose their gene status, if known, to study staff to ensure that the individuals administering the study protocol were blind to gene status. This study was approved by the local institutional review board (IUPUI IRB Study No. 0109–12) and all participants provided written informed consent.

The Unified Huntington's Disease Rating Scale (UHDRS)²⁴ was completed for all participants. An experienced movement disorder neurologist administered the motor portion of the UHDRS. As part of this examination, the neurologist assigned a rating to indicate her/his confidence that the motor signs observed on the examination were indicative of HD: (0) no abnormalities,

(1) nonspecific motor abnormalities (less than 50% confidence), (2) motor abnormalities that may be signs of HD (50–89% confidence), (3) motor abnormalities that are likely signs of HD (90–98% confidence), and (4) motor abnormalities that are unequivocal signs of HD ($\geq 99\%$ confidence).

Normal controls (NC; $n = 23$) were defined as those individuals having two unexpanded HD alleles (≤ 27 CAG repeats). Subjects with at least one expanded HD allele (≥ 38 CAG repeats) were considered CAG-expanded ($n = 40$). Those CAG-expanded individuals who received a UHDRS confidence level rating of 4 ($\geq 99\%$ confidence that motor signs are indicative of HD) were considered to have diagnosable HD (HD; $n = 19$). The remaining CAG expanded individuals were classified as prediagnostic HD (PDHD; $n = 21$). Most PDHD individuals ($n = 19$) received a UHDRS confidence level rating of 2 or less while two individuals were assigned a rating of 3. Demographic and clinical characteristics for the three groups of study participants are presented in Table 1. The groups did not differ significantly for age, education, and male/female ratio.

Participants were seated in front of a table (1/3 m from testing material) in a special chair. The participants were fitted with a headband mounted with two ultra-miniature video cameras. As part of the pretesting procedure, calibration and validation pretests were completed. Positions of both eyes during the pretests were analyzed and a primary eye (the right eye, by default) was set for future analysis. Binocular vision of participants was not tested.

For the DS test, the subject was presented with a page on which the digits, 1 through 9, were paired with particular symbols in a “key” along the top of the page (see Fig. 1). The remainder of the page contains a series of these 9 digits. Below each digit is a space for the subject to fill in the symbol corresponding to the digit as determined by the key at the top of the DS page. A cognitive examiner demonstrated how to complete the test and the participant was practiced on the first 10 items to ensure adequate understanding of instructions. The subject was then instructed to work as quickly and accurately as possible and was given 90 seconds to fill in the symbols corresponding to each digit, in the sequence presented. The participant's body position and head were not restrained; however, a neck support was used to discourage head movements and the subject was instructed to remain in the initial position until the test was completed. During the performance of the DS test, the participant's eye pupils were displayed on a computer monitor for visual observation. The coordinates of the pupils were recorded binocularly (EyelinkII, SR Inc, spatial resolution $< 0.1^\circ$, 250 Hz).

After completion of the DS test, a cognitive examiner assigned a DS score determined by the number of correctly written symbols. During the DS test, the participants employed a specialized visual scanning pattern and the recorded eye positions were analyzed using two complementary approaches to characterize this pattern. The first approach evaluated four measures: (1) the ratio of the time the participant's eyes spent in the lower part of the DS page, writing symbol correspondences (i.e. writing area), to the time the participant's eyes spent at the top of the page where the digit to symbol key is located (i.e. key area); (2) the total number of saccades; (3) the number of eye shifting maneuvers defined as up and down eye shifts separated by fixation and the average frequency of maneuvers, i.e. average number of maneuvers in 1 second; and (4) the ratio of the number of correctly written symbols to the number of maneuvers. A program written in MATLAB calculated measures (1–2) and identified all eye shifts (one, two, or three saccades made in the same direction and separated by a short time interval) with amplitude greater than 2.5° . The program presented the eye movement with the marked shifts on a computer screen. A research assistant verified manually that all eye shifting maneuvers were detected correctly.²⁰

