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Eye-tracking in Early Manifest Huntington's Disease: Heterogeneity of Deficits in Inhibitory and Fronto-Executive Control

Filipa Júlio[1,2], Cristina Januário[1,3], Miguel Castelo-Branco[1,4,5], Gina Caetano[4,6,*]

[1] CIBIT—Coimbra Institute for Biomedical Imaging and Translational Research, University of Coimbra, 3000-548 Coimbra, Portugal
[2] Faculty of Psychology and Education Sciences, University of Coimbra, 3000-115 Coimbra, Portugal
[3] CHUC—Centro Hospitalar e Universitário de Coimbra, 3000-075 Coimbra, Portugal
[4] Faculty of Medicine, University of Coimbra, 3000-548 Coimbra, Portugal
[5] ICNAS—Institute of Nuclear Sciences Applied to Health, University of Coimbra, 3000-548 Coimbra, Portugal
[6] ISR-Lisboa/LARSyS, Instituto Superior Técnico, University of Lisbon, 1049-001 Lisbon, Portugal

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ABSTRACT

Objectives: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that affects first basal ganglia and fronto-striatal circuitry. Cognitive decline and inhibitory control deficits are more subtle in the early stages of manifest disease, yet relevant to track disease progression. The current study aims to underpin and characterize the dysfunction of oculomotor inhibitory control mechanisms and executive function through working memory demands on fronto-executive load in a cohort of early manifest HD (Early-HD).

Methods: A comprehensive battery of neuropsychological tests was applied to assess cognitive functioning in 14 Early-HD and 22 Control participants. Oculomotor function was studied using an experimental paradigm comprising four oculomotor tasks: prosaccade, antisaccade, 1- or 2-back memory prosaccade, and 1- or 2-back memory antisaccade. The estimated metrics were success rate, direction errors, timing errors, and the primary saccade latency.

Results: The Early-HD group demonstrated cognitive deficits in visual and verbal memory, executive function, attention, visual perception, and verbal and non-verbal IQ domains. Regarding oculomotor performance, the clinical group had a decreased success rate and increased percentage of direction errors and early premature saccades while exhibiting faster response times than the Control group in the 1- or 2-back memory antisaccade task.

Conclusions: Our results demonstrate overt oculomotor dysfunction in Early-HD since inhibitory control mechanisms are necessary to perform the task. Furthermore, increasing working memory demands and fronto-executive load enhances impulsive response patterns. The dysfunction in goal-oriented oculomotor behavior, including more automatized responses and deficits in inhibition, is present in Early-HD patients with cognitive deficits but who remain functional and autonomous. These findings reinforce the notion that fronto-striatal impairment is a crucial event in HD and that more automatized oculomotor evaluation procedures help identify and stratify deficits in early manifest disease.

Keywords: Huntington's disease, manifest stage, oculomotor performance, inhibition, fronto-executive load.

Introduction

Huntington's disease (HD) is a rare autosomal inherited neurodegenerative disorder, characterized by motor dysfunction, neuropsychiatric disturbances, and a general cognitive decline leading to dementia [1-4]. The disease is caused by a trinucleotide CAG-repeat expansion (above 36 alleles in total, and of variable length) in the *huntingtin* (HTT) gene that encodes the HTT protein [5] and has no effective treatments until now. The mutated HTT protein is expressed throughout the body being all-pervasive with the highest levels in the brain [6], and its inherent toxic properties disrupt a number of cellular processes being at the root of disease causation [7]. The pathogenic pathways have become increasingly well-understood over the last two decades, with identification of potential therapeutic targets for preclinical and clinical trials [4,8-11].

In parallel, the research community has delved into the investigation and characterization of motor, cognitive, behavioural, and neuroimaging profiles of human HD, from pre-symptomatic and prodromal stages to early manifest disease, with the most impact from biomarkers' multicentre cohort studies TRACK-HD [12-14], PREDICT-HD [15-17], and IMAGE-HD [18]. In sharp contrast with the established clinical diagnosis based on the presence of motor signs with at least 99% in the Diagnostic Confidence Level scale of the Unified Huntington's Disease Rating Scale (UHDRS) [19], the novel findings inform of disease-related changes detected in quantitative imaging, motor and cognitive measures of up to two decades before the estimated disease onset [11,20,21].

A consensus seems to exist regarding the replicability of neuroimaging techniques to detect the earliest signs of quantifiable neurodegeneration in the basal ganglia structures [12,16,18,22-28]. Concurrently, experts in the field recognize that the first HD's measurable alterations are associated with cognitive and behavioural impairments [4,29-32], and that a close relationship exists between cognitive and motor dysfunction along HD progression [4,12,17,33-36].

Despite the awareness of a potential revision of HD diagnostic criteria based on these novel neurobiological findings, the translation to clinical practice and its application in experimental therapeutic trials is yet to be implemented, due to the need for further validation. For instance, the primary outcomes used to evaluate the effect of specific drugs in phase III clinical trials (e.g., safety and tolerability, efficacy, reduction of motor symptoms, protection from cognitive decline) rely on established measures [10], such as the UHDRS tool and its subscales [19], the Montreal Cognitive Assessment (MoCA) test for cognitive impairment and dementia screening [37], and of course the improvement of chorea symptoms or the emergence of adverse events, among others. Research has examined quantitative motor tasks to identify early impairments and to determine whether they are more sensitive to subtle changes in performance as the disease progresses [12,17,30,38]. The ability of these tasks to detect the interaction between HD motor and cognitive dysfunctions has also been studied. These tools comprise speeded and self-paced finger tapping, tongue force variability, grip force variability, and oculomotor assessments [39], of which some have already been included in clinical trials for comparison against the established tests [11].

