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Reflexive and voluntary saccadic eye movements as biomarker of Huntington's Disease

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ABSTRACT

Introduction. Subtle abnormalities in the preclinical stage of Huntington's Disease (HD) can be detected using saccadic eye movement assessment reflecting disease progression. This study was aimed to evaluate abnormalities in saccade parameters in asymptomatic carriers and symptomatic HD patients at various stages of HD.

Material and methods. The study enrolled 104 participants, including 14 asymptomatic carriers of HTT mutations, 44 symptomatic HD patients, and 46 control subjects. HD severity was measured using the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS–TMS) and Total Functional Capacity Scale (TFC). The evaluation of rapid eye movements (reflexive saccades, anti-saccades, memory-guided saccades) was carried out using 'Saccadometer Research'.

Results. Measures of reflexive and volitional saccades did not differ between the asymptomatic carriers and controls. Significant latency prolongation and increased physiological variability of latency times, as well as higher error rates among HD patients, were found in all saccade tasks ($p < 0.001$) compared to the controls. Abnormalities in saccade parameters were more pronounced in the advanced stages of the disease. Latency of saccades and error rate of volitional saccades correlated with the UHDRS–TMS and TFC scores.

Conclusions. The saccade parameters in asymptomatic HD carriers with a long time to disease development were similar to those in the control group. Saccade abnormalities appeared in symptomatic patients at the beginning of the disease, and correlated with HD severity.

Keywords: Huntington's Disease, saccadic eye movements, biomarkers

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Introduction

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder that manifests with progressive motor, cognitive, and behavioural abnormalities. Disease onset is preceded by an asymptomatic period without identifiable symptoms on routine neurological examinations. Subtle abnormalities can occur c.10–15 years before the onset of HD. In this preclinical stage, the first symptoms of the disease can be detected in an assessment of saccade eye movements [1, 2].

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Saccades are rapid, conjugated, and jerky eye movements that are generated when sight is shifted from the fixation point to the point of interest [3]. Saccade disorders are present at an early stage of HD among relatives of patients, and herald the imminent development of the disease [4]. Saccade deficits have been well documented in premanifest and manifest HD patients, and are considered potential biomarkers of disease development and progression [5–17]. The structural abnormalities of the optic nerve and retina displayed in pre-symptomatic HD carriers could be other potential biomarkers that would be of great interest in HD gene therapies [18]. Recently, impaired smooth pursuit of eye movement was described in an atypical motor presentation of HD with dominant dystonic symptoms at the onset of the disease [19]. A study of the occurrence of comorbidities in an HD population in Poland revealed that the prevalence of ophthalmological comorbidities was not significantly more frequent in both HD groups, i.e. pre-symptomatic (95 patients) or symptomatic (374 patients) HD patients compared to 74 control individuals [20].

This study aimed to evaluate reflexive and volitional saccade parameters in asymptomatic carriers and symptomatic HD patients at various stages of disease progression, and to compare them to saccade parameters in a control group. Importantly, our study established a correlation between saccade abnormalities and HD severity as measured by the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) and the Total Functional Capacity Scale (TFC).

Materials and methods

Study participants

This study was conducted on patients and asymptomatic carriers of HD mutations. The presence of mutations in the huntingtin gene was confirmed by the positive results of genetic testing performed in asymptomatic carriers and symptomatic patients. Patients were followed up at the Neurological Outpatient Clinics in Krakow, Gdansk, and Katowice, Poland between 2011 and 2015. Subjects who tested positive were subdivided into a group of asymptomatic mutation carriers and a group of symptomatic HD patients, according to the results of the UHDRS-TMS and Unified Huntington's Disease Rating Scale diagnostic confidence. Asymptomatic mutation carriers scored ≤ 5 points on the UHDRS–TMS and less than 4 points on the UHDRS diagnostic confidence score. Symptomatic HD patients scored more than 5 points on the UHDRS-TMS and 4 on the UHDRS diagnostic confidence score. In preclinical subjects with gene mutations, we calculated the estimated age at HD onset based on the mathematical formula devised by Langbehn et al. [21]. Symptomatic HD patients were further divided into three groups according to the severity of the disease based on the TFC scale: patients who scored 11-13 points in the TFC were assigned to the early HD subgroup; patients who received 7-10 points were assigned to the moderate-HD subgroup; and patients who scored 6 or less were assigned to the advanced HD subgroup.