The second approach to the analysis was based on the Fourier analysis of the recorded vertical coordinates of the eye position. Our goal was twofold: (1) to identify characteristics of the Fourier transform responsible for the frequency and regularity of the visual scanning in individuals; and (2) to study how these characteristics change over time, from the beginning of the testing period to the end. For this purpose, two 32-second segments, one at the beginning of the test (from the 10th to 42nd second) and the other at the end of the test (from the 55th to 87th second), were selected for further analysis. Blinks were removed from the records. Discrete Fourier transformation was applied to each segment. The power spectrum of the Fourier transform, a measure of the power at various frequencies, was calculated. The mean value and normalized standard deviation (ratio of standard deviation to mean) of frequency with respect to the power spectrum for each segment was computed. The measures were robust and did not change significantly with slight variations in the duration (30 or 32 seconds) or position (± 5 seconds) of the analyzed time intervals.

Statistical Analysis

Analysis of covariance (ANCOVA) with age and gender as covariates was performed to test for group effects for each of the visual scanning measures and the DS score. For measures that demonstrated a significant group effect, a linear trend test was used to evaluate whether there was a worsening of performance as motor signs of HD increased (i.e., from NC to PDHD to HD).

We then evaluated a change in eye-shifting pattern over the duration of the DS test. For each participant, the mean and normalized standard deviation (SD) of the frequency in the power spectrum was computed for the interval at the beginning and at the end of testing. We performed repeated measures analysis of variance (ANOVA) to compare the mean and SD across time (as within subject) for each study group (between subjects). Finally, Spearman correlation was used to test for significant correlation between DS score and measures of visual scanning (example of these measures were defined earlier) in each of the HD, PDHD, and NC groups. Additionally, we used stepwise forward-backward linear regression in the full sample to evaluate the contribution of visual scanning measures to the DS score.

Analyses were repeated removing the 2 PDHD subjects who received a UHDRS confidence level rating of 3. Results were essentially unchanged. Therefore all results presented below were obtained using all subjects.

RESULTS

We found a significant group effect on the DS score (Table 2), with a linear trend of worsening performance from NC to PDHD to HD ($P = 0.007$).

Visual Scanning Strategy

During the DS test, the participants employed a specialized eye-shifting pattern as illustrated in Figure 1A,B. Figure 1A depicts the scan path of the right eye of a NC participant during a 15-second time interval (from 25th to 40th seconds of DS test), and Figure 1B shows the vertical coordinates of the eye as a function of time during the same time interval. The participant repeated an up-down maneuver consisting of four steps: (I) shift of the eye to the key area; (II) fixation in the key area; (III) shift of the eye back to the writing area; and (IV) fixation in the writing area (Fig. 1B). Occasionally, the participant shifted their eye (step I) to the completed boxes in the previous (or current row of symbols) instead of to the keys at the top of the page, fixated at the completed boxes (step II), and then performed steps III–IV. As confirmed by visual observation, the participants typically wrote a symbol during step IV. Figure 2A,B shows the scan path and coordinates of vertical eye position for a PDHD participant. For each

participant, we calculated the total number of maneuvers (NM) across the DS test and the average frequency of maneuvers, i.e. number of maneuvers in 1 second.

The effect of group on the NM was significant (Table 2) with a linear trend of decreasing NM from NC to PDHD to HD ($P = 0.002$). Contrary to the results with NM, there was no significant effect of group on the total number of saccades which participants performed while completing the DS test (Table 2). The ratio of time that the participant's eyes spent in the writing area (filling in the symbol correspondences) to the time the participant's eyes spent at the top of the page in the key area was similar in the three groups. Based on this last result, we concluded that a deficit in writing (an increase in the fraction of time spent in the writing area) was not a leading factor in the observed group differences in the number of maneuvers.