We are particularly interested in the assessment of oculomotor performance since abnormalities in eye movements are among the first detectable alterations in HD gene carriers, are an unequivocal finding in manifest HD, and can provide objective and sensitive measures of disease development [39-41]. Considering HD-related early striatal-subcortical brain pathology [28] and the subsequent disruption of cortico-striatal circuitry [4,42], with an emphasis on prefrontal-striatal connectivity [43], oculomotor measures tackle several mechanisms disrupted along HD progression. Specifically, these mechanisms encompass motor planning [44] (selection of motor output), response inhibition [45,46] (inhibiting undesired responses), temporal control [47] over motor output, and the interplay with cognitive symptoms that include executive dysfunction (disinhibition, attentional deficits, and poor impulse control) [45,46,48,49]. For example, prodromal HD gene carriers show slower onset of goal-oriented primary saccades [50-52] and increased directional errors [50], whereas manifest HD patients show a much wider range of impairments, including deficits in the initiation of volitional saccades, a higher incidence of premature saccades, difficulty inhibiting reflexive saccades to distracting stimuli, increased latency and variability of latency of primary saccades, and increased directional errors [39,50,51,53-62]. The more "voluntary" types of saccades, such as anti-saccades and memory-guided saccades, are most often impacted close to HD clinical onset [39,54,61-63], in line with the disruption of prefrontal-striatal circuitry necessary for the proper functioning of top-down control mechanisms that inhibit overt motor acts or responses [45,46,49]. Importantly, in the healthy population, working memory fronto-executive load has been shown to influence oculomotor control, specifically interfering with saccadic inhibition [64,65]. We have previously proposed that an oculomotor protocol may be more sensitive and specific to the early neuropathological and functional alterations associated with HD because of the cognitive-oculomotor disruption that results from fronto-executive load [36]. Accordingly, we have demonstrated deterioration of oculomotor performance [41,66] with more automatic patterns and deficits in impulsivity and inhibitory control in a group of HD gene carriers far from the estimated clinical onset (> 21 years).

Here, we hypothesize that an oculomotor protocol with different levels of fronto-executive load will increase specificity and sensitivity to distinct patterns of neurodegeneration along the progression of manifest HD. In the context of rapid technological developments, this approach might be of added value for disease monitoring and objectively evaluating the outcomes of planned therapeutic interventions. This sought capacity is particularly relevant considering the well-documented heterogeneity of symptom presentation and progression in the early stages of manifest HD [67], also paralleled by heterogeneity in neurodegenerative processes [68-70].

Methods

PARTICIPANT

Thirty-six participants completed the eye-tracking and the neuropsychological assessment protocols, of which 14

HD patients and 22 healthy individuals (Control group). Huntington's disease patients were primarily recruited through the Movement Disorder Unit of the Neurology Department at Centro Hospitalar e Universitário de Coimbra, while recruitment also took place through the Huntington's Disease Portuguese Association.

The group of patients were in the early manifest HD stage (Early-HD, stage 1), had an expanded HD gene (≥36 CAG repeats), and presented sufficient symptoms to be clinically diagnosed with HD, with a diagnostic confidence score of 4 on the Unified Huntington's Disease Rating Scale–Motor scale (UHDRS-Motor), and a Total Motor Score (TMS) > 5, while remaining functional in their daily living chores with a Total Functional Capacity (TFC) score of 10–13 in the UHDRS subscale [19,71]. With the goal of investigating the association between the oculomotor component of the UHDRS–Motor subscale and oculomotor eye-tracking performance, a composite score OculoTMS was calculated from ocular pursuit, saccade initiation and saccade velocity items. A higher TMS indicates worse clinical symptoms, whereas the TFC rates different domains from 0 to 13, with a higher score corresponding to higher autonomy and independence in daily activities.

The control group was composed by participants who had a negative result on the HD genetic test, HD family members not at risk of inheriting the condition (e.g., spouses of individuals impacted by HD) and healthy individuals from the community without any HD-related history. Demographics are presented in **Table 1**.

Table 1 - Demographic characteristics of the Control and Early-HD groups

	Early-HD (n=14)		***Control (n=22)***	
	Gender (F:M) 10:4		*Gender (F:M) 15:7*	
	Handedness (R:L) 14:0		*Handedness (R:L) 19:3*	
	Median	***IQR***	***Median***	***IQR***
Age (years)	41	25	34	12
Education (years)	12	10	11.5	2
CAG repeats	44	4	-	-
UHDRS motor - TMS	27.5	23	-	-
UHDRS - OculoTMS	6	8	-	-
UHDRS - TFC	10	3	-	-

No significant differences were found between the Early-HD and the Control group in any of the demographic variables. IQR – Interquartile Range; CAG repeats – CAG repeat expansion confirmed by a genetic test; UHDRS – Unified Huntington's Disease Rating Scale [19]; TMS – Total Motor Scale of the UHDRS; OculoTMS – a composite score extracted from the sum of the oculomotor items of the UHDRS-Motor scale; TFC – Total Functional Capacity scale of the UHDRS.

