Saccades in presymptomatic and early stages of Huntington disease

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Abstract—Objective: To evaluate quantitative measures of eye movements as possible biomarkers in prediagnostic and early stages of Huntington disease (HD). Methods: The study sample (n = 215) included individuals both at risk and recently diagnosed with HD. All participants completed a uniform clinical evaluation which included administration of the Unified Huntington’s Disease Rating Scale (UHDRS) by a movement disorder neurologist and molecular testing to determine HD gene status. A high resolution, video-based eye tracking system was employed to quantify measures of eye movement (error rates, latencies, SD of latencies, velocities, and accuracies) during a computerized battery of saccadic and steady fixation tasks. Results: Prediagnostic HD gene carriers and individuals with early HD demonstrated three types of significant abnormalities while performing memory guided and anti-saccade tasks: increased error rate, increased saccade latency, and increased variability of saccade latency. The eye movement abnormalities increased with advancing motor signs of HD. Conclusions: Abnormalities in eye movement measures are a sensitive biomarker in the prediagnostic and early stages of Huntington disease (HD). These measures may be more sensitive to prediagnostic changes in HD than the currently employed neurologic motor assessment.

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Huntington disease (HD) is a neurodegenerative disorder resulting from an increased number of triplet (CAG) repeats in the huntingtin gene. HD is characterized by neuronal loss and gliosis in the striatum with vulnerability in the cortex and other brain regions. Growing evidence supports the concept that the neuronal deterioration is already advanced by the time of clinical diagnosis. Abnormalities in eye movement are an unequivocal finding in the clinical evaluation of manifest HD. Patients with advanced HD demonstrate a broad range of eye movement abnormalities including impairment of saccades, pursuit, optokinetic response, and fixation. Prominent abnormalities are also consistently noted in mildly to moderately affected patients, including deficits in the initiation of volitional saccades (elicited by command, without visual target, such as anti-saccade and memory guided saccades) and impairment of steady fixation. In contrast, studies of eye movements in prediagnostic HD have reported mixed findings, with some showing intact performance and others showing deficits. Thus, the potential use of eye movement testing as a biomarker in the prediagnosis and early periods of HD remains unclear.

In the current study we investigated eye movement measures as a biologic marker for prediagnostic and early stages of diagnosed HD. In a previous study, we assessed eye movement deficits in a small sample of at-risk individuals and found that individuals prediagnostic for HD demonstrated deficits of memory guided saccades. Based on those results, we emphasized measures of volitional saccades in the current battery of tests.

Method. Participants were recruited through the National Research Roster for Huntington Disease Patients and Families. All participants had a parent affected with HD and were either at risk or recently diagnosed with HD. All participants completed a uniform clinical evaluation which included administration of the Unified Huntington’s Disease Rating Scale (UHDRS) by a movement disorder neurologist and molecular testing to determine HD gene status. A high resolution, video-based eye tracking system was employed to quantify measures of eye movement (error rates, latencies, SD of latencies, velocities, and accuracies) during a computerized battery of saccadic and steady fixation tasks. Results: Prediagnostic HD gene carriers and individuals with early HD demonstrated three types of significant abnormalities while performing memory guided and anti-saccade tasks: increased error rate, increased saccade latency, and increased variability of saccade latency. The eye movement abnormalities increased with advancing motor signs of HD. Conclusions: Abnormalities in eye movement measures are a sensitive biomarker in the prediagnostic and early stages of Huntington disease (HD). These measures may be more sensitive to prediagnostic changes in HD than the currently employed neurologic motor assessment.
risk for HD but not diagnosed or had received an HD diagnosis within the past 2 years. The age of participants ranged from 19 to 65 years. None of the participants included in the analysis had concurrent neurologic illness or psychiatric disease such as schizophrenia or bipolar disorder. None of the participants had self-reported current alcohol or drug abuse. Approximately 26% of all participants were receiving medication to treat psychiatric symptoms such as sleep disorder, anxiety, and depression. Exclusion of those participants did not alter the results of statistical analysis. All participants had normal or corrected visual acuity, did not have a history of eye surgery, and did not report significant eye-related complaints.

