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Saccades, pupil response and blink abnormalities in Huntington's disease patients during free viewing ☆

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HIGHLIGHTS

- We used eye tracking to investigate the effect of early Huntington's disease on saccadic movements, pupil reaction and blink production.
- HD patients showed significant changes in all three behaviors while watching short videos in a free-viewing task.
- This suggests brain stem degeneration at an early stage of the disease detectable with a simple free viewing task.

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ABSTRACT

Objective: Video-based eye tracking was used to investigate saccade, pupil, and blink abnormalities among patients with Huntington's disease (HD) who watched sequences of short videos. HD, an autosomal dominant neurodegenerative disorder resulting from a CAG mutation on chromosome 4, produces motor and cognitive impairments including slow or irregular eye movements, which have been studied using structured tasks.
Methods: To explore how HD affects eye movements under instruction free conditions, we assessed 22 HD patients and their age matched controls in a 10-minute video-based free viewing task.
Results: Patients with HD experienced a significant reduction in saccade exploration rate following video clip transitions, an increase in pupil reactions to luminance changes after clip transitions, and a significant higher blink rate throughout the task compared to the control group.
Conclusions: These results show that HD has a significant impact on how patients visually explore and respond to their environment under unconstrained and ecologically natural conditions.
Significance: Eye tracking in HD patients revealed saccadic, pupil, and blink abnormalities in early HD patients, suggestive of brain circuitry abnormalities that probably involve brain stem deficits. Further research should explore the impact of these changes on the quality of life of the patients affected by the disease.

1. Introduction

Huntington's disease (HD) is a neurodegenerative condition resulting from an expanded CAG repeat in the IT15 gene, responsible for encoding the huntingtin protein (MacDonald et al., 1993). The disorder is marked by a progression of motor, cognitive, and psychiatric symptoms, arising from the misfolded huntingtin protein (Novak and Tabrizi, 2011). Among the cognitive and motor

☆ Sadly, Israel Vaca-Palomares passed away in July 2023. As this work was initiated with him, the rest of the authors decided to finish the research and to submit the paper with his name as coauthor. This is our tribute to our dear friend and collaborator.

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symptoms, oculomotor deficits, including deficits in saccades and fixation, are some of the earliest and most consistent signs of HD (Hicks et al., 2008; Leigh et al., 1983). As the disease progresses, both automatic and voluntary saccade control is affected, as indicated by an increased saccade latency and error rates in antisaccades, which correlate with disease severity. (Patel et al., 2012; Peltsch et al., 2008; Winograd-Gurvich et al., 2003). These deficits reflect dysfunction in the frontal eye fields, the supplementary eye fields, the basal ganglia and the superior colliculus, as well as cortico-striatal connections involved in generating and modulating saccadic commands (Klöppel et al., 2008; Rupp et al., 2012; Vaca-Palomares et al., 2017).

To date, almost all studies on oculomotor function in HD have used paradigms that involve structured tasks with instructions and discrete visual stimuli. These approaches are useful to control experimental variables but they do not represent natural viewing conditions and behavior. A more ecologically valid approach to assess oculomotor function in HD involves utilizing free viewing (FV) eye-tracking, allowing participants to explore complex visual scenes without specific instructions or tasks (Sears et al., 2019). Such a method could provide valuable insights into how HD patients allocate visual attention to salient stimuli and process visual information, variables that can affect how can patients interact with their environment during the daily living activities (Tseng et al., 2013). Presenting patients with brief video clips on a computer monitor allows them to watch the clips freely during video-based eye tracking, while affording an extensive examination of saccade, pupil, and blink behavior. This facilitates the detection of abnormalities with only ten minutes of testing, as has been used with several other neurological conditions (Habibi et al., 2022; Tseng et al., 2013). Additionally, the FV paradigm eliminates the need for extensive preparatory instructions, which is particularly advantageous when studying patients with neurodegenerative diseases who may experience cognitive decline or have difficulty following complex instructions such as patients with HD (Novak and Tabrizi, 2011).

Here, we measure oculomotor behavior in FV conditions in patients with HD compared to healthy controls. These FV conditions include video clip changes that alter the continuity of the visual input scenery, subsequently affecting saccade, pupil, and blink behavior (Fogarty and Stern, 1989). Based on previous findings of other neurodegenerative diseases affecting the basal ganglia, we predict deficits in all three effectors (Habibi et al., 2022; Kassavetis et al., 2022). We also explore the relationship between oculomotor performance and clinical variables, such as motor symptoms and cognitive function.

2. Methods

2.1. Participants

All patients were enrolled and evaluated at the Instituto Nacional de Neurología y Neurocirugía (INNN) in Mexico. Inclusion/exclusion criteria were established prior to conducting any data analysis, manipulations, or measurements, for the study. These criteria specifically included patients with a molecular diagnosis of trinucleotide repeat expansion (CAG) and individuals whose neurological/motor impairment, as assessed by a skilled neurologist, did not prevent them from performing the tests. Patients without CAG determination, those whose neurological/motor impairment hindered test performance, and those who had a neurological evaluation exceeding six months at the time of the initial interview were excluded from the study. Some participants of this cohort also participated in previous studies from our group (Vaca-Palomares et al., 2019, 2017).

The HD patients cohort consisted of 22 right-handed individuals, ranging in age from 29 to 68 years (13 females). The mean age was 49.6 ± 11.7 yrs., with an age at onset ranging from 25 to 62 years (mean: 44.5 ± 10.4 yrs.). The duration of early disease ranged from 1 to 10 years (mean: 4.6 ± 3.0 years), and the CAG repeat size ranged from 40 to 52 (mean: 44.3 ± 3.0). The educational background of the patients ranged from 9 to 18 years (mean: 13.7 ± 3.0 yrs). None of these patients was prescribed medication for their condition; however, they continued taking supplements such as Coenzyme Q-10 during the recording session, which has not been reported to have an effect on any of the metrics evaluated in this report. Clinical assessments of the HD patients were conducted by a specialist neurologist from the INNN, which included the Montreal Cognitive Assessment (MoCA) to evaluate overall cognitive function and the Unified Huntington's Disease Rating Scale (UHDRS) to assess disease progression. The patients' mean scores were 24.7 ± 3.4 (range 17–30) on the MoCA, 17.0 ± 12.6 (range 0–48) on the UHDRS motor (UHDRS-m) component, and 11.5 ± 2.1 (range 6–13) on the functional component of the UHDRS (UHDRS-f). It is important to note that the UHDRS motor component comprises standardized ratings for oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability.