Exclusion criteria included concurrent neurological pathology, severe ophthalmic disease, history of drug or alcohol abuse/dependence, and the presence of mild cognitive impairment, the latter assessed via the Montreal Cognitive Assessment [37,72] and identified if the score fell below the established normative threshold based on age and education [73]. In the case of Control participants, the use of psychotropic medication was an exclusion criterion. None of the Control participants were under medication, whereas in the Early-HD group, 10 patients were under antidepressants, 8 patients were taking antipsychotic medication, 7 patients were taking medication of the classes' anxiolytics/sedatives/hypnotics, and only 2 of the patients did not take any medication.

Enrolled participants were fully informed of the whole study protocol and gave their informed written consent. The results presented herein include part of a larger study cohort in Huntington's Disease [22,41,66]. The study was in accordance with the Declaration of Helsinki and approved by the local Ethics Committee at the Faculty of Medicine of the University of Coimbra.

NEUROPSYCHOLOGICAL ASSESSMENT

An extensive battery of neuropsychological tests was used, which included tests traditionally employed in HD cognitive assessment, with an emphasis on executive function, attention, and memory skills, to maximize sensitivity to cognitive control abilities and processes that recruit fronto-striatal circuitry [12,29,32,71,74,75]. The battery of tests comprised: the *MoCA* test [37,72] for mild cognitive impairment and dementia screening; the *Stroop* test [76] to assess executive function (cognitive flexibility and processing speed); the *Edinburgh Handedness Inventory* [77]; the *Digit Symbol* subtest of the *Wechsler Adult Intelligence Scale-III* [78,79] to assess psychomotor speed and working memory; the *Rey Auditory Verbal Learning* [80,81] test (total trials 1-5 and recall and recognition trials) to assess verbal memory; the 12-item short form of the *Raven Advanced Progressive Matrices* [82] (non-verbal intelligence); the *Corsi Block-Tapping task* [83,84] to assess psychomotor speed, working memory and executive function; the *Benton Visual Retention* test [85] for visual memory; the *Benton Visual Form Discrimination* test [86] for visual perception; the *Phonemic Verbal Fluency* [87] (3 letters) and the *Semantic Verbal Fluency* [88] tests to evaluate executive functioning, word generation and inhibition; the *Vocabulary of the WAIS-III* [78,79] to assess verbal intelligence; and the *Hospital Anxiety and Depression Scale – Snaith Irritability Scales (HADS-SIS)* [89,90] to assess psychiatric symptoms and prevalence of depression and anxiety.

The battery of tests was administered over a period of one and a half hour, in a predefined order, to avoid interferences associated with the evaluated domains in subsequent tasks, and to respect the time intervals required by specific tests.

OCULOMOTOR EXPERIMENT

Study participants completed four horizontal saccadic tasks: i) prosaccades (PS), ii) antisaccade (AS), iii) 1-or-2-back memory prosaccade (MPS), and iv) 1-or-2-back memory antisaccade (MAS). The design of the experimental protocol considered former evidence in healthy individuals that executive and memory load interfere with oculomotor inhibitory mechanisms [64,65]. We hypothesized that this interference effect would enable the identification of earliest functional disruptions in premanifest HD [41,66] and the stratification of the fronto-striatal dysfunction severity in early manifest HD. The oculomotor experiment was administered over a period of 40 to 60 minutes, with oculomotor tasks being performed in a pre-defined order of increasing executive and memory load (PS, AS, MPS, and MAS, respectively). Prior to each oculomotor task the participant was instructed verbally and rehearsed the task in a practice block, to ensure that the goal of the task was well understood and to avoid novelty effects during the experiment.