The study included clinical evaluation, molecular testing, oculomotor assessment, and questionnaires about medical history, current medications, substance use, and visual health. The participants were asked not to disclose their gene status, if known, to study staff to ensure that the individuals administering the testing 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.

Clinical evaluation. The Unified Huntington’s Disease Rating Scale (UHDRS), a standardized clinical rating scale, was completed for all participants. An experienced movement disorder neurologist administered the motor portions of the UHDRS including clinical evaluation of saccadic initiation and velocity. The neurologist was aware that the participants were at risk for HD but was blinded to gene status as well as the results of cognitive and behavioral assessments. The neurologist selected a confidence rating on a scale of 0 to 4 to represent the presence or absence of motor abnormalities and the likelihood that the presence of abnormalities was representative of HD. The ratings were defined as follows: (0) normal (no abnormalities), (1) nonspecific motor abnormalities (less than 50% confidence), (2) motor abnormalities that may be signs of HD (50 to 89% confidence), (3) motor abnormalities that are likely signs of HD (90 to 98% confidence), and (4) motor abnormalities that are unequivocal signs of HD (99% confidence).

Molecular testing. DNA was extracted from either a blood sample or a buccal swab using standard inorganics methods. A PCR-based test was performed to determine the number of CAG repeats in the huntingtin gene. Based on the results of the molecular testing and the diagnostic confidence level obtained from the UHDRS, individuals were assigned to one of four groups: 1) NGC—nongene carriers, defined as those individuals with two unexpanded HD alleles (0 CAG repeats); 2) PSGC1—presymptomatic individuals with an expanded HD gene (38 CAG repeats) who demonstrated either no signs or will signs of motor abnormalities, i.e., diagnostic confidence score was 0 or 1 on the UHDRS; 3) PSGC2—presymptomatic individuals with an expanded HD gene (38 CAG repeats) who demonstrated possible or likely signs of HD motor abnormalities (diagnostic confidence score was 2 on the UHDRS); and 4) HD—manifest HD, defined as those individuals with an expanded HD gene (38 CAG repeats) who had sufficient clinical findings to be diagnosed with HD (diagnostic confidence score was 4 on the UHDRS).

Oculomotor assessment. The vertical and horizontal positions of the participant’s pupils were recorded binocularly with two ultra-miniature high-speed (250 Hz) video cameras attached to a headband and digitized at 250 Hz for later analysis (Eyelink II, SR Research Ltd, spatial resolution < 0.1 degree).

Testing procedure. The participant was seated 1 meter from a large white screen, in front of a bar with target lights (light-emitting diodes, LED) located at 0° (central LED), 10°, and 20° to the right and left horizontally (figure 1A), and 10° up and down vertically from the central LED. The headband with video cameras was adjusted on the participant’s head and the participant’s head movements were restricted by a neck support. The room was darkened. Five saccadic tasks and a fixation task were performed in a fixed order. Before each task, the examiner instructed the participant verbally and performed a practice demonstration to ensure that the participant understood the oral task instructions correctly. Each of the saccadic tasks consisted of 25 trials.

Anti-saccade (AS) task. The participant was instructed to fixate on the central illuminated LED (0°). The central LED was extinguished simultaneously with illumination of a peripheral LED. The participant was instructed to look in the opposite direction to the left illuminated LED. The participant made a reflexive glance toward the left LED and then corrected this mistake. In the MG1 task, the participant was instructed to look at the remembered position of the flash after the central LED was turned off. Instead, the participant initiated a first saccade before the central LED was switched off.