The vertical coordinates of the eye position (Figs. 1B and 2B) show an oscillatory eye movement: one oscillation corresponded to one maneuver. We applied the Fourier analysis for a more detailed evaluation of this oscillatory eye movement across the DS test. Examples of the power spectrum of the Fourier transform of the vertical eye coordinates for the NC participant and PDHD subjects are presented in Figure 3A,B, respectively. The power spectrum of the NC participant (Fig. 3A) shows a strong peak. In contrast to the NC, the power spectrum of the PDHD individual shows scattered peaks (Fig. 3B). To quantify the difference in the structure of the power spectrum, we computed mean and normalized standard deviation (SD) of the frequency with respect to power spectrum. The mean of the frequency characterized the number of maneuvers in 1 second; the SD evaluated the regularity of the maneuvers across time.

ANCOVA revealed group effects (Table 2) for mean and SD of frequency with a linear trend of decreased frequency and increased SD from NC to PDHD and to HD ($P \leq 0.005$). We evaluated the frequency of maneuvers using two different methods: direct calculation of the number of maneuvers in 1 second and evaluation of the mean frequency using Fourier transform. Both methods gave similar results (correlation coefficient, $r = 0.86$; $P < 0.001$).

To evaluate a change in performance over the duration of the DS test, we calculated the power spectrum of the Fourier transform for time intervals in the beginning and at the end of the DS testing. Repeated measures ANOVA revealed a significant group effect for both the mean and SD of frequency ($P = 0.007$ and 0.001 , respectively). In addition, this analysis showed a significant difference between measures in the first and second time intervals ($P < 0.0001$). All groups demonstrated faster (higher frequency) and more regular (smaller SD) performance in the second time segment (Table 2). For these measures, none of the group by time interactions was significant, indicating that all three groups improved at a similar rate during the testing.

DS Scores and Measures of Visual Scanning

The DS score was highly correlated with the NM in each of the three study groups (NC, PDHD, and HD) ($r = 0.84, 0.8$, and 0.83 , $P < 0.0001$, respectively). Figure 4 shows a strong linear relationship between the DS scores and the NM. The stepwise linear regression demonstrated that NM accounted for 77% of the variability in the DS score ($r^2 = 0.77$, $P < 0.001$). Contrary to the NM, the impact of regularity (SD of power spectrum) on the DS score was not significant.

The ratio of the DS to the NM (i.e. the number of correctly written symbols for each maneuver) was slightly different in the three study groups (Table 2) with a linear trend demonstrating a decreasing ratio from NC to PDHD to HD ($P = 0.02$). The ratio was a nearly one to one correspondence in the NC, while in the HD, fewer correct symbols were written for each maneuver. The DS score correlated significantly with all visual scanning measures (number of saccades, $r = 0.45$, $P = 0.002$; ratio of time in the working area to the time in the key area, $r = 0.38$, $P = 0.03$; SD of frequency, $r = 0.66$, $P < 0.001$).

DISCUSSION

We have employed a novel approach to dissect the visual scanning strategy of participants while they completed the DS test, a widely used neuropsychological test for assessing cognitive performance in HD patients. We observed a significant group effect and a linear trend of worsening visual scanning from NC to PDHD to HD.

All three participant groups employed a similar and simple visual scanning strategy while completing the DS test. The participant's eye moved up and down from the lower, working area of the DS page where the subject wrote the corresponding symbol and then up to the key area to obtain the information for the next correspondence. The participant did not rely on their memory of the key correspondence; rather, typically, they obtained the correspondence *de novo* each time, using the up and down maneuver of eye shifting and fixation. The frequency, i.e. the number of maneuvers in 1 second and regularity of these repetitive maneuvers grew progressively worse as CAG-expanded individuals demonstrated more obvious clinical features, from NC to PDHD to HD. Contrary to the worsening of visual scanning from the NC to PDHD to HD, all groups improved slightly and in a parallel fashion, during the course of the DS test.

