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# Saccades in Huntington's Disease

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Eye movements include two classes: those that stabilise the image on the retina such as fixation, smooth pursuit, and vestibulocular and optokinetic reflexes; and those that shift the focus of the fovea toward interesting objects, namely saccades [1, 2].

The first group is generally reflexive or automatic and includes activation of older central nervous system (CNS) structures, whereas saccades, especially voluntary saccades, engage higher parts of the brain and therefore act as a sensitive marker of brain dysfunction [3]. Saccades abnormalities can reflect cognitive disabilities because they are easier and more quickly assessed than psychological tests to assess cognition [4].

Huntington's Disease (HD) is a movement disorder where a genetically determined (*HTT* gene dynamic mutation) neurodegenerative process leads to involuntary movements, cognitive deterioration, and behavioural disorders [5]. These three symptomatic domains related to CNS damage are accompanied by peripheral HD symptoms, including metabolic dysfunction and muscle degradation [6, 7]. Both motor and cognitive symptoms significantly affect eye movements [8]. This HD manifestation is clearly displayed in juvenile Huntington's disease (JHD), especially in Westphal variant, where 'oculomotor apraxia' with saccade initiation dysfunction has been observed [9, 10]. Saccades assessment has been a clinical biomarker in HD for several years (Tab. 1) [9, 11]. Involuntary saccades that disturb ocular pursuit have been described in premanifest individuals close to onset; therefore, they are recognised as one of the first HD signs [12]. Saccades disturbances observed in premanifest *HTT* gene mutation carriers consist of a delay in saccades initiation and an increase in variability of this delay [13–16]. To be specific, observed saccade abnormalities in premanifest individuals include significantly altered anti-saccades, delayed memory-guided saccades, increased saccade variability, and increased saccade error rates [1, 17–19].

Moreover, saccades disinhibition, namely affected saccade suppression, more anticipatory saccades (timing errors), higher error rates in memory-guided saccade tasks, delay in initiating voluntary saccades, and reflexive prosaccades delay have been reported by several authors [1, 20–22]. Most complicated and demanding tasks evoking saccades are affected early in HD, and can be used to discriminate *HTT* mutation carriers from healthy people [21, 22]. Impairment of frontostriatal inhibitory function in HD is displayed in altered anti-saccades and partly explains reduced ability for complex saccadic tasks [23, 24]. It has been reported that fronto-executive and memory load makes visible alterations in saccadic tasks in premanifest HD individuals. Inclusion tasks requiring inhibition and memory demands seem to be sensitive in discriminating between premanifest and healthy individuals [8]. A higher error rate of anti-saccades, and memory-guided saccades in a horizontal direction, and delayed horizontal and vertical anti-saccades, become more prominent before HD onset [19]. Abnormalities of complex saccadic tasks are highly evident in early HD [25].

Disturbed saccades in a manifest period of HD are characterised by reduced saccades velocity vertically and horizontally and reduced amplitude in all directions. Moreover, manifest HD presents continuously increasing errors in memory-guided saccades and saccades latency and duration variability [26, 27]. Later, gaze fixation is affected due to an inability to inhibit saccades toward a stimulus [28]. Slow and hypometric saccades can even turn into gaze palsy and ophthalmoplegia, especially in younger patients [10].

Eye movements in HD can be used as sensitive and easily accessible markers of disease progression and nicely reflect HD's motor and cognitive level; therefore, modern tools for automatic eye movement tracking were developed. An excellent example of such a device is the well-recognised, clinically validated, and used in many studies 'Saccadometer Research'

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**Table 1.** Saccade disturbances related to HD progression (based on literature review)

Saccade	Premanifest	Manifest	Advanced stage
Anti-saccades	Possible initiation delay, higher latency variability, erroneous, velocity and amplitude normal	Delayed initiation, slow, lower amplitude, erroneous, higher latency variability	Seriously disturbed, possible 'oculomotor apraxia'
Memory-guided saccades	Possible initiation delay, higher latency variability, erroneous, velocity and amplitude normal	Delayed initiation, slow, lower amplitude, erroneous, higher latency variability	Seriously disturbed, possible 'oculomotor apraxia'
Predictive/anticipatory saccades	Rather not disturbed	Possible initiation delay, higher onset variability, possible slow and low amplitude, erroneous	Seriously disturbed, possible 'oculomotor apraxia'
Prosaccades	Rather not disturbed	Possible initiation delay, higher onset variability, possible slow and low amplitude, erroneous	Seriously disturbed, possible 'oculomotor apraxia'
Reflexive saccades	Rather not disturbed	Possible initiation delay, higher onset variability, possible slow and low amplitude, erroneous	Seriously disturbed, possible 'oculomotor apraxia'
Involuntary saccades	Possible, interfere with pursuit	Present, interfere with pursuit	Present, interfere with pursuit if possible

by Ober Consulting [29, 30]. Saccades in several diseases, including HD, have been assessed with this or a similar tool [31–33]. A recently published paper [34] reporting the supportive function of reflexive and voluntary saccades analysis in HD staging also used 'Saccadometer Research'. The authors of this research paper measured saccades in premanifest carriers of *HTT* gene mutation and HD-affected individuals in different stages of this disease, looking for significant differences between groups. Moreover, they used control participants to build references for their analyses. Patient groups were relatively small, and therefore statistical significance was not always achieved e.g. in comparing reflexive to volitional saccades in controls and premanifest individuals. The authors found statistical differences in latency, latency variability, and the error rate of saccades (reflexive, anti-, memory-guided) when comparing affected participants to controls. Additionally, observed saccades' alterations progressed with clinical worsening and were significantly related to assessment scales. The authors noted however that saccades' assessment was more difficult in very advanced stages due to communication problems with patients.