Figure 1. (A) Schematic diagram of the experimental conditions in anti-saccade (AS) and memory guided (MG) tasks. In the AS task, a central light-emitting diode (LED) was illuminated, then the LED was switched off and simultaneously a peripheral LED (20° left) was switched on. In the MG1 task, the central LED was on while the peripheral LED was illuminated for short time (50 msec). After an additional delay (1 sec), the central LED was turned off. For each trial, the timing and position of peripheral LED was chosen randomly. (B) Horizontal position of the right eye while PSGC1 participant performed AS and MG1 tasks. Squares marked the time at which the central LED was turned off. Circles marked timing and direction (20° left) of peripheral LED. The participant made errors in both trials. In the AS task, the participant was instructed to look in the opposite direction to the left illuminated LED. The participant made a reflexive glance toward the left LED and then corrected this mistake. In the MG1 task, the participant was instructed to look at the remembered position of the flash after the central LED was turned off. Instead, the participant initiated a first saccade before the central LED was switched off.

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peripheral LEDs, both vertical and horizontal. The participant was instructed to look sequentially at the three remembered positions of the flashes.

**Fixation task.** During the fixation task, the central LED was illuminated for 60 seconds while flashes occurred at the peripheral LEDs. The participant was instructed to fix gaze on the central LED and to count the number of flashes.

**Data processing.** After the participant completed the testing procedure, an interactive computerized analysis of the right eye position was carried out by an experienced technician who was not aware of the results of neurologic and molecular testing. The first saccade (or sequence of saccades in the MG2 task) was identified in each trial and the correct trials were selected as those in which the first saccades were consistent with the task instructions. Next, the latency, peak velocity, and amplitude of the first saccades in the correct trials were computed. Finally, for each participant, four basic measures were computed for each of the VG, PR, AS, and MG1 tasks: 1) mean saccade latency, i.e., the mean reaction time; 2) SD of saccade latency, i.e., individual variability of latency from trial to trial; 3) mean accuracy of saccades, i.e., mean ratio of saccade amplitude to LED amplitude; and 4) peak velocity of the idealized 15-degree saccade. To evaluate the peak velocity of the 15-degree saccade, the amplitude (A, degree) and peak velocity (V, deg/second) of the saccades were fitted, using a least square regression algorithm, to a main sequence equation, \( V = B* \exp \left(-\frac{C}{A} \right) \) where B and C are constants.22 For the VG task, the horizontal and vertical saccades were analyzed separately. For the more challenging MG2 task, many participants did not perform enough correct trials to reliably calculate the basic measures of correct saccades.

Figure 1 shows a schematic diagram (figure 1A) and records of AS and MG1 trials of a PSGC1 participant (figure 1B). The participant made characteristic errors in both trials. In the AS trial, the participant made the first saccade in the incorrect direction (toward the stimulus) and then looked in the opposite (correct) direction. In the MG1 trial, the participant initiated the first saccade before the central light was extinguished (timing error). The other possible error in the MG tasks was a missed peripheral flash, i.e., the participant did not perform a saccade to the remembered position of the flash (or a sequence of saccades for the MG2 task). In the PR task, a typical error was related to the timing of the saccade; i.e., the participant initiated a saccade in anticipation of the light displacement, during the time interval from 300 msec before to 80 msec after the LED alternation. For each task the fractions of error trials were computed by dividing the number of trials performed with mistakes by the total number of trials completed during the task. For the MG2 task, the fraction of all trials that were in error due to missed peripheral flashes was also calculated.

For the fixation task, the foveation periods were defined as those periods of the fixation during which eye velocity was less than 4 deg/second and the eye position was less than 1 degree from the point of fixation. The primary measure for this task, fixation stability, was computed by dividing the time spent in the foveation periods by the total time of the fixation task.

**Results.** We analyzed 215 individuals. Demographic and clinical characteristics for the four study groups are shown in table 1. The four groups did not differ significantly in age, race, handedness, or education.