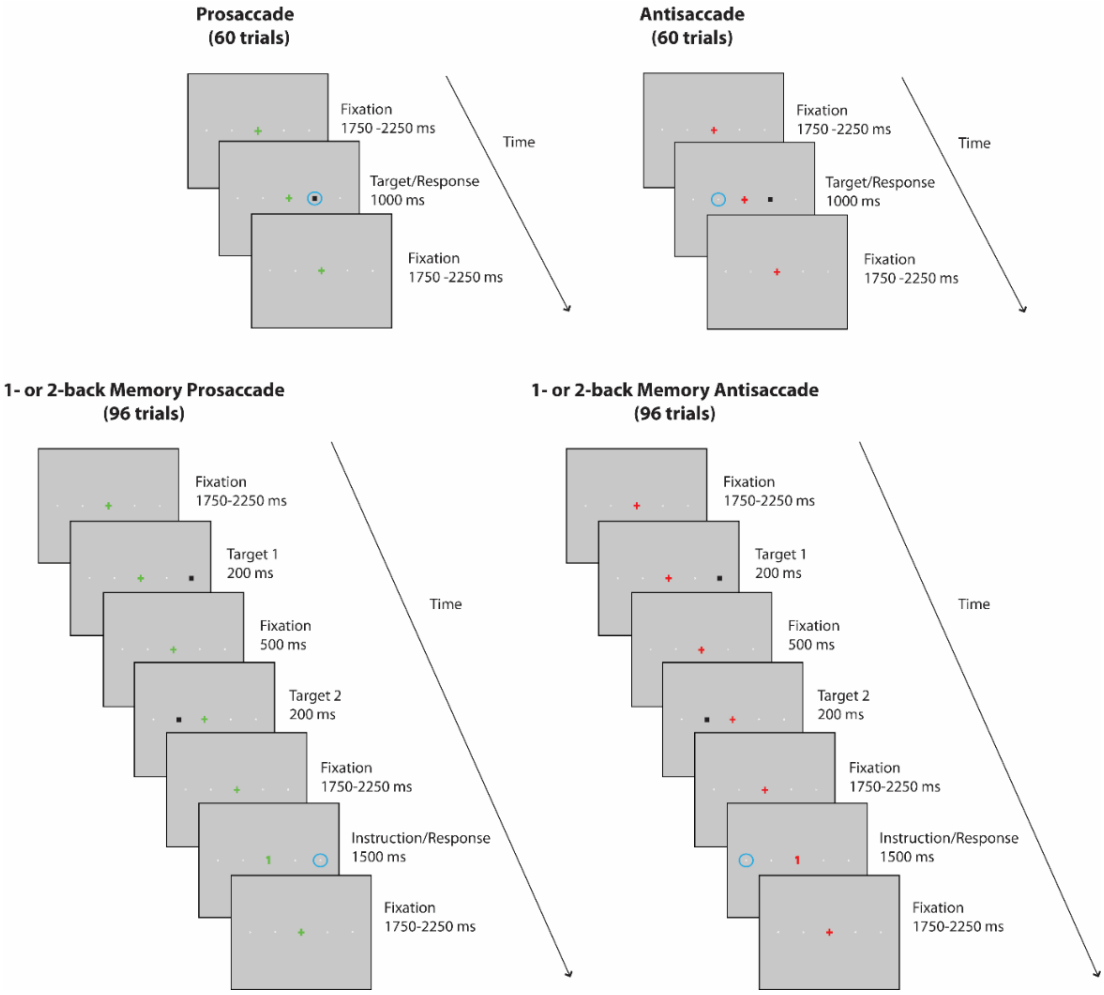
Material and data acquisition

The eye-movement data were acquired using an eye-tracking system (iView X Hi-Speed, 1.06 SensoMotoric Instruments, Teltow), with a sampling rate of 240 Hz, and a nine-point calibration performed for the dominant eye before the recording of each oculomotor task. The visual stimuli were presented on a 17-inch monitor, with a resolution of 1024 x 768 pixels, while participants were seated comfortably and with the head positioned in a stable chin-rest that was positioned at 52 cm from the monitor.

Oculomotor protocol and stimuli

In each task the stimuli were displayed into a grey background. A central fixation point was presented at the centre of the screen (cross shape, 1° diameter in visual angle) remaining visible throughout the entire experiment. Small position cues (* symbols, 0.24° diameter in visual angle, light grey colour) were positioned at each of four possible target positions for the saccadic tasks, at ±6° and ±12° visual angle. Peripheral visual targets (black square, 0.6° in visual angle) appeared randomly once at a time in one of the four target positions. Each saccadic task comprised a fixation phase, with temporal duration pseudo-randomly defined between 1,750 ms and 2,250 ms, followed by the stimulus presentation. Both the PS and the AS task consisted of 60 trials, while both the MPS and the MAS tasks consisted of 96 trials each. Detailed depiction of each task is presented in **Figure 1**.

Figure 1 – Experimental protocol design of the four horizontal saccadic tasks.



In the prosaccade task the participant was instructed to fixate the gaze on a central green cross and to look at the peripheral target as rapidly as possible once it appeared, in one of the four predefined positions, and then return the fixation gaze to the central green cross. The peripheral target was visible for 1,000 ms.

The antisaccade task requested the participant to fixate the gaze on a central red cross, and once the visual target appeared the subject had to look as rapidly as possible to the opposite mirror-like position, and then return the fixation gaze to the central red cross. The peripheral target was visible for 1,000 ms.

In the 1-or-2 back memory prosaccade task, the participant was instructed to fixate the gaze on a central green cross during the fixation phase and while two peripheral targets appeared sequentially, for 200 ms each and with an interval of 500 ms in between targets. The two targets appeared randomly in two of the predefined positions. A second fixation phase occurred, with temporal duration pseudo-randomly defined between 1,750 ms and 2,250 ms, and the task was assigned once the green cross was substituted by a green digit number. The digit number could take the values 1 or 2, for which the participant was requested to look as rapidly as possible at the remembered position of the first or second visual target, respectively.

Finally, in the 1-or-2 back memory antisaccade task, the participant was requested to fixate gaze on a central red cross during the fixation phase and while two peripheral targets appeared sequentially, for 200 ms each and with and interval of 500 ms in between targets. The participant was instructed to continue fixating on the central red cross for an additional period of 1,750 ms to 2,250 ms. The task was assigned once the red cross was substituted by a red digit number. The digit number could take the values 1 or 2, for which the participant was instructed to look as rapidly as possible to the opposite mirror-like position at which appeared the first or second visual target, respectively.

Oculomotor data processing

The eye-tracking data were analysed using the BeGaze software (version 3.4, SensoMotoric Instruments, Teltow). The detection of saccadic eye-movements was set by the parameters: i) peak velocity threshold of 40 °/ms; ii) fixation durations above 50 ms; iii) minimum saccade duration of 22 ms; iv) velocities of 15 °/ms and 85 °/ms to identify saccade initiation and termination, respectively. The computed data saccades, fixations and blinks were exported for further analysis in Matlab (R2013a).