The control group consisted of healthy volunteers with a negative family history of neurological diseases. These individuals were matched by sex and age (± 3 years) to participants in the asymptomatic and symptomatic stages of HD. The control group included family members unrelated to HD patients and healthy volunteers.

The evaluation of rapid eye movements was carried out using 'Saccadometer Research' (Ober Consulting, Boston, MA, USA) [22]. The analysis only included saccade repetition that met the following criteria: (1) saccades with a latency of 100–700 ms executed after the fixation point had expired; (2) saccades performed in directions in accordance with the instructions; and (3) saccades that were not immediately preceded by abnormal and additional saccades. Sixty repetitions of the reflexive saccade test were performed. Twenty repetitions were performed in the anti-saccade and memory-guided saccade tests. Each test was preceded by 20 repetitions in order to calibrate the device. The latency and physiological variability of latency were calculated only if participants performed > 30% of the correct repetitions in the anti-saccade and memory-guided saccade tests.

The following evaluation tests were conducted:

Reflexive saccades. Participants were instructed to focus on the centred fixation point. This point disappears when another light signal appears on the perimeter. The location of this point is random. Subjects were asked to shift their eyes to a signal that appeared on the periphery as quickly as possible. The latency time and physiological variability of the latency times of the saccades were evaluated.

Anti-saccades. Participants were instructed to focus on the centred fixation point. When the target point appeared on the perimeter, the subject had to look in the direction opposite to the displayed target point. This test required inhibition of the reflexive saccade followed by execution of the volitional saccade in the opposite direction to the visual stimulation. The rate of erroneously executed saccades, the latency, and the physiological variability of the latency time of correctly executed anti-saccades, were evaluated.

Memory-guided saccades. When the central fixation point was displayed, an additional light signal appeared on the perimeter, suggesting the location of the upcoming saccade. The test subjects were asked to keep their eyes fixed on the fixation point until the peripheral and centre points expired, and then to perform a volitional saccade towards the location of the peripheral point presented before. The trigger point reappeared to adjust the precision of the saccade. As in the anti-saccade test, it was necessary to inhibit the reflexive saccade and generate volitional saccades after the signal. The rate of erroneously executed saccades, the latency, and the physiological variability of latency times were evaluated for properly executed 10° and 20° saccades, respectively.

Table 1. Demographic and clinical data of HD and control group

	HD patients			All patients with HD	Control group for patients with HD	Patients with presymp-tomatic HD	Control group for patients with presymp-tomatic HD
	Early HD	Moderate HD	Advanced HD				
Number of participants	15	21	8	44	32	14	14
Age [years]; mean ± SD	47.5 ± 8.7	52.5 ± 12.6	54.5 ± 8.0	51.1 ± 10.8	46.5 ± 8.6	33.4 ± 7.6	33.2 ± 7.6
Women: men	8:7	11:10	3:8	22:22	16:16	8:6	8:6
Inheritance maternal: paternal	4:10	7:8	0:8	11:26	-	12:2	-
Number of CAG repeats; mean ± SD	42.2 ± 3.6	43.4 ± 3.5	43.3 ± 3.0	42.9 ± 3.4	-	41.9 ± 2.0	-
Age at onset of HD [years]; mean ± SD	43.0 ± 8.3	45.5 ± 11.3	42.6 ± 8.8	44.1 ± 9.8	-	-	-
Duration of HD [years]; mean ± SD	4.5 ± 2.2	6.6 ± 3.4	11.7 ± 3.4	6.8 ± 3.9	-	-	-
UHDRS — TMS score; mean ± SD	24.2 ± 10.2	39.0 ± 14.9	66.6 ± 14.7	38.9 ± 19.8	-	1.0 ± 1.6	-
UHDRS — TFC score; mean ± SD	11.7 ± 0.8	7.7 ± 0.9	4.1 ± 1.1	8.4 ± 2.9	-	13	-
Estimated age at HD onset in presymptomatic patients [years]; mean ± SD	-	-	-	-	-	54.0 ± 8.7	-

HD — Huntington's Disease; SD — standard deviation; CAG — cytosine-adenine-guanine; UHDRS — Unified Huntington's Disease Rating Scale; TMS — Total Motor Score; TFC — Total Functional Capacity

All participants received comprehensive information regarding the study protocol and consented to participate in the study. The research procedures were performed in accordance with the principles of the Declaration of Helsinki, and were approved by the Bioethics Committee of Jagiellonian University (No. KBET/253/B/2012).