In summary, eye movement disturbances, especially saccade alteration, are valuable clinical markers in HD. They allow us to assess the time to onset in premanifest, and the stage of the disease in manifest individuals. Electronic devices support eye movement assessment, and the development of these inexpensive and easy-to-use tools is highly recommended.

## References

- Anderson TJ, MacAskill MR. Eye movements in patients with neurodegenerative disorders. *Nat Rev Neurol.* 2013; 9(2): 74–85, doi: [10.1038/nrneurol.2012.273](https://doi.org/10.1038/nrneurol.2012.273), indexed in Pubmed: [23338283](https://pubmed.ncbi.nlm.nih.gov/23338283/).
- Leigh RJ, Zee DS. *The Neurology of Eye Movements.* 4th ed. New York: Oxford University Press. 2006.
- McDonald MA, Holdsworth SJ, Danesh-Meyer HV. Eye Movements in Mild Traumatic Brain Injury: Ocular Biomarkers. *J Eye Mov Res.* 2022; 15(2), doi: [10.16910/jemr.15.2.4](https://doi.org/10.16910/jemr.15.2.4), indexed in Pubmed: [36439911](https://pubmed.ncbi.nlm.nih.gov/36439911/).
- Wu J, Li M, Ma W, et al. 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(3): 321–335, doi: [10.1159/000526802](https://doi.org/10.1159/000526802), indexed in Pubmed: [36244337](https://pubmed.ncbi.nlm.nih.gov/36244337/).
- Kaczyńska J, Sitek EJ, Witkowski G, et al. Is deep brain stimulation effective in Huntington's Disease? - a systematic literature review. *Neurol Neurochir Pol.* 2022; 56(4): 299–307, doi: [10.5603/PJNNS.a2022.0050](https://doi.org/10.5603/PJNNS.a2022.0050), indexed in Pubmed: [35792559](https://pubmed.ncbi.nlm.nih.gov/35792559/).
- Gruber B, Kłaczko G, Jaworska M, et al. Huntington' disease–imbalance of amino acid levels in plasma of patients and mutation carriers. *Ann Agric Environ Med.* 2013; 20(4): 779–783, indexed in Pubmed: [24364452](https://pubmed.ncbi.nlm.nih.gov/24364452/).
- Zielonka D, Piotrowska I, Marcinkowski JT, et al. Skeletal muscle pathology in Huntington's disease. *Front Physiol.* 2014; 5: 380, doi: [10.3389/fphys.2014.00380](https://doi.org/10.3389/fphys.2014.00380), indexed in Pubmed: [25339908](https://pubmed.ncbi.nlm.nih.gov/25339908/).
- Júlio F, Caetano G, Januário C, et al. The effect of impulsivity and inhibitory control deficits in the saccadic behavior of premanifest Huntington's disease individuals. *Orphanet J Rare Dis.* 2019; 14(1): 246, doi: [10.1186/s13023-019-1218-y](https://doi.org/10.1186/s13023-019-1218-y), indexed in Pubmed: [31703597](https://pubmed.ncbi.nlm.nih.gov/31703597/).
- Markham CH, Knox JW. Observations on Huntington's chorea in childhood. *J Pediatr.* 1965; 67: 46–57, doi: [10.1016/s0022-3476\(65\)80303-1](https://doi.org/10.1016/s0022-3476(65)80303-1), indexed in Pubmed: [14301558](https://pubmed.ncbi.nlm.nih.gov/14301558/).
- Innes EA, Qiu J, Morales-Briceño H, et al. Oculomotor Apraxia as an Early Presenting Sign of Juvenile-Onset Huntington's Disease. *Mov Disord Clin Pract.* 2023; 10(Suppl 3): S12–S14, doi: [10.1002/mdc3.13775](https://doi.org/10.1002/mdc3.13775), indexed in Pubmed: [37636223](https://pubmed.ncbi.nlm.nih.gov/37636223/).
- Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. *Mov Disord.* 1996; 11(2): 136–142, doi: [10.1002/mds.870110204](https://doi.org/10.1002/mds.870110204), indexed in Pubmed: [8684382](https://pubmed.ncbi.nlm.nih.gov/8684382/).
- Winder JY, Roos RAC. Premanifest Huntington's disease: Examination of oculomotor abnormalities in clinical practice. *PLoS One.* 2018; 13(3): e0193866, doi: [10.1371/journal.pone.0193866](https://doi.org/10.1371/journal.pone.0193866), indexed in Pubmed: [29494703](https://pubmed.ncbi.nlm.nih.gov/29494703/).