For validation of trials, regions of interest (ROIs; ±2.5° x 4° of visual angle) were established surrounding the peripheral visual targets and the fixation position in the centre of the screen. Valid trials were defined utilizing the following criteria: (1) Trials contaminated by blinks were discarded from analysis (2) The trial had to contain a primary saccade performed in the correct direction, with a latency higher than 80 ms, initiated within the central fixation position ROI and with a horizontal amplitude path that enabled termination outside that ROI. If the latency was below 80 ms, the trial was classified as an anticipatory-latency saccade error. If the saccade was performed in the opposite direction, the trial was classified as a direction error; (3) The primary saccade had a latency below 700 ms for the PS and AS tasks, or below 1,000 ms for the MPS and MAS tasks. If the latency of the primary saccade was higher than these limits, respectively, the trial was classified as a long-latency error; (3) The saccadic movement ended within the ROI of the intended peripheral target, followed by the return to the central fixation position, otherwise the trial was discarded from analysis.

Table 2 – Oculomotor features estimated from saccadic tasks.

Saccadic Feature	Definition
Percentage of successful trials	Percentage of trials free of errors.
Latency	Primary saccade onset reaction time (milliseconds) from the target/task stimulus appearance, extracted from successful trials.
Percentage of anticipatory saccades errors	Percentage of premature primary saccades with onset latency lower than 80 ms from the target/task stimulus appearance.
Percentage of direction errors	Percentage of primary (reflexive) saccades performed in the opposite direction from the correct hit.

Participants included in the computation of saccadic-related measures (see **Table 2**) had more than 25% of valid trials, hence, a minimum of 15 valid trials out of 60 trials for the PS and AS tasks, and a minimum of 24 valid trials out of 96 trials for the MPS and the MAS tasks (see **Table 3**).

Table 3 – Participants included for the oculomotor analysis with the 25% valid trials criterion

Task	Included	Excluded (less than 25% valid trials)	Excluded (did not perform the task)
PS	22 CTRL 14 Early-HD	0 CTRL 0 Early-HD	0 CTRL 0 Early-HD
AS	22 CTRL 5 Early-HD	0 CTRL 8 Early-HD	0 CTRL 1 Early-HD
MPS	21 CTRL 8 Early-HD	1 CTRL 3 Early-HD	0 CTRL 3 Early-HD
MAS	20 CTRL 5 Early-HD	2 CTRL 4 Early-HD	0 CTRL 5 Early-HD

PS – Prosaccade; AS – Antisaccade; MPS – 1-or-2 back Memory Prosaccade; MAS – 1-or-2 back Memory Antisaccade. CTRL – Control; Early-HD – Early manifest HD patient

STATISTICS

Statistical analysis was performed with the IBM SPSS Statistics (v. 29) software. Non-parametric tests (Mann-Whitney U test) were used to inquire significant differences between groups in both the neuropsychological and saccadic performances ($p < 0.05$, exact, 2-sided).

The effect of saccadic task complexity (inhibitory and memory-executive load) was assessed with a repeated-

measures Friedman's Two-way analysis of Variance by Ranks (significance level $p < 0.05$, asymptotic, 2-sided), with all pairwise multiple comparisons corrected using the Bonferroni method. This approached was applied to the PS, AS, MPS, and MAS tasks (repeated measures) for each of the saccadic features (percentage of successful trials, percentage of direction errors, percentage of anticipatory saccade errors, and latency).

To infer on possible associations between demographic, UHDRS-motor scale related metrics and saccadic variables, two-tailed spearman correlations (Bonferroni corrected for multiple comparisons) were applied when the sample size for each of the variables was $N \geq 8$.

Results

NEUROPSYCHOLOGICAL PERFORMANCE

Early-HD patients performed worse than Controls in almost all the neuropsychological measures, as can be observed in **Table 4**, which displays 23 variables computed from the battery of neuropsychological tests. The Early-HD group also showed a statistically significant higher score in the depression subscale of the Hospital Anxiety and Depression Scale – Snaith Irritability Scale (HADS-SIS). All the participants completed the neuropsychological assessment (Early-HD N=14, Control N=22).

Table 4 – Comparison of neuropsychological performance between Early-HD and Control groups.