Statistical analysis

Statistical analysis was performed using Statistica 10 (StatSoft. Inc., PL). All variables presented a normal distribution, as verified using the Kolmogorov-Smirnov test. Results are presented as mean ± standard deviation (SD). To compare the two qualitative variables and determine whether they were related, the $\chi 2$ test was used. The test results showed that the study groups differed from one another. The Student's T test was used to examine the mean values of parameters between the groups and to show differences between them. In addition, the results demonstrate the significance of these differences. One-way analysis of variance (ANOVA) was used to determine the correlation between numerical variables. This applies to testing the differences in the saccade results among HD patients at different stages of the disease. Pearson's correlation coefficient was used to measure the linear correlation between two variables, and in our study was applied to show the correlation between clinical parameters and results of saccades in patients with HD. Statistical significance was set at $p < 0.05$.

Results

The study enrolled 104 participants, including 14 asymptomatic carriers of HTT mutation, 44 symptomatic HD patients, and 46 control subjects. The study groups did not differ in terms of sex or age. The demographic and clinical data of the participants is set out in Table 1. The subgroups of symptomatic HD patients differed significantly in terms of disease duration, TFC severity, and UHDRS-TMS score ($p < 0.001$ for each difference). Maternal inheritance was more prevalent in asymptomatic carriers, whereas paternal inheritance was more common in symptomatic HD patients ($p < 0.001$) (Tab.1).

The measures of reflexive and volitional saccades did not differ between asymptomatic carriers and controls. In contrast, saccade parameters in symptomatic HD patients were significantly different from the control group (Tables 2 and 3). Reflexive saccades in symptomatic HD patients had prolonged latency ($p < 0.001$) and increased physiological variability of latency times ($p < 0.001$). Significant latency prolongation and increased physiological variability of latency times, as well as a higher errors rate among HD patients, were found in the anti-saccade task ($p < 0.001$ for all differences). In the memory-guided saccade task, patients with HD showed a higher error rate ($p < 0.001$), prolonged latency, and increased physiological variability of latency times of 10° saccades ($p = 0.001$ and $p < 0.001$, respectively). Prolonged latency and increased physiological variability of latency of 20°

Table 2. Comparison of reflexive saccade parameters between HD patients and control subjects

	Patients with HD				All patients with HD	Control group for patients with HD	P-value	Patients with presympto-matic HD	Control group for patients with presympto-matic HD	P-value
	Early HD	Moderate HD	Advanced HD	P-value						
Latency (ms)	200.5 ± 32.8	260.9 ± 74.6	363.7 ± 145.7	0.004	259.0 ± 98.1	180.9 ± 26.5	< 0.001	177.2 ± 21.3	176.7 ± 18.4	> 0.05
SD of latency	48.9 ± 27.1	116.2 ± 62.3	187.2 ± 122.9	< 0.001	106.2 ± 83.2	43.1 ± 32.6	< 0.001	57.9 ± 45.1	41.2 ± 17.8	> 0.05