The slowing (decreased frequency) and irregularity (increased SD) of visual scanning in the HD and in the PDHD groups are in good agreement with the slowing and irregularity of volitional saccades, which have been demonstrated in early and prediagnosis HD.^{15,16,25,26} According to a current model of the neural mechanisms, the projection from the frontal lobe areas to the superior colliculus via the caudate nucleus and the substantia nigra pars reticulata SNpr is associated with the control of volitional saccades. This projection may be affected in prediagnostic HD.²⁷

We found a strong correlation between the cognitive DS score and the number of maneuvers (or frequency of maneuvers in 1 second). The worsening of the DS scores (and Digit Symbol Modalities score) has been reported previously in many studies of early and prediagnosis HD.^{11,12,28-30} We found an almost one-to-one correspondence between the DS score and the number of maneuvers in the NC group. Contrary to the NC group, the CAG-expanded group made extra maneuvers for each written symbol. Those extra movements may be related to a short-term memory deficit, which is required in order to retain digit symbol pairings long enough to write them on the DS test. Overall, the number of maneuvers accounted for 77% of the variability in the DS score. Based on these results, we suggest that worsening of visual scanning in CAG-expanded subjects is, at least in part, responsible for the decrease in the DS score.

This study protocol had some limitations. Because the participant's head was not completely restrained during DS testing, we could not determine the exact gaze location. In our experimental setting, possible head movements would be compensated by the vestibulo-ocular reflex. We believe that this compensational eye movement would not significantly alter our study results. The frequency of visual scanning was a robust measure which we evaluated by two different methods and found similar results.

Currently available data demonstrate substantial variability and nonuniform impairment in cognitive performance in prediagnostic HD subjects. It would be interesting to apply the joint analysis of eye movements and cognitive performance to dissect the constituent deficits in other neurocognitive tests which are affected early in the progression of HD. The use and development of such an approach will allow us to identify basic components of the deficit observed in HD and PDHD patients across various neuropsychological tests of cognitive and executive control functions and help us better understand the earliest stages and progression of HD.

Acknowledgments

The research was supported by NIH grants R01 NS042659, N01-NS-3-2357, and MO1 RR-00750 and an unrestricted grant from Research to Prevent Blindness, Inc. to the Department of Ophthalmology, Indiana University School of Medicine.

