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Reflexive and volitional saccades: Biomarkers of Huntington disease severity and progression

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ABSTRACT

Background: Huntington disease (HD) is a genetic, neurodegenerative disorder characterized by chorea, behavioral co-morbidities, cognitive deficits, and eye movement abnormalities. We sought to evaluate whether reflexive and voluntary orienting prove useful as biomarkers of disease severity in HD.
Methods: Eleven HD subjects were evaluated with the motor subscale of the Unified Huntington Disease Rating Scale (UHDRS) and the Montreal Cognitive Assessment. Using an infrared eye tracker, we also measured latency and error rates of horizontal and vertical saccades using prosaccade and antisaccade eye movement tasks. We calculated simple and age-controlled correlations between eye movement and clinical parameters.
Results: Prosaccade latency correlated with total chorea score. HD patients with greater clinical severity were significantly slower in the prosaccade task. Antisaccade error rate also correlated with UHDRS motor score and total chorea score. HD patients with greater clinical severity as measured by either measure made significantly more errors in the antisaccade task. All these correlations remained significant even when age was taken into account.
Conclusions: The results of the present age-controlled study show for the first time that both reflexive and voluntary eye motor control in HD patients decrease with increase in disease severity suggesting declines in both motor and cognitive function. Thus, relatively simple eye movement parameters (latency and error rate) obtained from simple tasks (prosaccade and antisaccade) may serve as quantitative biomarkers of sub-cortical and cortical disease severity in HD and could aid in predicting onset, distinguishing subtypes, or evaluating disease progression and novel therapies.

1. Introduction

Huntington disease (HD) is a genetic, neurodegenerative disorder characterized by chorea, behavioral co-morbidities, cognitive deficits, and eye movement abnormalities. The earliest documented cell loss in HD patients occurs in the basal ganglia, particularly in the striatal medium spiny neurons and the external segment of the global pallidus [1,2]. Eventually, degeneration is widespread and includes the brainstem [1,3].

Eye movements critically depend on the coordinated functioning of the brainstem, thalamus, basal ganglia, and cortex. All these structures are affected in HD and it is, therefore, not surprising that multiple eye movement deficits exist in patients with HD [4–22]. As a result of recent research focusing on further discriminating types of saccadic eye movements, two parallel systems have been proposed that differentially govern reflexive and volitional saccades [23–25]. Frontal structures and the basal ganglia play a key role in both voluntary saccades and control (tonic inhibition) of reflexive saccades. In addition, both systems share common motor brainstem output nuclei. Thus, specific lesions will differentially impair the two types of saccades. More importantly, specific changes in saccadic eye movement performance will provide a basis to infer specific neuropathological changes in HD.

Eye movement deficits, particularly in voluntary saccades [4,8,12,16,20,21,26,27] and in fixation maintenance [8,10,12], have been well documented in HD patients, even in early stages. Some studies have shown that even presymptomatic HD patients have voluntary saccade deficits [21,22,28–30]. The performance of reflexive saccades in HD patients is less consistent, with some studies finding slowing [4,5,7,11–15] and others reporting them as intact [20–22]. The saccadic slowing affecting both reflexive and voluntary saccades, is usually attributed to the development of brainstem dysfunction [12,16,17,25].

Despite numerous eye movement studies in HD, only a few have correlated eye movement parameters with HD severity as measured by the Unified Huntington Disease Rating Scale (UHDRS) motor subscale to determine their usefulness as a biomarker for disease severity and progression [4]. Moreover, the only previous study [4] we are aware of that established any correlation between eye movement

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Table 1
Demographic information.

Subject number	Age (year)	Gender	UHDRS total motor score	MoCA	CAG repeats	Tetrabenazine dose (mg/day)
201	33	Female	0	30	42	
202	56	Female	41	20		
204	63	Male	32	17		
205	27	Female	4	27	52	
206	43	Female	44	22	45	75
207	69	Female	41	25	41	50
209	31	Male	5	28	47	
210	70	Female	47	26	41	25
211	35	Male	38	24		
212	44	Male	9	27	42	75
213	53	Male	38	25	45	75
Mean ± SE	47.6 ± 4.7		27.2 ± 5.6	24.6 ± 1.1	44.4 ± 1.3	

parameters and the UHDRS did not take into account age. Age is known to affect reflexive and voluntary eye movements [31]. Establishment of simple, non-invasive and age-controlled biomarkers of motor and cognitive disease severity is important for monitoring progression, preclinical diagnosis, differentiating subtypes, and development and evaluation of treatments [32]. Eye movement deficits, themselves, are also associated with increased risk of developing HD [13,33].