**Oculomotor control.** There was a group effect for the fraction of error trials in the AS, MG1, and MG2 tasks (\( p < 0.0001 \); table 2, figure 2). Post hoc comparisons showed that the PSGC1, PSGC2, and HD groups made more errors than the NGC group in each of the three tasks (PSGC1 vs NGC, \( p < 0.008 \); PSGC2 vs NGC, \( p < 0.006 \); HD vs NGC, \( p < 0.0005 \)). There was a linear trend demonstrating an increasing fraction of error trials as the gene carriers manifested more motor signs of HD (i.e., NGC < PSGC1 < PSGC2 < HD, \( p \) value for the linear trend < 0.0001). In the MG2 task, the fraction of trials with missed flashes yielded the same pattern of increasing abnormality with advancing motor signs (PSGC1 vs NGC: \( p < 0.02 \); PSGC2 vs NGC: \( p < 0.002 \); HD vs NGC, \( p < 0.0001 \)).

**Table 1: Demographic and clinical characteristics of the 215 study participants**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>HD, n = 30</th>
<th>PSGC2, n = 16</th>
<th>PSGC1, n = 27</th>
<th>NGC, n = 142</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean ± SD</strong></td>
<td>50 ± 9</td>
<td>44 ± 13</td>
<td>45 ± 10</td>
<td>47 ± 11</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Education, y, mean ± SD</strong></td>
<td>16 ± 3</td>
<td>16 ± 3</td>
<td>16 ± 2</td>
<td>15 ± 2</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Male/female ratio</strong></td>
<td>12/18</td>
<td>7/9</td>
<td>11/16</td>
<td>31/111</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Race, % white</strong></td>
<td>97</td>
<td>100</td>
<td>96</td>
<td>97</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Handedness, % right</strong></td>
<td>90</td>
<td>94</td>
<td>93</td>
<td>89</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>UHDRS summed motor score, mean ± SD</strong></td>
<td>26 ± 10</td>
<td>15 ± 6</td>
<td>5 ± 4</td>
<td>5 ± 4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>UHDRS functional independence score, mean, minimum</strong></td>
<td>97, 70</td>
<td>99, 80</td>
<td>100, 100</td>
<td>100, 90</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>CAG, large no. repeat, mean ± SD</strong></td>
<td>43 ± 2</td>
<td>42 ± 2</td>
<td>42 ± 2</td>
<td>N/A</td>
<td>0.20</td>
</tr>
</tbody>
</table>

* Ratio, percentages, and Unified Huntington’s Disease Rating Scale (UHDRS) functional independence score evaluated by Fisher exact test. All other comparisons performed by analysis of variance.
† The sum of the motor assessment scores (1 to 15) of the UHDRS.
group differences were observed when comparing the fraction of error trials for the VG and PR tasks.

Group effects were also observed for saccade latency in the AS, PR, and MG1 tasks \((p < 0.001; \text{table 2})\). Post hoc comparisons showed that the PSGC2 and HD groups had prolonged latency for all three tasks as compared with the NGC \((p < 0.05)\) group. Saccade latency for the PSGC1 group differed from the NGC group on the MG1 task only \((p = 0.03)\), again demonstrating a linear trend of increasing abnormality with advancing motor signs \((\text{NGC} < \text{PSGC1} < \text{PSGC2} < \text{HD}, p < 0.0001)\).

Typically, there is random variation in saccade latency from trial to trial. Computing the SD of saccade latency quantifies the extent of individual variability across trials. Similar to the results obtained when analyzing saccade latency, analyses of the SD of saccade latency revealed a group effect for the PR, AS, and MG1 tasks \((p < 0.005)\) (table 2). Post hoc analyses demonstrated that the PSGC2 and HD groups had an increase in latency variability in the AS and MG1 tasks \((\text{AS}; p = 0.007; \text{MG1}; p = 0.02)\). An increase in SD was also observed in the MG1 task for the PSGC1 group as compared to the NGC group \((p = 0.001)\). Similar to the error rates and latencies, there was a linear trend of greater SD in those with more motor signs \((p < 0.002)\). No significant group differences were observed for either velocity or accuracy for any of the four saccadic tests.