REFERENCES

1. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;72:971–983. [PubMed: 8458085]
2. Vonsattel JP, Myers RH, Stevens TJ, et al. Neuropathological classification of Huntington's disease. *J Neuropathol Exp Neurol* 1985;44:559–577. [PubMed: 2932539]
3. Aylward EH, Li Q, Stine OC, et al. Longitudinal change in basal ganglia volume in patients with Huntington's disease. *Neurology* 1997;48:394–399. [PubMed: 9040728]
4. Aylward EH, Codori AM, Rosenblatt A, et al. Rate of caudate atrophy in presymptomatic and symptomatic stages of Huntington's disease. *Mov Disord* 2000;15:552–560. [PubMed: 10830423]
5. Rosas HD, Liu AK, Hersch S, et al. Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology* 2002;58:695–701. [PubMed: 11889230]
6. Rosas HD, Koroshetz WJ, Chen YI, et al. Evidence for more widespread cerebral pathology in early HD: an MRI-based morphometric analysis. *Neurology* 2003;60:1615–1620. [PubMed: 12771251]
7. Beglinger LJ, Nopoulos PC, Jorge RE, et al. White matter volume and cognitive dysfunction in early Huntington's disease. *Cogn Behav Neurol* 2005;18:102–107. [PubMed: 15970729]
8. Paulsen JS, Magnotta VA, Mikos AE, et al. Brain structure in preclinical Huntington's disease. *Biol Psychiatry* 2006;59:57–63. [PubMed: 16112655]
9. Reading SA, Yassa MA, Bakker A, et al. Regional white matter change in pre-symptomatic Huntington's disease: A diffusion tensor imaging study. *Psychiatry Res* 2005;140:55–62. [PubMed: 16199141]
10. Kirkwood SC, Siemers E, Hodes ME, et al. Subtle changes among presymptomatic carriers of the Huntington's disease gene. *J Neurol Neurosurg Psychiatry* 2000;69:773–779. [PubMed: 11080230]
11. Paulsen JS, Zhao H, Stout JS, et al. Clinical markers of early disease in persons near onset of Huntington's disease. *Neurology* 2001;57:658–662. [PubMed: 11524475]
12. Snowden JS, Craufurd D, Thompson J, et al. Psychomotor, executive, and memory function in preclinical Huntington's disease. *J Clin Exp Neuropsychol* 2002;24:133–145. [PubMed: 11992196]
13. Farrow M, Chua P, Churchyard A, et al. Proximity to clinical onset influences motor and cognitive performance in presymptomatic Huntington disease gene carriers. *Cogn Behav Neurol* 2006;19:208–216. [PubMed: 17159618]
14. Feigin A, Ghilardi MF, Huang C, et al. Preclinical Huntington's disease: compensatory brain responses during learning. *Ann Neurol* 2006;59:53–59. [PubMed: 16261565]
15. Golding CV, Danchavijitr C, Hodgson TL, et al. Identification of an oculomotor biomarker of preclinical Huntington disease. *Neurology* 2006;67:485–487. [PubMed: 16625001]
16. Blekher T, Johnson SA, Marshall J, et al. Saccades in presymptomatic and early stages of Huntington disease. *Neurology* 2006;67:394–399. [PubMed: 16855205]
17. Yarbus, A. Plenum Press; New York: 1967. *Movements of the eyes*.
18. Land M, Furneaux S. The knowledge base of the oculomotor system. *Phil Trans R Soc Lond B* 1997;352:1231–1239. [PubMed: 9304689]
19. Ballard DH, Hayhoe MM, Pook PK, Rao RPN. Deictic codes for the embodiment of cognition. *Behav Brain Sci* 1997;20:723–767. [PubMed: 10097009]
20. Blekher TM, Yee RD, Kirkwood SC, et al. Oculomotor control in asymptomatic and recently diagnosed individuals with the genetic marker for Huntington's disease. *Vision Res* 2004;44:2729–2736. [PubMed: 15358067]
21. Wechsler, D. Wechsler adult intelligence scale—revised. Psychological Corp; New York, NY: 1981.

22. Lahiri DK, Bye S, Nurnberger JI Jr, Hodes ME, Crisp M. A non-organic and non-enzymatic extraction method gives higher yields of genomic DNA from whole-blood samples than do nine other methods tested. *J Biochem Biophys Methods* 1992;25:193–205. [PubMed: 1494032]
23. Bond CE, Hodes ME. Direct amplification of the CAG repeat of huntingtin without amplification of CCG. *Clin Chem* 1996;42:773–774. [PubMed: 8653908]
24. The Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord* 1996;11:136–142. [PubMed: 8684382]
25. Lasker AG, Zee DS, Hain TC, Folstein SE, Singer HS. Saccades in Huntington's disease: initiation defects and distractibility. *Neurology* 1987;37:364–370. [PubMed: 2950337]
26. Tian JR, Zee DS, Lasker AG, Folstein SE. Saccades in Huntington's disease: predictive tracking and interaction between release of fixation and initiation of saccades. *Neurology* 1991;41:875–881. [PubMed: 1828547]
27. Lasker AG, Zee DS. Ocular motor abnormalities in Huntington's disease. *Vision Res* 1997;37:3639–3645. [PubMed: 9425536]
28. Witjes-Ané MN, Vegter-van der Vlis M, van Vugt JP, et al. Cognitive and motor functioning in gene carriers for Huntington's disease: a baseline study. *J Neuropsychiatry Clin Neurosci* 2003;15:7–16. [PubMed: 12556566]
29. Kirkwood SC, Siemers E, Stout JC, et al. Longitudinal cognitive and motor changes among presymptomatic Huntington disease gene carriers. *Arch Neurol* 1999;56:563–568. [PubMed: 10328251]
30. Foroud T, Siemers E, Kleindorfer D, et al. Cognitive scores in carriers of Huntington's disease gene compared to noncarriers. *Ann Neurol* 1995;37:657–664. [PubMed: 7755361]

FIG. 1.