2. Methods

2.1. Subject recruitment and demographics

All study participants gave informed consent at the start of each testing session. The study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston and the Institutional Review Board at the Baylor College of Medicine (BCM).

Thirteen subjects were recruited from the Movement Disorders Clinic at BCM, Houston, Texas. One subject did not complete the behavioral tasks and one elderly subject was excluded due to incomplete data. All eleven remaining subjects (aged 27–70 years; 5 males and 6 females) met clinical and genetic criteria for HD with a mean of 44.4 ± 1.3 SE CAG repeats, (range 41–52) in the *huntingtin* gene (Table 1). Subjects were assessed clinically using the UHDRS motor score (Table 2). The rater was blind to the eye movement data. A higher UHDRS motor score indicates worse clinical symptomatology. The Montreal Cognitive Assessment (MoCA) was used to assess cognitive function. Six of the HD subjects were not receiving medication for HD.

2.2. Eye tracking apparatus and saccade criteria

Saccadic eye movements were recorded using an infrared ISCAN RK-826 PCI eye tracking system. Subjects were seated in front of a 17-inch CRT monitor with their heads placed in a stable chin rest that was positioned 72 cm from the screen. The spatial and temporal resolutions of the eye tracker were approximately 0.5° visual angle and 4 ms (240 Hz), respectively. Before the start of an eye movement recording session, the subject was calibrated by moving their eyes to nine positions on the screen indicated by 0.2° × 0.2° white boxes on a black background. For the eye movement tasks, a gray fixation point (0.2° diameter) was illuminated in the center of the black screen. Target stimuli were 0.2° × 0.2° white squares that appeared in landmark boxes (1.1° by 1.1°) 7° to the top, bottom, right and left of the fixation point. Saccade initiation and termination were defined by areal and velocity criteria. Specifically, for saccade initiation, eye velocity had to be above 47.5°/s, and for saccade termination, eye velocity had to be both below 12°/s and within 4.4° of the eye movement goal (areal criterion). The correct eye movement goal was the target for the prosaccade task and the opposite or mirror-image location for the antisaccade task.

Table 2
UHDRS motor.

	N	Minimum	Maximum	Mean	Std. error
Total	11	0	47	27.2	5.6
Select subscales					
Total chorea	11	0	21	11.2	2.5
Bradykinesia	11	0	2	0.9	0.3
Ocular pursuit	11	0	2	0.8	0.3
Saccade initiation	11	0	6	2.2	0.6
Saccade velocity	11	0	4	2.0	0.4
Finger taps	11	0	4	2.3	0.6
Luria	11	0	4	1.0	0.4

2.3. Procedure

After administration of all clinical and cognitive testing, prosaccade and antisaccade tasks (48 trials each) were administered to all HD subjects. Trials interrupted by a blink were aborted and randomly re-presented. Each task was preceded by an 8-trial practice block and instructions were verbally repeated before each task began. For each task, target position was balanced for target location (i.e., equal presentation in the left, right, upper and lower visual field). Trials were self-paced; to begin a trial, the subject had to fixate a point located straight