HD — Huntington's Disease; SD — standard deviation; ms — milliseconds

Table 3. Volitional saccade parameters in HD patients and control subjects

	Patients with HD				All patients with HD	Control group for patients with HD	P-value	Patients with presymptomatic HD	Control group for patients with presymptomatic HD	P-value
	Early HD	Moderate HD	Advanced HD	P-value						
Anti-saccades — error rate [%]	65.3 ± 6.1	85.0 ± 5.3	81.9 ± 8.4	> 0.05	78.0 ± 24.4	19.5 ± 15.2	< 0.001	15.4 ± 19.9	12.1 ± 13.8	> 0.05
Anti-saccades latency [ms]	334.3 ± 74.9	546.5 ± 105.9	357.1 ± 149.8	> 0.05	398.2 ± 217.9	278.5 ± 50.8	< 0.001	288.5 ± 46.4	264.7 ± 53.7	> 0.05
SD of Anti-saccades latency [ms]	147.2 ± 50.7	177.4 ± 67.1	260.4 ± 94.9	> 0.05	173.9 ± 129.2	61.3 ± 28.5	< 0.001	53.6 ± 16.0	56.7 ± 33.4	> 0.05
Memory-guided saccades — error rate [%]	67.0 ± 7.2	87.7 ± 6.2	98.1 ± 9.8	0.027	83.1 ± 29.1	32.7 ± 22.2	< 0.001	28.2 ± 15.1	20.7 ± 17.9	> 0.05
10° memory-guided saccades latency [ms]	409.1 ± 84.2	451.8 ± 119.0	*	> 0.05	423.3 ± 194.0	282.4 ± 67.5	0.001	306.7 ± 93.6	302.5 ± 67.4	> 0.05
SD of 10° memory-guided saccades latency [ms]	173.7 ± 65.1	254.9 ± 92	*	> 0.05	200.8 ± 154.5	78.9 ± 48.9	< 0.001	178.4 ± 162.5	121.6 ± 67.3	> 0.05
20° memory-guided saccades latency [ms]	368.6 ± 56.9	414.8 ± 80.5	*	> 0.05	383.9 ± 132.4	298.8 ± 92.3	0.035	303.8 ± 55.3	342.5 ± 142.9	> 0.05
SD of 20° memory-guided saccades latency [ms]	137.5 ± 47.4	248.5 ± 82.1	*	> 0.05	165.3 ± 119.1	100.8 ± 65.7	0.047	139.9 ± 106.6	138.4 ± 132.2	> 0.05

It was impossible to compare latency of memory-guided saccades due to insufficient number of properly performed saccades.
HD — Huntington's Disease; SD — standard deviation; ms — milliseconds

Table 4. Correlation between clinical parameters and saccadic results in HD patients

Saccade parameters	Clinical parameters				
	Duration of HD	Age at onset of HD	Number of CAG repeats	UHDRS-TFC	UHDRS-TMS
Latency of reflexive saccades	0.3308	0.0277	–0.0766	–0.3002	0.5854
	p = 0.002	p = 0.800	p = 0.494	p = 0.007	p = 0.008
Anti-saccades — error rate	0.2631	0.1077	–0.0146	–0.4479	0.3226
	p = 0.068	p = 0.461	p = 0.921	p = 0.001	p = 0.024
Latency of antisaccades	–0.1208	0.4536	0.2448	–0.0183	–0.0396
	p = 0.681	p = 0.103	p = 0.399	p = 0.950	p = 0.893
Memory-guided saccades — error rate	0.2058	0.0036	0.0195	–0.4696	0.3269
	p = 0.156	p = 0.980	p = 0.894	p = 0.001	p = 0.022
Latency of 10° memory-guided saccades	–0.0291	0.0761	–0.2027	0.2528	0.0070
	p = 0.932	p = 0.824	p = 0.550	p = 0.453	p = 0.984
Latency of 20° memory-guided saccades	–0.0155	–0.0191	–0.3676	0.1738	0.1689
	p = 0.964	p = 0.955	p = 0.266	p = 0.609	p = 0.620

HD — Huntington's Disease; CAG — cytosine-adenine-guanine; UHDRS — Unified Huntington's Disease Rating Scale; TMS — Total Motor Score; TFC — Total Functional Capacity

memory-guided saccades were also significant, although the value of this significance was not as high as in other parameters (p = 0.035 and p = 0.047, respectively). Abnormalities in saccade parameters were more pronounced in moderate and advanced stages of the disease. Reflexive saccades had prolonged latency (p = 0.004) and increased physiological variability in latency times (p < 0.001) in more advanced disease. Tests of volitional saccades revealed an increased rate of errors in a memory-guided saccade task in more advanced disease (p = 0.027). Due to the low number of properly performed saccades in the subgroup of patients with advanced disease, it was impossible to compare the latency and physiological variability of latency times of memory-guided saccades between groups. Anti-saccade parameters also worsened in patients with more advanced disease. We observed increased error rate, prolonged latency, and increased physiological variability of latency times, but the differences were not statistically significant (Tab. 1, 2).