The control group (CTRL) comprised 23 healthy right-handed volunteers, aged between 30 and 64 years (13 females), who were recruited from friends and non-consanguine family of the patients in Mexico City. The mean age was 49.9 ± 10.6 yrs., and the educational background ranged from 9 to 20 years (mean: 15.9 ± 3.3 yrs.). Control participants matched the patients in terms of age and sex, and had no reported visual, neurological, or psychiatric disorders, achieving MoCA scores of $\geq$24 (mean 27.2 ± 1.6).

Previous studies in HD utilizing eye-tracking methodologies have demonstrated significant differences between the patient and control groups, even with fewer than 20 participants in each group (Anderson and MacAskill, 2013; MacAskill and Anderson, 2016; Peltsch et al., 2008; Vaca-Palomares et al., 2017). Therefore, the sample size of 22 and 23 participants in the HD and healthy control groups respectively, was judged sufficient to provide power to detect differences between the groups.

2.2. Procedure and experimental paradigm

We recorded the right-eye positions from all participants using a video-based eye tracker (Eyelink-1000 Plus monocular-arm; SR Research, Mississauga, ON, Canada) at a rate of 500 Hz, capturing monocular pupil size and eye position. The stimulus presentation and data acquisition were controlled by Eyelink Experiment Builder and EYELINK software. Participants were seated in a dark room, and stimuli were presented on a 17-inch LCD monitor with a screen resolution of 1280 × 1024 pixels (60-Hz refresh rate), resulting in a viewing angle of 32° × 26°. The distance between the monitor and the participants' eyes was 60 cm. (See supplementary material for a picture of the experimental setup and Eyelink-1000 monitor, and raw data samples from two control and two patients with HD participants).

All participants viewed ten movies, each approximately 1 min in duration, consisting of 15–17 video clips ranging from approximately 2 to 5 s in duration (mean = 3.76). The video clips included scenes with and without humans, animals, buildings, and cars, and were randomly assembled to replicate the experience of watching TV and changing channels every few seconds (and changing the scene every few seconds). The clips followed a fixed sequence within each movie, but the order of the ten movies was pseudo-randomized for each participant, where the first five were played in random order then the last five were played in random order. The task required no specific instructions; participants simply watched the video clips. The instantaneous transitions between

clips induced significant visual perturbations, stimulating the central retina and generating a large visual transient signal (White et al., 2017), which affected ongoing saccade and pupil behavior.

2.3. Saccade analyses

We analyzed saccades using two approaches: (1) responses to clip changes; and (2) low-level statistics independent of the video content. MATLAB scripts were employed to automatically identify each trial and record all eye behaviors, including saccades, fixations, and pupil size. For each saccade, we measured its direction, amplitude, peak velocity, and duration. Detailed descriptions of how these metrics were determined have been published previously (Coe et al., 2024). Following previous studies (Martinez-Conde et al., 2006, 2000; Otero-Millan et al., 2013), we categorized saccades as macro-saccades (≥2° amplitude) or micro-saccades (<2° amplitude). By utilizing the fixation coordinates, we generated gaze distribution maps and calculated the center bias, representing the inclination to gaze more at the screen's center (Tseng et al., 2009). The center bias was computed as probability of gaze around the center ±5° of the gaze distribution map for each participant. Additionally, we computed the frequency (saccade-count/viewing-duration) and average saccade amplitude for 60 different saccade directions (each bin measuring 6° in polar angle).

We performed separate analyses for horizontal and vertical saccades. Horizontal saccades were defined as those within ±22.5° (45° wedge) of the horizontal meridian, while vertical saccades were defined as those within ±22.5° of the vertical meridian. To examine the relationship between saccade peak velocity and logarithm of amplitude, we plotted all saccades >2° for each participant, revealing a linear relationship known as the main sequence (Bahill et al., 1975) The main sequence provides insights into the integrity of the brainstem saccade premotor circuit. By converting to the log of the amplitude, the main sequence showed a linear relationship, and allowed us to then fit a linear function to the data, which allowed a simpler means of comparing between groups. Furthermore, we calculated the rates of macro- and micro-saccades (saccades/s) for each participant using a *peri*-stimulus time histogram (PSTH) with a bin width of 2 ms, considering the 500 Hz sample rate. We then applied a Lowess model (locally weighted linear regression) to fit a smooth curve to the saccade rate data. This method preserved the underlying structure of the curves while adding just enough smoothing in order to discern meaningful variation in the saccade rate over time. Notably, the transitions between video clips induced transient changes in saccade and pupil behavior.

We computed several parameters for both macro-saccades and micro-saccades for each participant. These parameters included the baseline rate (mean rate from −200 to +50 ms relative to clip change), suppression magnitude and timing (the minimum response from 70 to 200 ms after clip change [400 ms for micro saccades], and the time of that nadir), peak rate following clip transition (maximum value from suppression time to 300 ms after suppression time), and steady-state rate (average from 1000 to 3000 ms after clip change). To obtain these parameters, we used the PSTHs.

2.4. Pupil analysis

We assessed the mean global luminance of each frame in the movie. This was achieved by calculating the luminance of individual pixels using the luminance gamma functions of the red, green, and blue color gamuts. We then examined the correlation between the mean pupil size and the mean screen luminance (cd/m2) for each participant, extracting the y-intercept and slope values. Additionally, we measured the luminance change at each clip transition and selected the 30 clip changes with the most significant increase and decrease in luminance that resulted in pupil constriction and dilation respectively. This allowed us to investigate the impact of clip changes on pupil behavior, including delta (the minimum normalized, zeroed at clip change, pupil size from ±100 ms from the end of significant velocity period) and steady state (the average normalized, zeroed at clip change, pupil size from 1000 ms to 3000 ms post clip change for the 30 constriction clips) for both, constriction and dilation. Furthermore, we explored the correlation between all eye movement parameters and clinical scores to investigate the relationship between disease severity and oculomotor and pupillometry parameters.

2.5. Blink analyses

We use the starting and ending points of lost data from the eye-tracker during the task, together with the smoothed absolute velocity of the pupil area changes to define blinks (Coe et al., 2024). We then assessed blink frequency and duration and its possible relation to clip changes, and clinical scores.