Eye movement of a NC subject. **A:** Eye path on DS page illustration; **B:** Vertical coordinates of the eye position as a function of time during a 15-second interval (from 25th to 40th seconds of DS testing). The participant was writing symbols at the beginning of the second row. The participant's eye moved back and forth from the writing area to the key area. I, II, III, IV shows a typical periodic maneuver that included: (I) shift to the key area, (II) fixation in key area, (III) shift back to the second row, and (IV) fixation on the second row of digits. During step IV, the participant wrote a symbol in the writing area. The maneuver I-IV was repeated 11 times in 15 seconds time interval and 11 symbols were written in the second row of the DS page.

FIG. 2. Eye movement of a PDHD subject. **A:** Eye path on DS page illustration; **B:** Vertical coordinates of the eye position as a function of time during a 15-second interval. The participant was writing symbols at the beginning of the second row.

FIG. 3. Power spectrum of the Fourier transform of vertical eye coordinates (32-second interval at the beginning of DS testing, from 10th to 42nd second). For all participants, more than 95% of power spectrum was allocated between 0 and 2 Hz frequencies. **A:** NC subject; **B:** PDHD subject. ◆ shows mean frequency.

FIG. 4.
DS scores and number of maneuvers.

TABLE 1

Demographic and clinical characteristics of the three groups of study participants

Demographic	HD (n = 19)	PDHD (n = 21)	NC (n = 23)	P-value
Age (yr, mean $\pm$ SD; range)	51.5 $\pm$ 7.4 34-61	51.0 $\pm$ 7.5 36-63	51.1 $\pm$ 6.2 41-62	0.97
Education (yr, mean $\pm$ SD; range)	16.2 $\pm$ 2.8 12-24	16.2 $\pm$ 2.6 12-22	14.9 $\pm$ 2.5 12-21	0.18
Male-female ratio ^a	5/14	7/14	8/15	0.84
UHDRS functional independence score (mean, minimum) ^a	95,70	100, 100	100, 100	0.007
UHDRS sum of motor scores (mean $\pm$ SD)	33.3 $\pm$ 14.4	11.4 $\pm$ 7.1	1.1 $\pm$ 1.3	<0.0001
CAG repeat length	42.7 $\pm$ 2.3	42.1 $\pm$ 1.8	N/A	0.37

^a Male-female ratio and UHDRS functional independence score evaluated by Fisher's exact test statistic. All other comparisons performed by ANOVA.

TABLE 2

Measures of visual scanning obtained while completing the digit symbol test

	HD	PDHD	NC	<i>P</i> -value [*]
Number of correctly written symbols ^a	40 ± 3	48 ± 3	54 ± 3	0.003
Number of maneuvers ^a	44 ± 2	49 ± 2	55 ± 2	0.006
Number of maneuvers in 1 s ^a	0.49 ± 0.03	0.54 ± 0.03	0.61 ± 0.03	0.006
Number of saccades ^a	104 ± 6	112 ± 6	113 ± 5	0.4
Ratio of correctly written symbols to the number of maneuvers ^a	0.90 ± 0.03	0.98 ± 0.03	1.00 ± 0.03	0.05
Ratio of time in the working area to time in the key area ^a	1.3 ± 0.1	1.25 ± 0.1	1.3 ± 0.1	0.92
Frequency with respect to the power spectrum (first time segment) ^a	0.45 ± 0.03	0.51 ± 0.03	0.58 ± 0.03	0.01
Frequency with respect to the power spectrum (second time segment) ^a	0.52 ± 0.03	0.59 ± 0.03	0.64 ± 0.02	0.003
SD of frequency (first time segment) ^a	0.96 ± 0.06	0.80 ± 0.05	0.70 ± 0.05	0.005
SD of frequency (second time segment) ^a	0.78 ± 0.04	0.66 ± 0.03	0.61 ± 0.03	0.002

* *P*-value corresponds to ANCOVA for the three main effects of groups. Age and gender were not significant covariates for the visual scanning measures.

^a Adjusted mean ± standard error.