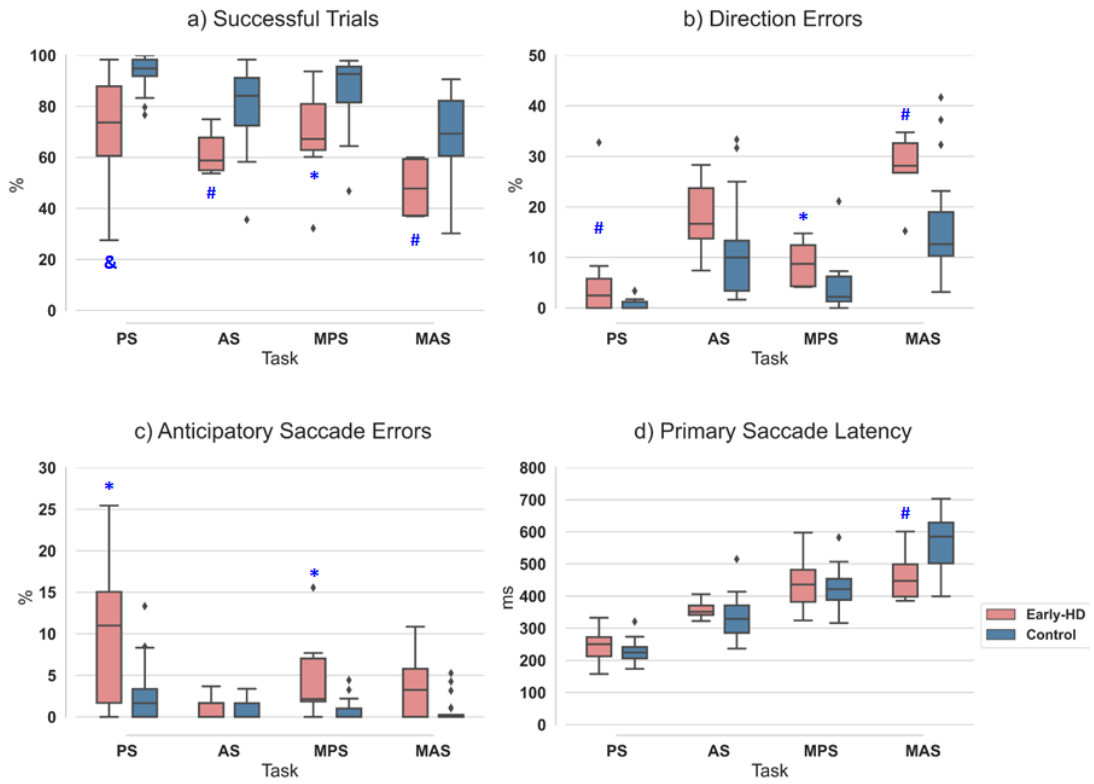
	Early-HD (n=14)		*Control (n=22)*	
	Median	***IQR***	***Median***	***IQR***
Hospital Anxiety and Depression Scale – Snaith Irritability Scale (HADS-SIS) – Anxiety	7.5	11	6.0	7
Hospital Anxiety and Depression Scale – Snaith Irritability Scale (HADS-SIS) – Depression	8.0 #	6	4.0	5
Montreal Cognitive Assessment (MoCA)	24.5 *	3	26.0	3
Raven advanced progressive matrices (classic version – set 1)	6.5 *	3	8.0	2
Vocabulary – WAIS III (raw score)	29.0	20	36.5	15
Stroop word reading test – total correct	56.0 &	28	89.0	21
Stroop colour naming test – total correct	44.0 &	25	70.0	19
Stroop interference test – total correct	27.5 &	15	41.5	12
Symbol digit modality – total correct	27.0 &	27	57.5	9
Symbol digit modality – total errors	0	1	0	1
Auditory verbal learning test – total trials 1-5	37.5 #	20	49.5	5
Auditory verbal learning test – recall	7.5 #	8	12.0	4
Auditory verbal learning test – recognition	29.0 *	5	30.0	1
Corsi block tapping task – direct	35.0 &	16	54.0	17
Corsi block tapping task – inverse	32.5 &	18	54.0	22
Benton visual retention test – total correct	5.0 &	3	8.0	1
Benton visual retention test – total errors	9.5 &	9	3.0	3
Benton visual form discrimination test – total correct	29.0	4	30.5	3
Verbal fluency test (letters PMR) – total correct	16.0 #	21	34.0	8
Verbal fluency test P – total correct	7.0 *	7	12.5	4
Verbal fluency test M – total correct	5.5 #	6	10.0	6
Verbal fluency test R – total correct	5.0 *	7	10.5	6
Verbal fluency test (category animals) – total correct	16.0 *	5	20.0	10

*Mann-Whitney U test: # ($p < 0.05$), * ($p < 0.01$), & ($p < 0.001$); IQR – Interquartile range.*

OCULOMOTOR PERFORMANCE

As expected, the subgroup of Early-HD patients with enough successful trials for inclusion in the analysis showed significant alterations in all the saccadic tasks (see **Figure 2**). Namely, the Early-HD subgroup presented a smaller number of valid trials (PS: $p < 0.001$; MPS: $p < 0.01$; AS and MAS: $p < 0.05$), a higher percentage of direction errors (PS and MAS: $p < 0.05$; MPS: $p < 0.01$), a higher percentage of anticipatory saccades (PS and MPS: $p < 0.01$), and a shorter primary saccade latency for the MAS task ($p < 0.05$). The latter implies a significantly faster reaction time than the Control group.

Figure 2–Comparison of the Control and Early-HD groups across the four conditions.



Boxplot and significant differences. *PS: Prosaccade; AS: Antisaccade; MPS: 1- or 2-back Memory Prosaccade; MAS: 1- or 2-back Memory Antisaccade.*
*Mann-Whitney U test (2-sided, exact significance); Early-HD ≠ Controls: # (p ‹ 0.05) ; * (p ‹ 0.01); & (p ‹ 0.001).*

The within-group effect of task complexity was statistically significant across the four conditions (see **Table 5**), in both the Early-HD and the Control groups, for the percentage of successful trials and the percentage of direction errors. The percentage of successful trials was highest for the PS task, followed by the MPS task, whereas the AS and the MAS tasks had lower overall values, with MAS being the least successful task (as expected). The percentage of direction errors was lowest for the PS task, followed by the MPS task, while the AS and the MAS tasks had higher overall values, with the highest percentage of direction errors occurring for the MAS task. Regarding the percentage of anticipatory saccade errors, no task effect was observed for the Early-HD group, whilst in the Control group significant values did not survive the Bonferroni correction.