2.6. Statistical analysis

In IBM SPSS 28.0.1.1 statistics (IBM Corp., 2020, IBM SPSS Statistics version 28.0.1.1), we employed the Mann-Whitney *U* test, a pairwise non-parametric test, for all statistical comparisons. To examine correlations between eye parameters and clinical scores, we conducted nonparametric Spearman partial correlations while controlling for age and years of schooling.

3. Results

3.1. Saccade behavior

Clip changes, which resulted in a large transient change in the visual input to the brain, caused a brief suppression of macro-saccade rate starting about 65 ms after the change, followed by a rebound in macro saccade production that started around 120 ms and peaked at 200–250 ms (Fig. 1A). The saccade rate then returned to the beginning of the steady state after 400–500 ms for the remainder of the clip. The baseline saccade rate before the clip change was similar in HD and CTRL groups (CTRL M: 1.37 saccades/s, SD: 0.37; HD M: 1.32 saccades/s, SD: 0.43) (U = 240, p = 0.76). However, the saccade rebound was significantly weaker in HD than in CTRL, both early in the rebound (120–180 ms after clip change) (CTRL M: 2.57 saccades/s, SD: 1.14; HD M: 1.43 saccades/s, SD: 1.09), (U = 100, p < 0.001), and at the peak (CTRL M: 4.7 saccades/s, SD:0.82; HD M: 4.04 saccades/s, SD: 1.14), (U = 150, p = 0.019) (Fig. 1B). This difference disappeared later in the rebound (CTRL M: 3.2 saccades/s, SD: 0.45; HD M: 2.94 saccades/s, SD: 0.65; U = 187.5, p = 0.13) and in the steady state period (1000–3000 ms after the clip change) (CTRL M:1.46 saccades/s, SD: 0.33; HD M: 1.35 saccades/s, SD: 0.4; U = 228, p = 0.57) (Fig. 1B early, late and steady state stages respectively).

Clip changes also influenced micro-saccade rate (Fig. 1C). In CTRL, micro-saccade rate decreased about 70 ms after the change and remained low until about 500 ms before returning to steady state. This suppression was significantly reduced in HD compared to CTRL (CTRL M: −0.78, SD: 0.26; HD M: −0.66, SD: 0.23; U = 159, p = 0.03) (Fig. 1D mean suppression). However, the steady state (SS) micro-saccade rate (1000–3000 ms after the clip change) was similar between the groups (CTRL M: 0.83, SD: 0.28; HD M: 0.76, SD: 0.32; U = 201, p = 0.23) (Fig. 1D SS).

3.2. Low-level saccade analyses

The FV paradigm provides low-level saccade information. We include those analyses as Supplementary Material 1 because we have previously reported low-level saccade analysis from this HD patient cohort [6, 10]. Specifically, we analyzed the gaze distribution (Sup. Fig. 1), as well as the macro and micro-saccade frequency, amplitude, and fixation duration, and found no differences between groups (Sup. Fig. 2). Our analysis also showed no between group differences in saccade rate or amplitude in different saccade directions (Sup. Fig. 3 and Sup. Fig. 4 respectively). The only low-level significant difference between groups was in the saccade amplitude-velocity relationship (Sup. Fig. 5), where the results showed a significant decrease in velocity with larger amplitude in HD, which is consistent with previous literature [4].

3.3. Pupil responses

Participants with HD had dramatically larger pupil size compared to controls during the FV paradigm (Fig. 2A, B, D). (CTRL M: 1021, SD: 367; HD M: 1368, SD: 522.1; U = 149, p = 0.018), but only a trend in the response to luminance (CTRL M: −4.64, SD: 2.26; HD M: −6.06, SD: 2.71; U = 174, p = 0.07) (Fig. 2B and C). We found no differences in the pupillary constriction response latency (CTRL M: 234 ms, SD: 37; HD M: 235 ms, SD: 36.1; U = 241, p = 0.78) or dilation response latency (CTRL M: 412 ms, SD: 89; HD M: 357 ms, SD: 96.1; U = 151, p = 0.38).

We also examined how significant luminance increases or decreases resulting from clip changes affected pupil constriction and dilation responses, respectively. For the top 20% of clip changes with the greatest luminance increase (Fig. 3A), the pupil constricted sharply starting 300 ms after the increase and reached the minimum size at about 800 ms, then slowly dilated over the next 2 s. Patients with HD had a significant larger pupil constriction response than CTRL (CTRL M: −267.93, SD: 135.18; HD M: −365.67, SD: 178.05; U = 165, p = 0.046) (Fig. 3B). Further, the pupil constriction response in the steady state after the luminance increase was larger in HD than in CTRL (CTRL M: −189.67, SD: 99.09; HD M: −256.18, SD: 119.1; U = 166, p = 0.048) (Fig. 3C). For the 20% of clip changes that had the greatest luminance decrease, the pupil dilated rapidly 400 ms after the change and continued to increase until it reached a steady size after about 1000 ms (Fig. 3D). The initial dilation response was similar in HD and CTRL groups (CTRL M: 105.16, SD: 58.28; HD M: 122.26, SD: 49.89; U = 134, p = 0.18) (Fig. 3E). However, the pupil size in the steady state was significantly larger in HD than in CTRL (CTRL M: 118.95, SD: 63.6; HD M: 155.91, SD: 66.11; U = 213, p = 0.043) (Fig. 3F).

3.4. Blink behavior

We also analyzed blink behavior during the FV task. The analysis of the blink rate showed differences between CTRL and HD groups. Patients with HD had a significantly higher blink rate than CTRL (CTRL M: 9.39, SD: 6.08; HD M: 16.16, SD: 10.62; U = 150.5, p = 0.02) (Fig. 4A). Notably, the median blink duration was similar between groups (CTRL M: 168.11, SD: 33.71; HD M: 179.03, SD: 39.96; U = 233, p = 0.65) (Fig. 4B), showing that the HD group had normal blink metrics but greatly increased occurrence.