Saccade abnormalities correlated with clinical parameters. The study revealed a mild positive correlation between the latency of reflexive saccades and disease duration (r = 0.3308, p = 0.002). Latency of reflexive saccades and error rate of anti-saccades and memory-guided saccades were negatively correlated with disease progression, as measured by the TFC scale (r = –0.3002, p = 0.007; r = –0.4479, p = 0.001 and r = –0.4696, p = 0.001). Additionally, saccade disturbances were correlated with motor function abnormalities. A positive correlation was observed between the latency of reflexive saccades and the UHDRS-TMS scale (r = 0.5854, p = 0.008). Mild positive correlations were found between the anti-saccade error rate and the UHDRS-TMS scale (r = 0.3226, p = 0.024) and between the memory-guided saccade error rate and the UHDRS-TMS (r = 0.3269, p = 0.022). Age at onset of HD and the number of CAG repeats did not appear to influence saccade abnormalities (Tab. 4)

Discussion

Our study showed abnormalities of reflexive and volitional saccades parameters in symptomatic patients with HD, reflecting the disease duration. These disturbances were not confirmed in the preclinical stage of the disease, which puts in question the usefulness of saccade assessment in predicting the onset of symptoms in asymptomatic gene carriers. Moreover, the study demonstrated a good correlation between the severity of saccade abnormalities and clinical parameters, such as disease duration, motor disturbances, and disease progression.

Our results confirm that saccade disturbances correlate with motor function abnormalities as assessed by the UHDRS-TMS and with disease progression measured by the TFC [9–11].

Differences in saccade parameters between the presymptomatic HD gene carriers and controls were shown. This data is in contrast with those of other studies. Prolonged latency and increased latency variability of volitional saccades in presymptomatic carriers was previously noted [12–14]. Similar results were obtained by Golding et al., who showed prolonged latency of memory-guided saccades and increased variability of saccades latency [10]. Volitional saccade abnormalities have been noted by Blekher et al. They provided information on the decreased number of correct memory-guided saccades and prolonged latency of these saccades. Furthermore, prolonged latency and decreased number of anti-saccades have been reported [15, 16]. The study by Rupp et al. showed that saccade parameters in premanifest mutation carriers were like

the results of saccades tests in a healthy control group [17]. When pre-symptomatic carriers were closer to the estimated time of onset of the clinical manifestation, abnormalities of saccades appeared, and a significantly increased error rate in anti-saccades and memory-guided saccades in the horizontal direction, as well as anti-saccade latency in the vertical and horizontal directions, have been noted [23]. Another study revealed that in premanifest mutation carriers, first saccades abnormalities were seen in a double-complex test, consisting of elements of anti-saccade and memory-guided saccade tests. Increased latency and error rate of saccades were observed. These abnormalities progressed during the pre-manifest period, and were most severe in the early stages of HD. Participants made more mistakes in parts of the test where anti-saccades were required [24]. Robert et al. [25] noted that the more complex the task in a saccadometric test, the higher the probability of differentiation between presymptomatic HD patients and controls. Nevertheless, saccade abnormalities were described in patients with a short estimated time of HD onset of c.10 years.

In our study, presymptomatic mutation carriers were young, with an estimated age at onset of the disease of c.18 years. A prolonged time taken to estimate the time of HD onset could have strongly influenced the results of our study. From this point of view, the results of our study did not contradict the abovementioned studies. We observed some trends in abnormal saccade parameters in our study. Presymptomatic HD subjects had prolonged latency and increased error rate in anti-saccade and memory-guided saccades. The differences were not statistically significant, but could result from the insufficient number of participants and the prolonged estimated time of HD onset. Additionally, we applied only basic tests of anti-saccade and memory-guided saccades in the horizontal direction. All these factors might have resulted in non-significant data.

Our results demonstrate that traditional saccadometric tests are insufficient to detect saccade abnormalities in an early prodromal stage of the disease, especially in pre-symptomatic patients who are likely to enter the symptomatic stage in the remote future. Consistently with previous findings, future studies should use more complex tests assessing volitional saccades, consisting of anti-saccade and memory-guided elements, in both horizontal and vertical directions [16, 24, 25].