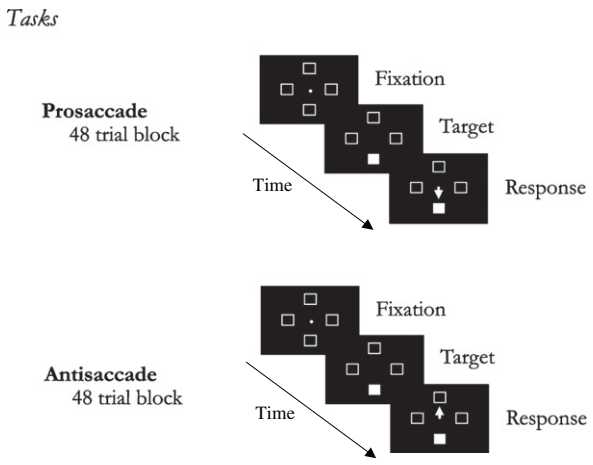

Fig. 1. Illustration of the prosaccade and antisaccade tasks. In each task, four square landmarks along with a central fixation point initially are displayed on the computer monitor. After a delay, a bright square target appears within one of the four landmarks. Before each trial block, the subject is instructed to make a saccade to the target (prosaccade task) or make a saccade to the opposite location of the target (antisaccade task). The white arrow illustrates a correct eye movement response. The prosaccade and antisaccade tasks were run in separate 48 trial blocks.

ahead. After a fixation period of 400 ms, the target randomly appeared 7° to the top, bottom, right or left of the fixation point (Fig. 1). For the prosaccade task, the subject had to look as quickly as possible *at* the peripheral target, while for the antisaccade task the subject had to look to the *opposite* side or mirror-image location of the peripheral target. For both tasks, auditory and visual feedback was provided to the subjects if the eye movement was incorrect. The target remained on the screen until the eye movement was completed or until the trial timed out after 1492 ms. The order of prosaccade and antisaccade tasks was counterbalanced across all participants.

2.4. Statistical analyses

2.4.1. Inclusion criteria

For all the eye movement analyses reported here, data were collapsed across target locations for each observer. Furthermore, trials with response latencies below 100 ms and above 900 ms were excluded from the analyses (6.3% and 10.2% for prosaccades and antisaccades respectively).

2.4.2. Calculation of error rate

Direction errors were defined as eye movements that did not meet our areal and velocity criteria (see Eye tracking apparatus and saccade criteria section above). For each task type (prosaccade or antisaccade), the error rate was calculated by dividing the number of trials with direction errors (incorrect trials) by the total number of trials that met the inclusion criteria described above. A higher error rate indicates poorer performance.

2.4.3. Calculation of latency

Calculation of mean saccade latencies included only correct trials that met the inclusion criteria described above. Correct trials were trimmed if they were greater than 2.5 standard deviations around the mean of each subject, separately for the prosaccade and antisaccade tasks, eliminating 1.9% and 1.2% of the remaining trials for prosaccades and antisaccades, respectively. After the additional trimming, 87.7% and 47% of the total trials were left for analyses of correct trial saccade latency in the prosaccade and the antisaccade tasks, respectively. The difference in the percentage of trials used for latency analyses in the prosaccade and the antisaccade tasks is mainly because subjects made substantially more correct prosaccades (mean percent correct = 95.2%, SD = 4.5%) compared to antisaccades (mean percent correct = 50.9%, SD = 31.4%). A longer latency indicates poorer (slower) performance.

2.4.4. Correlation of eye movement and clinical measurements

Using SPSS for Macintosh (Somers, NY), latency and error rate in the prosaccade and antisaccade tasks were correlated with the UHDRS motor score as well as several subscales including total chorea, bradykinesia, ocular pursuit, saccade initiation, saccade velocity, finger taps, and Luria. Pearson correlation coefficients were calculated in each case. Simple correlations as well as age-controlled partial correlations were computed in each case.

2.4.5. Analysis of eye movement measurements with clinical severity below the first and above the third quartile

Subjects were divided into those belonging to below the first or above the third quartile range for a given clinical parameter. The clinical parameters that were used for these analyses were the UHDRS motor, total chorea, and finger taps scores. For each clinical parameter, average values of eye movement variables were compared for subjects below the first and above the third quartile clinical range using independent samples *t*-test assuming unequal variance. The clinical and eye movement parameters for this analysis were the same that showed significant correlations in the previous analyses. The average values of eye movement variables were not adjusted for age.

3. Results

Given that subject demographics might affect UHDRS motor score, a mixed model analysis with gender and medication status as main factors and age as a covariate was performed prior to further analyses. This analysis did not show a significant effect of gender or medication status on UHDRS motor scores of HD subjects. There was, however, a marginally significant effect of age on UHDRS motor scores of HD subjects ($t(7) = 2.2$, $p = 0.06$). Age was marginally correlated with prosaccade ($r = 0.56$, $p = 0.07$) and antisaccade ($r = 0.53$, $p = 0.09$) latencies, and, significantly correlated with prosaccade ($r = 0.86$, $p = 0.001$) and antisaccade ($r = 0.69$, $p = 0.02$) error rates in HD subjects. Because age was not identical for mild and severe clinical symptomatology, when testing for correlations between eye movement variables and clinical symptomatology, we performed both simple and age-controlled correlations that controlled for any age differences.