3.5. Correlations between oculomotor and clinical assessment

We used partial correlation analysis to test the relationship between the oculomotor variables and the clinical scores in HD patients, while adjusting for age and education as confounding variables. The Spearman partial correlation showed significant

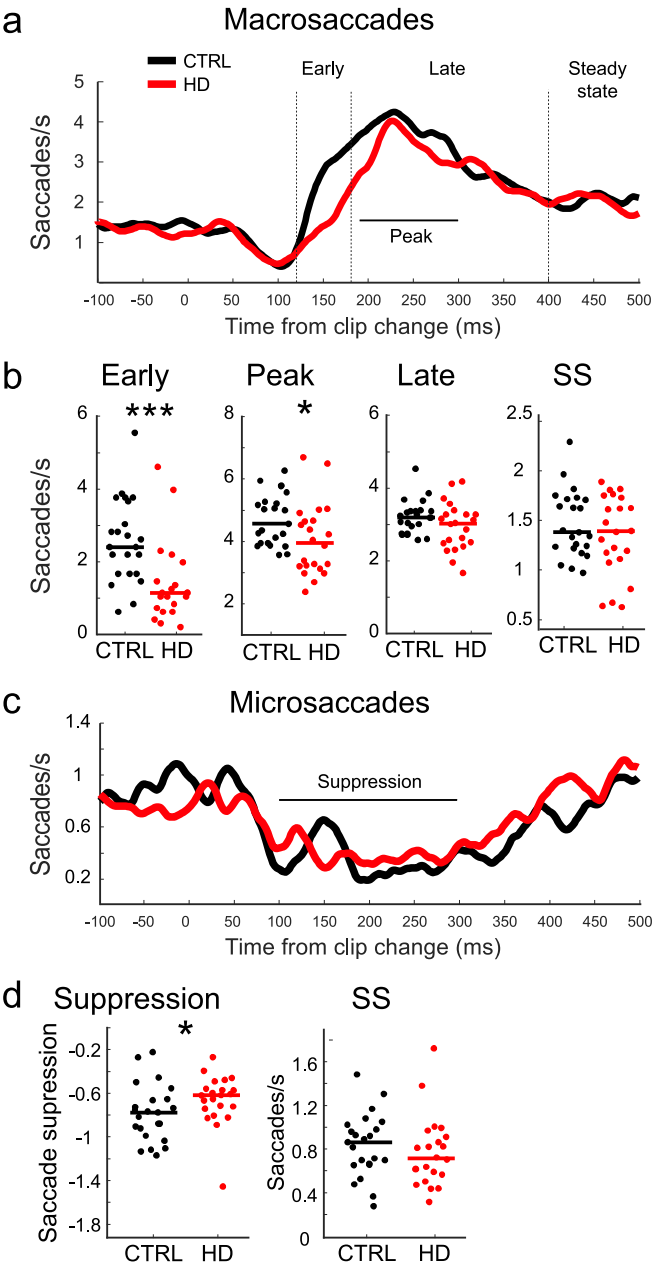

Fig. 1. Saccade Rate after Clip Change. a. Macro-saccade rate after a clip change. The dashed vertical lines separate the baseline, and the early, late, and steady state phases following the clip change. The horizontal line indicates the peak epoch. Each trace represents the mean macro-saccades of all participants in all trials for each group. b. Median macro-saccade rate during early, peak, late and steady state (SS) epochs showing each participant rate within each group. c. Mean micro-saccade rate after clip change of all participants in all trials. The black horizontal line indicates the micro-saccade rate suppression epoch. d. Median micro-saccade suppression magnitude (left) and micro SS saccade rate (left and right respectively) showing each participant rate within each group. Control group (CTRL), Huntington's disease group (HD) for all figures. ***p < 0.001, *p < 0.05.

negative association between the saccade rebound (saccade peak rate) and UHDRS-m (r(18) = −0.53, p = 0.01), suggesting that larger motor impairments are associated with lower saccade rebound. Similarly, the significant association between UHDRS-f and saccadic peak rate suggest a positive association between better functional capacity with higher saccadic peak rates (r(18) = 0.58, p = 0.006). Finally a significant positive association between MoCA and saccadic peak rates also suggest a better cognitive capacity is associated to higher number at the saccade rebound peak (r

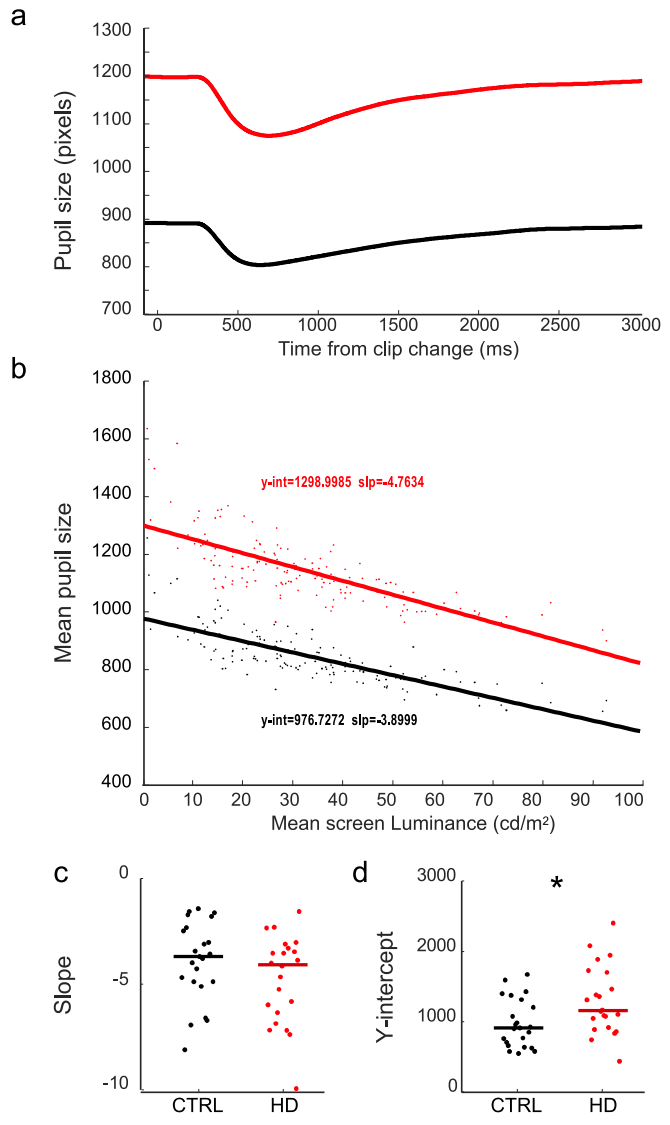

Fig. 2. Pupil Response. a. Average pupil size following all clip changes. Note the larger pupil size for the HD group. b. Mean pupil size as a function of screen luminance across the different clips. c and d, slope and Y-intercept from correlations of pupil size versus screen luminance for all participants. *$p < 0.05$.