For the latency of the primary saccade onset, a significant effect in the Early-HD group was only observed between the PS and the MAS conditions, while the Control group showed a consistent effect of task complexity. The latencies of the primary saccades increased from the PS, AS, and MPS to the MAS task, respectively.

Table 5 – Within-group effect of task complexity.

	%Successful Trials *Friedman test* *Pairwise Comparisons*	**%Anticipatory Saccade Errors** *Friedman test* *Pairwise Comparisons*	**%Direction Errors** *Friedman test* *Pairwise Comparisons*	**Primary Saccade Latency** *Friedman test* *Pairwise Comparisons*
Early-HD	$\chi^2(3) = 14.04$ $p = 0.003$ **PS-MAS:** p = 0.004 **MPS-MAS:** p = 0.042	$\chi^2(3) = 0.68$ $p = 0.877$ –	$\chi^2(3) = 15.00$ $p = 0.002$ **PS-MAS:** p = 0.001	$\chi^2(3) = 13.56$ $p = 0.004$ **PS-MAS:** p = 0.001
Control	$\chi^2(3) = 34.38$ $p < 0.0001$ **PS-AS:** p = 0.042 **PS-MAS:** p < 0.0001 **AS-MAS:** p = 0.029 **MPS-MAS:** p < 0.0001	$\chi^2(3) = 10.84$ $p = 0.013$ –	$\chi^2(3) = 45.26$ $p < 0.0001$ **PS-AS:** p < 0.0001 **PS-MAS:** p < 0.0001 **MPS-MAS:** p = 0.001	$\chi^2(3) = 57.84$ $p < 0.0001$ **PS-AS:** p = 0.042 **PS-MPS:** p < 0.0001 **PS-MAS:** p < 0.0001 **AS-MAS:** p < 0.0001 **MPS-MAS:** p = 0.042

PS: Prosaccade; AS: Antisaccade; MPS: 1- or 2-back Memory Prosaccade; MAS: 1- or 2-back Memory Antisaccade.
Friedman test (asymptotic significances 2-sided, p < 0.05); PostHoc pairwise multiple comparisons with the Bonferroni correction method. Only significant results are reported. Only participants that performed all the tasks were considered (Early-HD N=5; Control N=20)

Finally, one of the most striking results arose when comparing the exclusion rate between groups and across the four task conditions in the Early-HD group. The more challenging the task, the more Early-HD participants were discarded from further saccadic performance analysis (see **Table 3**), whereas in the Control group, the exclusion of datasets due to a low number of valid trials only occurred for the most demanding MPS (n = 1) and MAS tasks (n = 2). The Early-HD group had no datasets excluded in the PS task but showed the highest exclusion rates in tasks that implied directly saccadic inhibition (AS, n = 9; MAS, n = 9). Yet, for the AS task, eight exclusions were due to a low number of valid trials (< 25%) and only one exclusion due to the incapacity to perform the task, whilst an increased number of exclusions due to the incapacity to perform the task was observed in the conditions with the highest memory and fronto-executive load (MPS, n = 3; MAS, n = 5). Note that despite the marked reduction in Early-HD sample size for the more demanding saccadic conditions, it remained without statistically significant differences from the Control group regarding age and education.

The PS and MPS tasks were the only ones used for the correlation analysis between the clinical, UHDRS, and saccadic measures due to the high prevalence of Early-HD exclusion for the AS and MAS tasks (N < 8).

In the PS condition, an age effect existed for the Early-HD group (Spearman's rho = 0.698, p < 0.01 Bonferroni corrected) but not for the Control group. In the Early-HD subgroup, we found additional correlations between the percentage of direction errors in the MPS task and the duration of the disease (Spearman's rho = 0.896, p < 0.01 Bonferroni corrected), the percentage of direction errors in PS task and the UHDRS-TMS (Spearman's rho = 0.689, p < 0.01 Bonferroni corrected), as well as between the UHDRS-TMS and the percentage of anticipatory saccade errors in the MPS task (Spearman's rho=0.916; p < 0.01 Bonferroni corrected). Conversely, no significant associations were identified between the saccadic metrics and the CAG repeat length or the OculoTMS.

Discussion

The current study aimed to underpin and characterize dysfunction of oculomotor performance, and its relationship with cognitive functioning, via the recruitment of inhibitory control mechanisms and executive function through working memory demands on fronto-executive load in a cohort of early manifest HD (Early-HD). The hypothesis of improved sensitivity and specificity to the heterogeneity of HD symptoms progression and status was confirmed, not only by the trajectory and latency errors on the more cognitively preserved patients but also by the inability to perform the most demanding tasks (MPS and MAS) in patients with higher cognitive dysfunction.

Our findings significantly add to the body of research on the cognitive profile of HD patients [4,12,29,35,91-93] by showing that, even in the early stages of the disease, manifest HD individuals exhibit significant impairments in the majority of neuropsychological measures, with more pronounced deficits in executive functions, visual perception, verbal and visual memory, and psychomotor speed. These results suggest a global cognitive dysfunction, particularly a dysexecutive syndrome, instead of specific impairments in one or two cognitive domains, as suggested by some authors [35]. Interestingly, these deficits do not necessarily translate into gross functional impairments, given that the pool of Early-HD patients in this study were relatively autonomous and independent in their daily living chores, as demonstrated by TFC scores.