3.1. Reflexive orienting

Our results showed that HD patients' reflexive saccades slow with an increase in disease severity. There was a significant positive correlation between UHDRS motor scores and prosaccade latency ($r(9) = 0.64$, $p = 0.035$) (Fig. 2A). When age of the subjects was taken into account, the correlation, however, decreased to 0.40 ($df = 8$, $p = 0.25$). The subjects above the third quartile on their UHDRS score had significantly longer prosaccade latency compared to those below the first quartile (*mean difference* = 90.1 ms, $SE = 24.2$ ms, $t(4.9) = 3.7$, $p = 0.014$) (Fig. 2B).

There was a significant positive correlation between total chorea and prosaccade latency ($r(9) = 0.79$, $p = 0.004$) and this correlation remained significant after taking age into account ($r(8) = 0.69$, $p = 0.029$) (Fig. 2C). The subjects above the third quartile on their total chorea score had significantly longer prosaccade latency compared to those below the first quartile (*mean difference* = 107.5 ms, $SE = 23.4$ ms, $t(4) = 4.6$, $p = 0.01$) (Fig. 2D).

3.2. Voluntary orienting

The results of voluntary orienting show that voluntary control in HD patients decreased with increased disease severity, as evidenced both by an increase in voluntary saccade latency and an increase in errors. There was a significant positive correlation between antisaccade latency and UHDRS motor score ($r(9) = 0.63$, $p = 0.04$), but when age of the subjects was taken into account, the correlation decreased to 0.41 ($df = 8$, $p = 0.24$). The subjects above the third quartile on their UHDRS motor score had higher antisaccade latency compared to those below the first quartile but the difference was not significant (*mean difference* = 130.9 ms, $SE = 65.1$ ms, $p = 0.14$).

There was also a significant positive correlation between antisaccade latency and total chorea ($r(9) = 0.73$, $p = 0.012$), but this correlation showed only a trend after taking age into account ($r(8) = 0.6$, $p = 0.068$). The subjects above the third quartile on their total chorea score had higher antisaccade latency compared to those below the first quartile, but this difference was not significant (*mean difference* = 165.5 ms, $SE = 60.4$ ms, $t(2.2) = 2.7$, $p = 0.10$).

Antisaccade error rate in HD subjects increased significantly with increase in UHDRS motor score ($r(9) = 0.89$, $p < 0.001$) (Fig. 3A) and this correlation remained significant even after taking into account the age of subjects ($r(8) = 0.78$, $p = 0.008$). The subjects above the third quartile on their UHDRS motor score had a significantly higher antisaccade error rate compared to those below the first quartile (*mean difference* = 61.7%, $SE = 13.3$%, $t(3.1) = 4.6$, $p = 0.017$) (Fig. 3B).

Antisaccade error rate in HD subjects also increased significantly with an increase in total chorea score ($r(9) = 0.94$, $p < 0.001$) (Fig. 3C) and this correlation remained highly significant even after taking into account the age of subjects ($r(8) = 0.9$, $p < 0.001$). The subjects above