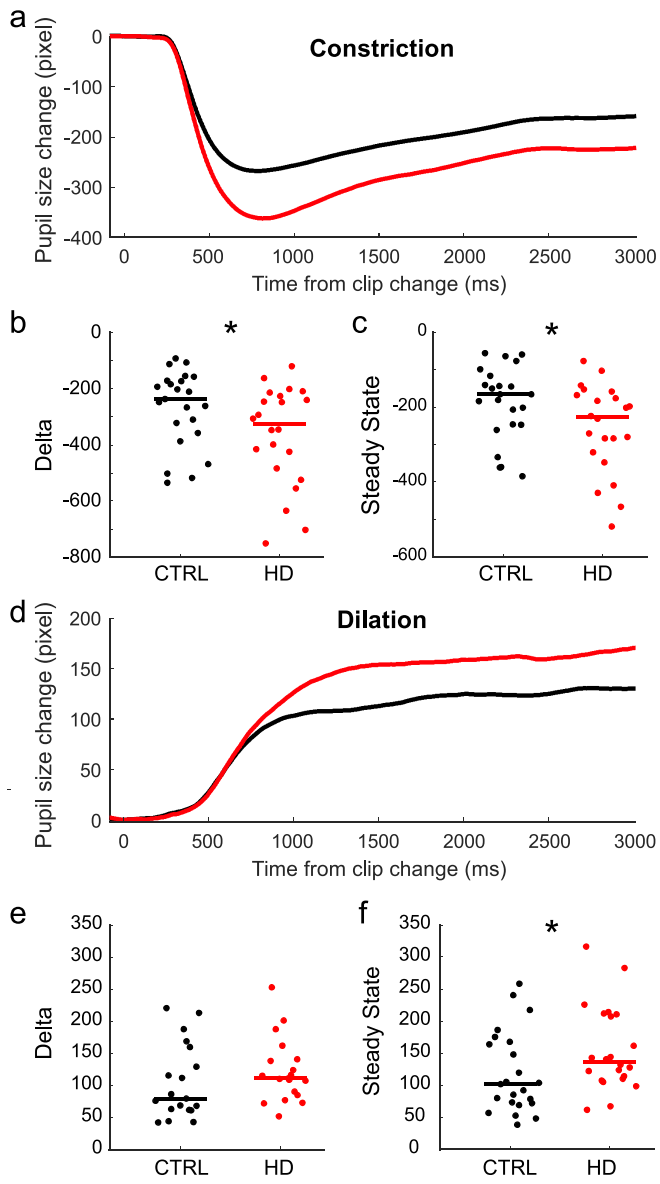

Fig. 3. Pupil response according to luminance change. a. Pupil constriction following clip change with the 20% greatest positive luminance change. Time zero denotes the onset of the clip change. b. Median pupil constriction delta is presented for each participant. c. Median pupil size during the steady state after a constriction. D. Pupil dilation after a clip change with the greatest 20% luminance decrease. E. Median pupil dilation delta. F. Median pupil size during the steady state after a dilation. *$p < 0.05$.

(18) = 0.63, $p = 0.002$) (Fig. 5A–C, respectively). None of the other saccade, pupil, or blink variables had significant correlations with the clinical scores, or with CAG expansion, age at onset or disease duration.

4. Discussion

In this study, we explored how HD affected saccadic movements, pupillary responses, and eye blinking behavior under conditions of free viewing of video clips. Previous studies have analyzed these variables in structured visually guided saccade tasks, however, the FV paradigm allowed us to explore them in an unstructured task while the participants viewed short video clips during only 10 min (Habibi et al., 2022; Tseng et al., 2013). The analyses of the oculomotor behavior uncovered significant differences contingent to clip changes in both saccades and pupil responses in patients with HD, while also revealing significant differences in eye-blinking frequency.

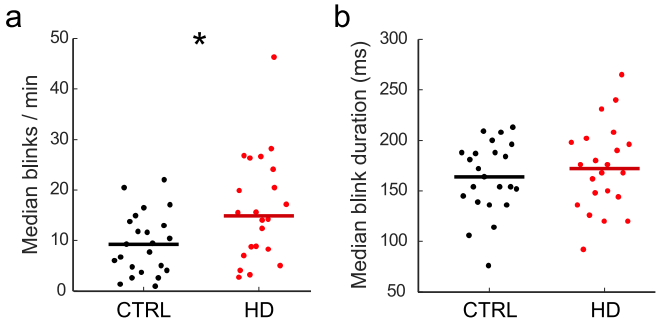

Fig. 4. Blink comparison between groups. a. Median blink rate. b. Median blink duration.

4.1. Saccades

There is a long history of studies describing saccades abnormalities in patients with HD, mainly using paradigms that involve structured tasks (Lasker et al., 1987; Leigh et al., 1983; Peltsch et al., 2008). Initial findings demonstrated that the earliest deficits consisted of problems with initiating voluntary saccades on command and maintaining visual fixation that has been linked to basal ganglia degeneration (Coe et al., 2019; Leigh et al., 1983; Peltsch et al., 2008). Deficits consisting of slower saccades and longer reaction times to initiate them have also been linked to the neurodegeneration of areas at different brain levels affected in HD (Rees et al., 2014; Rüb et al., 2014). Postmortem assessment of the degeneration of different regions of the raphe interpositus nucleus, which house the omnipause neurons that inhibit the initiation of saccades, was associated with saccade deficits observed in the clinical history of HD patients (Rüb et al., 2014). Cerebellar degeneration also has been suggested to contribute to saccade problems in HD, due to deterioration of white matter integrity in the cerebellum that correlated with the patients impaired saccade initiation (Padron-Rivera et al., 2021; Rees et al., 2014). Our study has revealed further HD oculomotor deficits under more natural conditions, including a notably reduced rebound of saccades after a clip change in HD patients compared to CTRL, which is consistent with saccade initiation deficits.