As for the eye-tracking protocol, the Early-HD patients showed signs of impaired oculomotor performance for saccade trajectory and latency. These impairments were evident in the percentage of successful trials, direction errors and anticipatory saccades, all of which differed significantly from the Control group. Early-HD patients showed a significantly lower success rate and a higher percentage of anticipatory (timing) and directional errors, even in the less demanding PS task. Task difficulty appeared to accentuate these deficiencies in oculomotor performance, as observed by increasing fronto-executive/memory load and requesting inhibitory control. Supporting this claim is the fact that about 43% of datasets for the Early-HD group were excluded from data analysis once a 25% successful trial criterion was applied, revealing the high level of impairment in these patients. All datasets were included in the analysis of the PS condition, whilst only 36% of datasets were included for the AS and MAS conditions—which required inhibition of voluntary saccades—and about 57% in the MPS task—which essentially involves memory load. These findings support earlier research[50,53,55,62], including the suggestion that an AS task can provide a sensitive index of oculomotor dysfunction in HD [94]. We also provide novel insights on how the motor and cognitive aspects of saccadic behavior in manifest HD are related to one another. Because cognitive impairments were common among Early-HD patients, we identified that worse cognitive performance was associated with more severe oculomotor deficits. As there is typically a high level of heterogeneity in the presentation and progression of symptoms in the early stages of manifest HD [67], this is particularly important for differentiating the status of cognitive and motor-related deficits.

The saccadic metrics computed from the individuals that satisfied the 25% successful valid trials criterion (for each task), who also presented a more preserved cognitive profile, confirmed the effect of task difficulty and the expected differences between patient and control groups [50,53,55,62]. The higher percentage of direction errors and a lower percentage of successful trials varied linearly with task demands on executive load and inhibitory control, from the PS, MPS, AS, to the MAS task, irrespective of group. However, the low number of Early-HD patients who managed to perform the whole protocol implied a steep decrease in statistical power and a lower-than-expected significant variations. The percentage of anticipatory saccades presented a contrasting pattern, with higher values for the PS and MPS tasks, and for the Early-HD. Yet, results suggest that the impairments in impulse and inhibitory control found in the Early-HD patients, who are cognitively more preserved, are widespread and relatively independent of the nature of the task [39,50,54,55]. Interestingly, the sub-

group of more cognitively preserved Early-HD patients also presented faster response times than control participants in the most demanding MAS task, thus presenting a more automatic and impulsive response profile [29,35,39,41,45,66,92,95-97] in contrast to a strategy to ensure a successful performance with higher accuracy levels.

From a biological standpoint, these findings support the notion that an impairment of fronto-striatal circuits is a critical event in HD, linking the motor and cognitive components of oculomotor behavior and incorporating the well-documented frontal lobe symptoms in manifest HD, which include impulsivity and related inhibitory control dysfunction [3,12,48].

Finally, the only significant association with saccadic measures included disease duration for the MPS task and the UHDRS-TMS for the PS and MPS tasks. Other clinical measures such as CAG repeat length and OculoTMS showed no significant associations with saccadic metrics computed from valid trials. This may indicate that CAG expansion has a lower impact on individuals' overt behavior in the early manifest HD stage, in agreement with former findings [55], and that the oculomotor items in the traditional motor assessment scale may not be the best measures of change in HD individuals, as also formerly suggested [12,98]. Yet, one cannot discard that only the PS and MPS tasks were included in the correlation analysis due to the low sample size for the AS and the MAS tasks, and that the patients excluded from saccadic metrics analysis in the most demanding tasks also had worse overall scores in the UHDRS (TMS, OculoTMS, TFC). Future work might clarify some of these findings and reveal other relevant associations.

Limitations

The principal limitation of this study is the small number of patients enrolled. A larger sample size would be necessary to better identify and characterize subgroups within the clinical stage of Huntington's disease, how oculomotor function is impaired for each, and how the cognitive decline interacts with specific oculomotor features. Also, our cut-off criterion of 25% valid trials is merely empirical, defined to guarantee a minimum number of trials to compute saccade metrics, such as latency, while being consistent with former research in HD [94].

Conclusions

With the rapid technological developments, eye-tracking may provide additional value for disease monitoring, objectively assessing the state of HD symptoms and the effectiveness of novel therapeutics. The healthcare and MedTech industry is taking the first steps towards more decentralized platforms, with the recent PREDICTOM project [99] proposing a multimodal and disease-status-related AI-driven screening platform for dementia, which also includes home-based cognitive and eye-tracking assessments. Our results further support the relevance of eye-tracking and its potential to the follow-up of prodromal and early manifest stages of Huntington's Disease.

Author Contributions

Study concept and design, G.C. and M.C.-B.; Project Administration and Supervision, G.C.; recruitment and evaluation of participants, F.J. (neuropsychology) and C.J. (clinical); data acquisition, G.C. and F.J.; formal analysis, G.C. and F.J.; writing, review and editing, G.C. and F.J.; manuscript revision, G.C., F.J., M.C.-B. and C.J.; All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Faculdade de Medicina da Universidade de Coimbra (official reference code 18-CE-2011).

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Conflict of Interest Statement

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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