In symptomatic HD patients, we identified abnormalities in reflexive and volitional saccade parameters such as prolonged latency, increased variability of latency, and increased error rate of volitional saccades, which reflect increasing dysfunction of the frontal cortex and basal ganglia. These abnormalities were noted even at the early stage of the disease, and tended to worsen with HD progression. Impaired initiation of voluntary saccades, reflected by increased latency of saccades and difficulties in maintaining steady fixation, was reported at the early stage of the disease as the most prominent defect [5]. Fixation defects were introduced in the anti-saccades test and memory-guided saccades when patients were unable to suppress reflexive saccades in response to the novel visual stimulus. This behaviour resulted in an increased error rate for voluntary saccades. Abnormalities were more common in the anti-saccade test [6]. On the other hand, HD patients had problems in making volitional saccades towards a remembered target, which has been previously seen. This behaviour could be another cause for the increased error rate in the memory-guided test. These data was confirmed in later studies [6, 8]. The latency of reflexive saccades was also significantly increased in symptomatic patients compared to healthy controls, but the ability to produce reflexive saccades was largely intact, and this prolongation was not as pronounced as in the case of volitional saccades [6, 8]. Even though these abnormalities of saccade parameters were the most common, other saccade characteristics were studied, namely amplitude, velocity, and duration of saccades. Reflexive and volitional saccades were characterised by decreased velocity, decreased amplitude, increased rate of erroneous memory-guided saccades, physiological variability of latency, and duration of saccades [5–10].

Our study provided additional information. Although the assessment of volitional saccades parameters is a very useful tool for the evaluation of premanifest and early-stage HD patients, this procedure seems impractical in patients with advanced HD. In our study, the analysis of anti-saccades and memory-guided saccades parameters was impossible in patients who scored 6 or fewer points in the TFC scale due to an insufficient number of saccades. These patients are unable to maintain steady fixation, suppress reflexive saccades, or make volitional saccades according to instructions. Anti-saccades and memory-guided saccade tasks require engaging executive functions and could be a sensitive marker of cognitive impairment, which is widely observed in the advanced stage of HD. This results in a decrease in the number of correctly made saccades. In advanced symptomatic patients, the use of reflexive saccades parameters, such as latency and latency variability, seem to be a more appropriate tool for disease progression monitoring.

Saccades parameters did not correlate with age at HD onset or the number of CAG repeats, which could indicate that they were not dependent on each other. The number of CAG repeats is inversely correlated with the age at onset of HD [26]. The lack of correlation between both parameters and saccade evaluation was consistent. Therefore, higher CAG expansion is not a risk factor for earlier saccade disturbances, or more prominent saccade abnormalities. The presence of a defective gene did not correlate with eye movement abnormalities. Saccades disturbances could be a valuable diagnostic marker to identifying the onset of HD. Our data is consistent with that of other studies [27]. However, some saccade parameters were correlated with clinical assessments. Latency of reflexive saccades showed correlation with duration of the disease, the TFC scale, and the UHDRS–TMS scale, as well as the error rate of anti-saccades and memory-guided saccades correlated

with the TFC scale and the UHDRS–TMS scale. The TFC and the UHDRS-TMS scales are widely used in clinical studies for clinical assessments. The latency of reflexive saccades and the error rate of volitional saccades decline during disease progression, according to the TFC and the UHDRS–TMS scales. Further studies are needed to determine whether these saccade outcomes could track disease progression. However, this study demonstrated the potential usefulness of these saccade parameters as biomarkers of HD progression in symptomatic patients.

We acknowledge that some limitations of our study may be due to the influence of medical treatment on symptomatic patients with HD. The study participants continued their usual treatment during the study. We considered medication withdrawal would have been unethical given the neurological status of patients. However, according to other studies, medications do not have major impacts on the results [5, 7, 8, 28, 29].

Another limitation is that this was a cross-sectional study conducted on a small group of pre-symptomatic and symptomatic patients with HD. A longitudinal investigation of a larger study group would provide valuable confirmation (or negation) of our results. We did not assess the impact of deep brain stimulation on saccade performance. However, this method of treatment for severe drug-resistant chorea is still considered investigational, and we did not include patients with DBS in our study [30].

One more limitation of this study is the lack of investigation into the differentiation of saccade parameters based on gender. A recent study by Zielonka et al. revealed differences in the clinical picture and progression of HD between women and men [31]. Therefore, the assessment of the relationship between saccade parameters and sex in preclinical and symptomatic patients could be a valuable complement to our research.

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