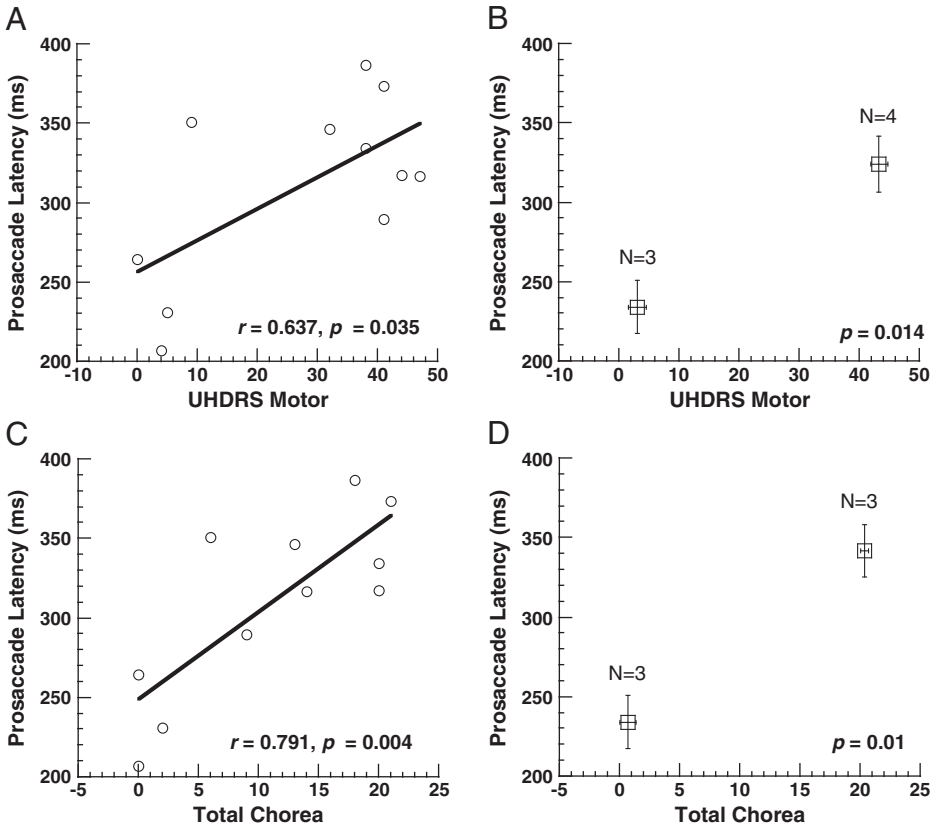

Fig. 2. Correlation between reflexive eye movement parameters and clinical scores. A. The simple correlation between latency in the prosaccade task and UHDRS motor score using data from all the subjects. The numbers reported in the bottom right of the left panel (for all other figures as well) represent the Pearson's correlation coefficient (r) and the p-value (p) associated with the correlation. B. Average prosaccade latency for subjects that had UHDRS motor scores below the first and above the third quartile. The error bars represent ± 1 SEM. The number in the bottom right part of right panel represents the p-value obtained from an independent sample t-test comparing the data for subjects below the first and above the third quartile (for all other figures as well). The numbers above each data point indicate the number of subjects (for all other figures as well). C. Simple correlation between latency in prosaccade task and total chorea score using data from all the subjects. D. Average prosaccade latency for subjects that had total chorea score below the first and above the third quartile.

the third quartile on their total chorea score had a significantly higher antisaccade error rate compared to those below the first quartile (*mean difference* = 69.8%, $SE = 5.8\%$, $t(2.5) = 12.1$, $p = 0.003$) (Fig. 3D).

Antisaccade error rate in HD subjects also increased significantly with increase in finger tap score ($r(9) = 0.78$, $p = 0.004$), but this correlation became only a trend after taking into account the age of subjects ($r(8) = 0.62$, $p = 0.059$). The subjects above the third quartile on their finger tap score had a significantly higher antisaccade error rate compared to those below the first quartile (*mean difference* = 52.4%, $SE = 11.8\%$, $t(6.4) = 4.4$, $p = 0.004$).

4. Discussion

Our findings show that age is an important variable when examining correlations between clinical and eye movement measures. For example, we found significant correlations between latency (prosaccade or antisaccade) and UHDRS motor score. However, these correlations were absent when the ages of the subjects were taken into account. Age has not been controlled in previous eye movement studies on HD patients [4,18,20,28,30]. Nevertheless, after taking age into account, we found that [1] latency in the prosaccade task was significantly correlated with the total chorea score; and [2] error rate in the antisaccade task was significantly correlated with both UHDRS motor scale and total chorea score. Hence, the results of the present study show that reflexive and voluntary control of saccadic eye movements decreased with an increase in HD disease severity as characterized by the UHDRS motor score and total chorea subscale. The findings of this study suggest that relatively simple eye movement parameters (latency and error rate) obtained from simple tasks (prosaccade and antisaccade) may serve as quantitative biomarkers of disease severity and progression in HD.