4.2. Pupil

Only a limited number of studies have described pupillary responses in participants with HD, yielding mixed results (Den Heijer et al., 1988; Hamedani et al., 2020). Our results show a larger than normal pupil size in patients with HD. This pupil size difference persisted across a range of luminance levels (Fig. 2b). However, both CTRL and HD groups had similar pupil sensitivity to different screen luminance conditions (Fig. 2c). The large baseline difference but similar sensitivity to light change shows how HD pathophysiology affects different parts of pupil control circuit (Joshi and Gold, 2020; Wang and Munoz, 2015). The elevated baseline is likely the result of abnormal input to LC in HD. Pupil responses to dynamic luminance changes at each clip transition were also different between groups. Patients with HD exhibited a more pronounced pupil response (indicated by a larger delta) to clip luminance changes, whether constriction or dilation was triggered by the luminance change. This exaggerated pupil response to clip changes could be associated with autonomic nervous system dysfunction. Prior research has indicated that even clinically presymptomatic HD mutation carriers display impairments in this system (Kobal et al., 2014). Moreover, studies have suggested the involvement of deteriorating Edinger-Westphal nucleus as a potential contributor to pupillary light reflex changes in HD (Den Heijer et al., 1988), particularly given the pathological evidence of neuronal intranuclear inclusions across the dorsal brain stem in HD (Rüb et al., 2014; Yamada et al., 2000).

4.3. Blinking

Previous studies have examined blinking in patients with HD, primarily focusing on the prolonged response latencies of the blink reflex (Caraceni et al., 1976; de Tommaso et al., 2001). Although natural blink behavior has been investigated in HD, the available literature consists mainly of anecdotal or qualitative reports suggesting an increase in the blink rate (Karson et al., 1984; Muñoz et al., 2003; Xing et al., 2008). However, our quantitative results unequivocally demonstrate a significantly higher blink rate in patients with HD. Similar alterations in blinking have also been observed in patients with other basal ganglia disorders (Bologna et al., 2009; Karson et al., 1984, 1982). Notably, in the context of Parkinson's disease, reduced blinking rates have been linked to decreased dopaminergic levels, although the relationship between blinking and the dopamine system in HD patients remains less clear (Schwab et al., 2015). Importantly, it should be emphasized as described earlier, that the patients in this cohort were not taking any drugs, including those known to affect the dopaminergic system, such as tetrabenazine (Frank et al., 2016).

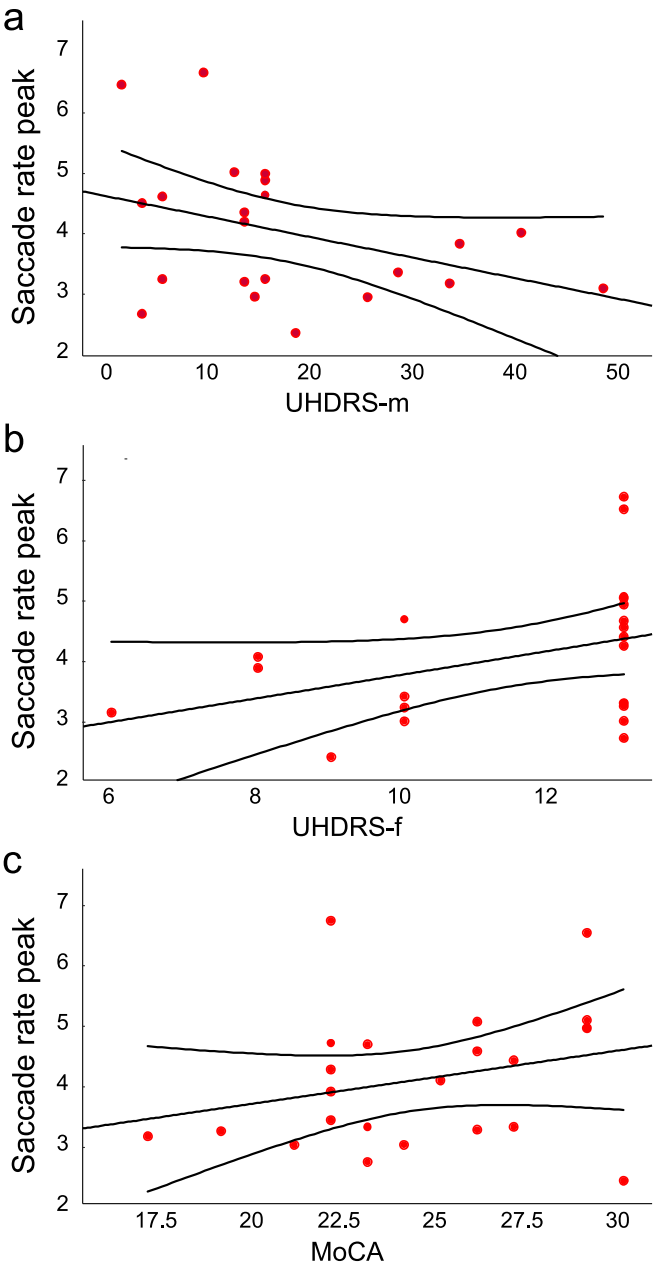

Fig. 5. Relation between the peak saccade rebound, and UHDRS-m, UHDRS-f-III and MoCA. a Negative significant correlation between the peak rate and UHDRS-m score. b Positive significant correlation between peak rate and UHDRS-f score. c. Positive significant correlation between peak rate and MoCA score. Solid lines show the linear fit and confidence intervals.

4.4. Links to clinical assessment

Our analyses showed significant correlations between peak saccade rebound after clip changes and the UHDRS functional and clinical scores, a finding that is supported by previous reports using

structured tasks (Ali et al., 2006; Patel et al., 2012). These results suggest that saccades parameters could be used for tracking and quantifying HD progression (Patel et al., 2012; Peltsch et al., 2008). This finding is of particular significance when considering that saccade deficits are detectable even in a substantial proportion of clinically at-risk HD subjects (Penney Jr et al., 1990). Our analyses also revealed a significant correlation between MoCA and saccade rate peak. This finding aligns with earlier research that correlated MoCA performance with various saccadic metrics under different conditions (Stuart et al., 2019; Wu et al., 2023), reinforcing the utility of saccade testing in capturing variables that are indicative of both motor and cognitive decline.

4.5. Limitations

Due to the specific requirements of our study, we included patients capable of completing the behavioral tests. For instance, patients with significant chorea were unsuitable for the eyetracking setup used in this research. Consequently, our study included only a limited number of HD patients, with CAG repeat lengths ranging from 40 to 52 and clinical manifestations of the disease spanning 1–10 years, as detailed in the methods section. Exploring potential oculomotor abnormalities in patients with more severe manifestations of the disease remains a challenging yet important area for future research.