A group effect was observed for fixation stability \((p < 0.0001)\). Post hoc analyses revealed that the group effect was due to the significant decrease in fixation stability of the HD group. There was a similar trend suggesting a decrease in fixation stability of the PSGC2 group as compared to the NGC group.

**Saccade measures—UHDRS vs oculomotor control measures.** A group effect was observed for the UHDRS latency and velocity scores for horizontal saccades \((p < 0.0001)\). Post hoc comparisons indicated that the group effect was due to the increase in latency and velocity scores of the HD and PSGC2 groups as compared to the NGC group. The PSGC1 and NGC groups did not differ on these measures. The UHDRS saccade evaluation procedure and the PR tests resemble each other and the UHDRS latency initiation score was correlated with the calculated average latency of saccades in the PR test (Spearman correlation, \(p = 0.04\)). The correlation between the UHDRS saccade velocity scores and the velocity measure of the PR task was not significant. However, upon closer inspection, saccade velocity of almost all participants was rated as either normal (score 0) or mildly slow (score 1) on the UHDRS. Only five participants (3 HD and 2 PSGC2) were rated as showing moderate slowing (score 2) on the UHDRS velocity score and those five participants demonstrated slowing of quantitative measures of velocity.

**Table 2 Primary saccade measures for the HD, PSGC2, PSGC1, and NGC groups**

<table>
<thead>
<tr>
<th>Saccade measures</th>
<th>HD</th>
<th>PSGC2</th>
<th>PSGC1</th>
<th>NGC</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Error rates</strong></td>
<td>(0.53 \pm 0.2)</td>
<td>(0.41 \pm 0.3)</td>
<td>(0.36 \pm 0.2)</td>
<td>(0.27 \pm 0.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(0.45 \pm 0.2)</td>
<td>(0.32 \pm 0.2)</td>
<td>(0.27 \pm 0.2)</td>
<td>(0.19 \pm 0.1)</td>
<td>(0.0001)</td>
<td></td>
</tr>
<tr>
<td>(0.58 \pm 0.2)</td>
<td>(0.51 \pm 0.2)</td>
<td>(0.48 \pm 0.3)</td>
<td>(0.28 \pm 0.2)</td>
<td>(0.0001)</td>
<td></td>
</tr>
<tr>
<td>(0.34 \pm 0.2)</td>
<td>(0.29 \pm 0.2)</td>
<td>(0.2 \pm 0.2)</td>
<td>(0.1 \pm 0.1)</td>
<td>(0.0001)</td>
<td></td>
</tr>
<tr>
<td><strong>Latency</strong></td>
<td>(443 \pm 70)</td>
<td>(397 \pm 93)</td>
<td>(380 \pm 80)</td>
<td>(375 \pm 63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(256 \pm 61)</td>
<td>(252 \pm 52)</td>
<td>(218 \pm 41)</td>
<td>(221 \pm 40)</td>
<td>(0.001)</td>
<td></td>
</tr>
<tr>
<td>(366 \pm 77)</td>
<td>(322 \pm 44)</td>
<td>(312 \pm 41)</td>
<td>(293 \pm 44)</td>
<td>(0.001)</td>
<td></td>
</tr>
<tr>
<td><strong>Variability of latency</strong></td>
<td>(101 \pm 35)</td>
<td>(91 \pm 22)</td>
<td>(80 \pm 27)</td>
<td>(78 \pm 25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(78 \pm 30)</td>
<td>(58 \pm 28)</td>
<td>(59 \pm 30)</td>
<td>(58 \pm 30)</td>
<td>(0.005)</td>
<td></td>
</tr>
<tr>
<td>(102 \pm 31)</td>
<td>(91 \pm 31)</td>
<td>(95 \pm 31)</td>
<td>(77 \pm 26)</td>
<td>(0.001)</td>
<td></td>
</tr>
</tbody>
</table>

Values represent mean ± SD. Analysis of covariance (ANCOVA) was performed to detect group effects \((p < 0.01)\). The error rates \((i.e., \text{the fraction of trials completed with errors})\) refer to anti-saccades (AS) and two versions of memory guided saccades (MG1 and MG2). MG2-m presents the fraction of trials completed with errors. The latency and variability of latency \((\text{in msec})\) refer to AS, predictable (PR), and MG1 saccades.