One advantage of using eye movements as a quantitative biomarker for disease severity and progression in HD is that they offer a continuous scale with much finer gradations compared to the UHDRS motor scale and, therefore, are likely to detect smaller changes in HD progression. This may be critical in HD patients for detecting onset of disease, discriminating between rates of progression, or evaluating treatment efficacy. A second advantage is that eye movement measures show sensitivity [34] and reliability at an individual level [35,36]. A third advantage of using eye movements as a quantitative biomarker for disease severity and progression in HD is the specificity they offer about localization of the degeneration. For instance, much work now implicates frontal cortical dysfunction [37] for the high errors on the antisaccade task [38]. The antisaccade task is thought to be a sensitive marker of cognitive deficits because the task requires several key "executive functions" [37,39–44]. Namely, the antisaccade task requires response inhibition (i.e., the ability to inhibit a prepotent response to a sudden target onset), voluntary response control (i.e., the ability to generate a willful movement, when there is no external target), and working memory (i.e., the ability to hold in mind the instructions to look in the opposite direction). HD patients showed a significant increase in voluntary saccade deficits (both latency and error rate) with disease severity. While HD is a movement disorder, these findings suggest that HD patients develop marked cognitive impairment, which is just as critical to detect and treat as the motor symptoms for improved quality of life.

Given that all saccadic eye movements share a common motor output through brainstem regions, a slowing in response that may first only be present in voluntary eye movements but then, as the disease progresses,

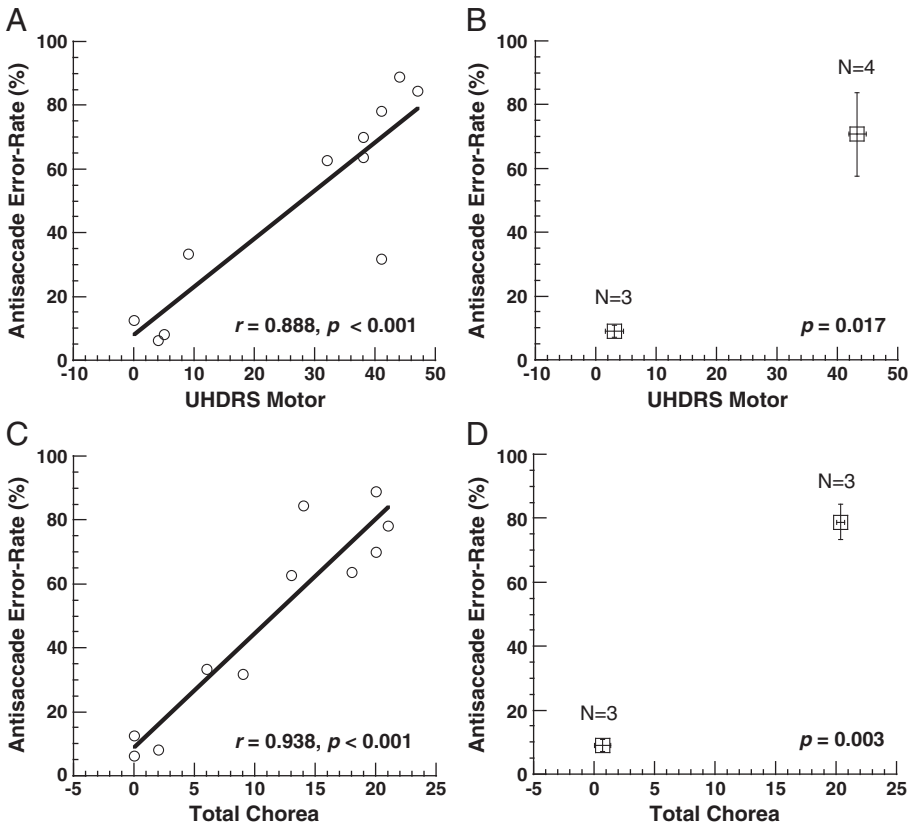

Fig. 3. Correlation between voluntary eye movement parameters and clinical scores. A. Simple correlation between latency in antisaccade task and UHDRS motor score using data from all the subjects. B. Average antisaccade latency for subjects that had UHDRS motor score below the first and above the third quartile. C. Simple correlation between latency in antisaccade task and total chorea score using data from all the subjects. D. Average antisaccade latency for subjects that had total chorea score below the first and above the third quartile.

appear also in reflexive eye movements could specifically implicate onset of degeneration in brainstem regions in HD patients. Also, since vertical and horizontal eye movement control segregate in the brainstem, differences between vertical and horizontal eye movements at particular stages of the disease may be useful for identifying and differentiating different patterns of progression.