5. Conclusions

Here, we have demonstrated that HD not only affects fundamental aspects of saccade execution as identified in studies using structured tasks, but also impact other processes that become evident when patients are tested under more ecologically valid conditions. Our findings reveal substantial changes in pupil responses to luminance shifts, a notable increase in eye-blinking behavior, and significant alterations in saccadic patterns that could reduce the exploration of new visual scenes. Further studies are warranted to gain a deeper understanding of how HD affects the underlying processes driving these changes, and the impact of these changes on the quality of life of the patients affected by the disease.

Author contributions

MRL, IVP, JFR, and DPM contributed to the conceptualization of the study. DPM, BJW, DCB, and BCC participated in the methodology development. BJW, DCB, and BCC did the software programming for eye movement analysis. MRL, IVP, DJDOM, and JFR performed data curation. The original draft of the manuscript was written by JFR, IVP, and MRL, while BJW, DCB, and BCC provided the visualization of the data and spearheaded the investigation process of the study. JFR and DJDOM offered supervision and oversight for the research project. Additionally, BJW, DCB, and BCC contributed to the software development and validation of the analysis results. Lastly, MRL, JFR, and DPM were responsible for reviewing and editing the manuscript to ensure its accuracy and readability.

Ethical approval and informed consent

This investigation was granted approval by the Human Research Ethics Committees at both the Universidad Nacional Autónoma de México, Ciudad de Mexico, and Queen's University, Kingston ON, Canada. In compliance with the Declaration of Helsinki (World Medical Association, 2013), written informed consent was procured from all participants, encompassing both patients and control subjects. The present report delineates the methodology employed for sample size determination, data exclusion and inclusion/exclusion criteria establishment (prior to data analysis), and all manipulations and measures utilized in the study.

Statements and declarations

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.clinph.2024.06.012.

References

Ali F, Michell A, Barker R, Carpenter R. The use of quantitative oculometry in the assessment of Huntington's disease. Exp Brain Res 2006;169:237–45.
Anderson TJ, MacAskill MR. Eye movements in patients with neurodegenerative disorders. Nat Rev Neurol 2013;9:74–85.
Bahill AT, Clark MR, Stark L. The main sequence, a tool for studying human eye movements. Math Biosci 1975;24:191–204.
Bologna M, Agostino R, Gregori B, Belvisi D, Ottaviani D, Colosimo C, et al. Voluntary, spontaneous and reflex blinking in patients with clinically probable progressive supranuclear palsy. Brain 2009;132:502–10.
Caraceni T, Avanzini G, Spreafico R, Negri S, Broggi G, Girotti F. Study of the excitability cycle of the blink reflex in Huntington's chorea. Eur Neurol 1976;14:465–72.
Coe BC, Huang J, Brien DC, White BJ, Yep R, Munoz DP. Automated analysis pipeline for extracting saccade, pupil, and blink parameters using video-based eye tracking. Vision 2024;8:14.
Coe BC, Trappenberg T, Munoz DP. Modeling saccadic action selection: Cortical and basal ganglia signals coalesce in the superior colliculus. Front Syst Neurosci 2019;13:3.
Den Heijer JC, Bollen WL, Reulen JP, van Dijk JG, Kramer CG, Roos RA, et al. Autonomic nervous function in Huntington's disease. Arch Neurol 1988;45:309–12.
Fogarty C, Stern JA. Eye movements and blinks: their relationship to higher cognitive processes. Int J Psychophysiol 1989;8:35–42.
Frank S, Testa CM, Stamler D, Kayson E, Davis C, Edmondson MC, et al. Effect of deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. Jama 2016;316:40–50.
Habibi M, Oertel WH, White BJ, Brien DC, Coe BC, Riek HC, et al. Eye tracking identifies biomarkers in α-synucleinopathies versus progressive supranuclear palsy. J Neurol 2022;269:4920–38. https://doi.org/10.1007/s00415-022-11136-5.
Hamedani AG, Bardakjian T, Balcer LJ, Gonzalez-Alegre P. Contrast acuity and the King-Devick test in Huntington's disease. Neuro-Ophthalmol 2020;44:219–25.
Hicks SL, Robert MPA, Golding CVP, Tabrizi SJ, Kennard C. Chapter 6.9 – Oculomotor deficits indicate the progression of Huntington's Disease. In: Kennard C, Leigh RJ, editors. Prog. Brain Res. 2008;vol. 171. Elsevier; 2008. p. 555–8. https://doi.org/10.1016/S0079-6123(08)00678-X.
Joshi S, Gold JI. Pupil Size as a Window on Neural Substrates of Cognition. Trends Cogn Sci 2020;24:466–80. https://doi.org/10.1016/j.tics.2020.03.005.
Karson CN, Burns RS, LeWitt PA, Foster NL, Newman RP. Blink rates and disorders of movement. Neurology 1984;34:677.
Karson CN, Lewitt PA, Calne DB, Wyatt RJ. Blink rates in parkinsonism. Ann Neurol Off J Am Neurol Assoc Child Neurol Soc 1982;12:580–3.
Kassavetis P, Kaski D, Anderson T, Hallett M. Eye movement disorders in movement disorders. Mov Disord Clin Pract 2022;9:284–95.
Klöppel S, Draganski B, Golding CV, Chu C, Nagy Z, Cook PA, et al. White matter connections reflect changes in voluntary-guided saccades in pre-symptomatic Huntington's disease. Brain 2008;131:196–204. https://doi.org/10.1093/brain/awm275.