HD = individuals who had been recently diagnosed with HD; PSGC2 = presymptomatic individuals with an expanded HD gene who demonstrate possible or likely signs of motor abnormalities; PSGC1 = presymptomatic individuals with an expanded HD gene who demonstrate either no signs or soft signs of motor abnormalities; NGC = nongene carriers.
Discussion. We found that prediagnostic HD gene carriers showed impairment of saccades as compared to the nongene carriers, and the difference was most prominent in anti-saccade and memory-guided tasks. Specifically, the HD gene carriers that had normal or mildly abnormal motor examinations (0 or 1 on UHDRS motor confidence rating, PSGC1) showed a 50% increase in error rate and the gene carriers that had moderately abnormal motor exam (2 or 3 on UHDRS motor confidence rating, PSGC2) showed a 65% increase in error rate (figure 2). Similarly, the latency and variability of latency were significantly greater in the PSGC2 group (10% increase in latency and 20% increase in variability of latency). Furthermore, the PSGC1 group showed increased latency and increased variability of latency during memory-guided saccade task. The current findings demonstrate high sensitivity of saccade measures in discriminating prediagnostic and early HD gene carriers from nongene carriers (figure 2).

We compared the sensitivity of the quantitative saccade measures with ratings of saccades from the UHDRS. Although the UHDRS saccade scores indicated more impairment for the PSGC2 group, they did not differentiate the PSGC1 and nongene carriers. Similar results were found for the summed UHDRS motor score and other components of UHDRS motor assessment. Thus, the anti-saccades and memory-guided measures turned out to be more sensitive than the UHDRS motor examination. Since the quantified saccade measures demonstrate high-test retest reliability and modest change over time, assessment of memory-guided and anti-saccades may provide an objective and sensitive method to study early stages of HD.

We found also that the saccade abnormalities increased across the gene carrier groups with advancing motor signs of HD (i.e., NCG < PSGC1 < PSGC2 < HD). This finding suggests that the abnormalities may be associated with the underlying progressive degenerative processes. According to a current model of neural mechanisms, the projection from frontal lobe areas to the superior colliculus via the caudate and the substantia nigra pars reticulata is associated with the control of memory-guided saccades and anti-saccades. The increase in the number of errors, latency, and variability of the saccades points to a disruption of this projection during the prediagnostic stage of HD. Longitudinal studies of oculomotor control may shed light on the progression of the neurobiological substrates in HD, from the earliest stages to the onset of manifest neurologic symptoms.

It is important to consider the clinical implications of abnormal saccadic performance. Saccade performance is essential for adequate visual perception. It has been reported that patients with HD are five times more likely to be involved in traffic collisions than control individuals. Saccade abnormalities may play a significant role in those collisions and thus, early testing of eye movements may be an important method for identifying individuals with prediagnostic HD at risk for failure during visually demanding activities such as driving.

Overall, our results suggest that oculomotor control measures are sensitive to early changes in HD and thus, may be important biomarkers of early disease progression. Recent developments in eye movement recording techniques allow for accurate and noninvasive measures of oculomotor control. Laboratory testing of eye movements must be expanded to determine whether these techniques may be adapted for use in the clinical setting to detect early changes in prediagnostic HD. Results from laboratory testing may also be used to guide the clinical evaluation of oculomotor function; inclusion of quantitative measures of anti-saccade and memory guided saccades may increase the sensitivity of the clinical examination. Current efforts to develop therapeutics target the prediagnosis period, and several compounds have been identified which are ready or near ready for testing in prediagnostic HD. The quantitative measures of oculomotor control may be sensitive indices of disease progression and may serve as valuable tools in future clinical trials aimed at delaying the onset or progression of HD.

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References


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