Although longer CAG repeats predict earlier onset, accounting for as much as 50–70% of variance in age of onset [45], there is a weaker association with clinical severity and progression [46]. It is generally thought that intervention and treatment in the very early, preclinical stages of degeneration may be most beneficial [32,47]. Hence there is a need to identify sensitive, stable, and quantitative biomarkers of change in patients with preclinical and early-stage HD [27,48].

Saccadic abnormalities have been known for a long time to be present even in early stages of HD. In the initial study that led to the discovery of the HD gene involving 593 members of a large kindred in Venezuela, generation of fine motor movements and of saccades was found to be impaired in about 50% of at-risk individuals [28]. Since these at-risk individuals were more likely than those without them to develop overt HD within several years, these abnormalities were thought to represent the earliest clinical manifestations of the disease. HD patients seem to have greater defects in initiating volitional (internally) than reflexive (externally) generated saccades [33]. In 215 individuals at risk for HD or recently diagnosed with HD, a high resolution, video-based eye tracking system was used to demonstrate three types of voluntary saccade abnormalities while performing memory guided and antisaccade tasks: increased error rate, increased saccade latency, and increased variability of saccade latency [20]. In another study, initiation deficits of voluntary-guided, but not reflexive saccades, were found in individuals with preclinical HD [21]. A recent report suggests that oculomotor defects may be seen even in presymptomatic patients with a predicted time to clinical onset of up to 10 years [49]. These findings demonstrate the feasibility of using eye movements for detection of preclinical abnormalities. This fact in combination with the present findings of significant correlations of both voluntary and reflexive eye movement variables with clinical disease severity suggests that these eye movement variables may be able to serve as sensitive, reliable, and quantitative measures of the earliest, preclinical stages of degeneration. Studies measuring the rate of progression of reflexive saccade abnormalities in premanifest HD patients have shown significant and systematic changes from year to year in certain parameters related to saccade latency [48,50].

Although our study provides strong evidence for correlation between eye movement abnormalities and clinical severity of HD, the results must be interpreted cautiously as our sample size was relatively small and our study was cross-sectional. Larger and longitudinal studies will be necessary to determine whether the observed oculomotor abnormalities will be useful biomarkers for the presymptomatic detection of HD and progression of the disease. In addition to abnormal saccades, patients with HD demonstrate other neuro-ophthalmologic abnormalities that may also prove to be sensitive and quantifiable biomarkers of presymptomatic disease severity and progression, such as increased blink rates [51], irregular elevations of eyebrows due to choreic contractions of the frontalis muscles, eye closures with irregular narrowings of palpebral fissures, rarely leading to frank blepharospasm, and apraxia of eyelid opening and closure [52, 53].

In conclusion, infrared eye tracking is a quick, noninvasive, and objective method of characterizing disease severity in HD. Our results show that with increasing clinical severity, HD patients show a deficit in the inhibition of reflexive eye movements and dysfunction of executive control (increased antisaccade errors). HD patients also show a slowing in eye movement latencies for reflexive and voluntary saccades with increasing clinical severity. Thus, eye tracking has great potential in HD for detecting early onset, differentiating subtypes that may

predict differential progression, and evaluating treatments on specific symptoms.

Author roles

SP conducted the data analysis and wrote the initial draft of the manuscript. JJ conceived the collaboration, recruited the patients, directed the clinical and genetic evaluations, and co-wrote the manuscript. AH collected the eye movement data, conducted the initial data analysis, helped with the literature search and edited the manuscript. CJ collected the eye-movement data, helped in the initial data analysis and edited the manuscript. AS designed the study, and co-wrote the manuscript.

Conflict of interest

Nothing to report.

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