Kobal J, Melik Z, Cankar K, Strucl M. Cognitive and autonomic dysfunction in presymptomatic and early Huntington's disease. J Neurol 2014;261:1119–25.
Lasker A, Zee D, Hain T, Folstein SE, Singer H. Saccades in Huntington's disease: initiation defects and distractibility. Neurology 1987;37:364.
Leigh RJ, Newman SA, Folstein SE, Lasker AG, Jensen BA. Abnormal ocular motor control in Huntington's disease. Neurology 1983;33:1268. https://doi.org/10.1212/WNL.33.10.1268.
MacAskill MR, Anderson TJ. Eye movements in neurodegenerative diseases. Curr Opin Neurol 2016;29:61–8.
MacDonald ME, Ambrose CM, Duyao MP, Myers RH, Lin C, Srinidhi L, et al. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 1993;72:971–83. https://doi.org/10.1016/0092-8674(93)90585-E.
Martinez-Conde S, Macknik SL, Hubel DH. Microsaccadic eye movements and firing of single cells in the striate cortex of macaque monkeys. Nat Neurosci 2000;3:251–8.
Martinez-Conde S, Macknik SL, Troncoso XG, Dyar TA. Microsaccades counteract visual fading during fixation. Neuron 2006;49:297–305.
Muñoz E, Cervera A, Valls-Solé J. Neurophysiological study of facial chorea in patients with Huntington's disease. Clin Neurophysiol 2003;114:1246–52.
Novak MJU, Tabrizi SJ. Huntington's disease: clinical presentation and treatment. In: Brotchie J, Bezard E, Jenner P, editors. Int. Rev. Neurobiol. 2011;vol. 98. Academic Press; 2011. p. 297–323. https://doi.org/10.1016/B978-0-12-381328-2.00013-4.
Otero-Millan J, Schneider R, Leigh RJ, Macknik SL, Martinez-Conde S. Saccades during attempted fixation in parkinsonian disorders and recessive ataxia: from microsaccades to square-wave jerks. PLoS One 2013;8:e58535.
Padron-Rivera G, Diaz R, Vaca-Palomares I, Ochoa A, Hernandez-Castillo CR, Fernandez-Ruiz J. Cerebellar degeneration signature in Huntington's disease. The Cerebellum 2021;20:942–5.
Patel SS, Jankovic J, Hood AJ, Jeter CB, Sereno AB. Reflexive and volitional saccades: Biomarkers of Huntington disease severity and progression. J Neurol Sci 2012;313:35–41. https://doi.org/10.1016/j.jns.2011.09.035.
Peltsch A, Hoffman A, Armstrong I, Pari G, Munoz DP. Saccadic impairments in Huntington's disease. Exp Brain Res 2008;186:457–69. https://doi.org/10.1007/s00221-007-1248-x.
Penney Jr JB, Young AB, Shoulson I, Starosta-Rubenstein S, Snodgrass SR, Sanchez-Ramos J, et al. Huntington's disease in Venezuela: 7 years of follow-up on symptomatic and asymptomatic individuals. Mov Disord Off J Mov Disord Soc 1990;5:93–9.
Rees EM, Farmer R, Cole JH, Haider S, Durr A, Landwehrmeyer B, et al. Cerebellar abnormalities in Huntington's disease: a role in motor and psychiatric impairment? Mov Disord 2014;29:1648–54.
Rüb U, Hentschel M, Stratmann K, Brunt E, Heinsen H, Seidel K, et al. Huntington's Disease (HD): degeneration of select nuclei, widespread occurrence of neuronal nuclear and axonal inclusions in the brainstem. Brain Pathol 2014;24:247–60.
Rupp J, Dzemidzic M, Blekher T, West J, Hui S, Wojcieszek J, et al. Comparison of vertical and horizontal saccade measures and their relation to gray matter changes in premanifest and manifest Huntington disease. J Neurol 2012;259:267–76. https://doi.org/10.1007/s00415-011-6172-0.
Schwab LC, Garas SN, Drouin-Ouellet J, Mason SL, Stott SR, Barker RA. Dopamine and Huntington's disease. Expert Rev Neurother 2015;15:445–58.
Sears C, Quigley L, Fernandez A, Newman K, Dobson K. The reliability of attentional biases for emotional images measured using a free-viewing eye-tracking paradigm. Behav Res Methods 2019;51:2748–60. https://doi.org/10.3758/s13428-018-1147-z.
Stuart S, Lawson RA, Yarnall AJ, Nell J, Alcock L, Duncan GW, et al. Pro-saccades predict cognitive decline in Parkinson's disease: ICICLE-PD. Mov Disord 2019;34:1690–8.
de Tommaso M, Sciruicchio V, Spinelli A, Specchio N, Difruscolo O, Puca F, et al. Features of the blink reflex in individuals at risk for Huntington's disease. Muscle Nerve 2001;24:1520–5.
Tseng P-H, Cameron IG, Pari G, Reynolds JN, Munoz DP, Itti L. High-throughput classification of clinical populations from natural viewing eye movements. J Neurol 2013;260:275–84.
Tseng P-H, Carmi R, Cameron IG, Munoz DP, Itti L. Quantifying center bias of observers in free viewing of dynamic natural scenes. J Vis 2009;9:4.
Vaca-Palomares I, Brien DC, Coe BC, Ochoa-Morales A, Martínez-Ruano L, Munoz DP, et al. Implicit learning impairment identified via predictive saccades in Huntington's disease correlates with extended cortico-striatal atrophy. Cortex 2019;121:89–103.
Vaca-Palomares I, Coe BC, Brien DC, Campos-Romo A, Munoz DP, Fernandez-Ruiz J. Voluntary saccade inhibition deficits correlate with extended white-matter cortico-basal atrophy in Huntington's disease. NeuroImage Clin 2017;15:502–12. https://doi.org/10.1016/j.nicl.2017.06.007.
Wang C-A, Munoz DP. A circuit for pupil orienting responses: implications for cognitive modulation of pupil size. Curr Opin Neurobiol 2015;33:134–40.
White BJ, Berg DJ, Kan JY, Marino RA, Itti L, Munoz DP. Superior colliculus neurons encode a visual saliency map during free viewing of natural dynamic video. Nat Commun 2017;8:14263.
Winograd-Gurvich CT, Georgiou-Karistianis N, Evans A, Millist L, Bradshaw JL, Churchyard A, et al. Hypometric primary saccades and increased variability in visually-guided saccades in Huntington's disease. Neuropsychologia 2003;41:1683–92. https://doi.org/10.1016/S0028-3932(03)00096-4.
Wu J, Li M, Ma W, Zhang Z, Zhang M, Li X. The performance of saccade tasks correlates with cognitive test scores in elderly population: evidence for the usefulness of oculomotor tests in cognitive assessment. Gerontology 2023;69:321–35.
Xing S, Chen L, Chen X, Pei Z, Zeng J, Li J. Excessive blinking as an initial manifestation of juvenile Huntington's disease. Neurol Sci 2008;29:275–7.
Yamada M, Tsuji S, Takahashi H. Pathology of CAG repeat diseases. Neuropathology 2000;20:319–25.