13. Siemers E, Foroud T, Bill DJ, et al. Motor changes in presymptomatic Huntington disease gene carriers. *Arch Neurol*. 1996; 53(6): 487–492, doi: [10.1001/archneur.1996.00550060029011](https://doi.org/10.1001/archneur.1996.00550060029011), indexed in Pubmed: [8660148](https://pubmed.ncbi.nlm.nih.gov/8660148/).
14. Kirkwood SC, Siemers E, Hodes ME, et al. Subtle changes among presymptomatic carriers of the Huntington's disease gene. *J Neurol Neurosurg Psychiatry*. 2000; 69(6): 773–779, doi: [10.1136/jnnp.69.6.773](https://doi.org/10.1136/jnnp.69.6.773), indexed in Pubmed: [11080230](https://pubmed.ncbi.nlm.nih.gov/11080230/).
15. Cutsuridis V, Jiang S, Dunn MJ, et al. Neural modeling of antisaccade performance of healthy controls and early Huntington's disease patients. *Chaos*. 2021; 31(1): 013121, doi: [10.1063/5.0021584](https://doi.org/10.1063/5.0021584), indexed in Pubmed: [33754760](https://pubmed.ncbi.nlm.nih.gov/33754760/).
16. Golding CVP, Danchavijitr C, Hodgson TL, et al. Identification of an oculomotor biomarker of preclinical Huntington disease. *Neurology*. 2006; 67(3): 485–487, doi: [10.1212/01.wnl.0000218215.43328.88](https://doi.org/10.1212/01.wnl.0000218215.43328.88), indexed in Pubmed: [16625001](https://pubmed.ncbi.nlm.nih.gov/16625001/).
17. Patel SS, Jankovic J, Hood AJ, et al. Reflexive and volitional saccades: biomarkers of Huntington disease severity and progression. *J Neurol Sci*. 2012; 313(1-2): 35–41, doi: [10.1016/j.jns.2011.09.035](https://doi.org/10.1016/j.jns.2011.09.035), indexed in Pubmed: [22018763](https://pubmed.ncbi.nlm.nih.gov/22018763/).
18. Tabrizi SJ, Reilmann R, Roos RAC, et al. TRACK-HD investigators. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. *Lancet Neurol*. 2012; 11(1): 42–53, doi: [10.1016/S1474-4422\(11\)70263-0](https://doi.org/10.1016/S1474-4422(11)70263-0), indexed in Pubmed: [22137354](https://pubmed.ncbi.nlm.nih.gov/22137354/).
19. Rupp J, Dzemidzic M, Blekher T, 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(2): 267–276, doi: [10.1007/s00415-011-6172-0](https://doi.org/10.1007/s00415-011-6172-0), indexed in Pubmed: [21850389](https://pubmed.ncbi.nlm.nih.gov/21850389/).
20. Blekher TM, Yee RD, Kirkwood SC, et al. Oculomotor control in asymptomatic and recently diagnosed individuals with the genetic marker for Huntington's disease. *Vision Res*. 2004; 44(23): 2729–2736, doi: [10.1016/j.visres.2004.06.006](https://doi.org/10.1016/j.visres.2004.06.006), indexed in Pubmed: [15358067](https://pubmed.ncbi.nlm.nih.gov/15358067/).
21. Turner TH, Goldstein J, Hamilton JM, et al. Behavioral measures of saccade latency and inhibition in manifest and premanifest Huntington's disease. *J Mot Behav*. 2011; 43(4): 295–302, doi: [10.1080/00222895.2011.580390](https://doi.org/10.1080/00222895.2011.580390), indexed in Pubmed: [21774606](https://pubmed.ncbi.nlm.nih.gov/21774606/).
22. Antoniadou CA, Xu Z, Mason SL, et al. Huntington's disease: changes in saccades and hand-tapping over 3 years. *J Neurol*. 2010; 257(11): 1890–1898, doi: [10.1007/s00415-010-5632-2](https://doi.org/10.1007/s00415-010-5632-2), indexed in Pubmed: [20585954](https://pubmed.ncbi.nlm.nih.gov/20585954/).
23. Mitchell JP, Macrae CN, Gilchrist ID. Working memory and the suppression of reflexive saccades. *J Cogn Neurosci*. 2002; 14(1): 95–103, doi: [10.1162/089892902317205357](https://doi.org/10.1162/089892902317205357), indexed in Pubmed: [11798390](https://pubmed.ncbi.nlm.nih.gov/11798390/).
24. Van der Stigchel S. The search for oculomotor inhibition: interactions with working memory. *Exp Psychol*. 2010; 57(6): 429–435, doi: [10.1027/1618-3169/a000053](https://doi.org/10.1027/1618-3169/a000053), indexed in Pubmed: [20178939](https://pubmed.ncbi.nlm.nih.gov/20178939/).
25. Hicks SL, Robert MPA, Golding CVP, et al. Oculomotor deficits indicate the progression of Huntington's disease. *Prog Brain Res*. 2008; 171: 555–558, doi: [10.1016/S0079-6123\(08\)00678-X](https://doi.org/10.1016/S0079-6123(08)00678-X), indexed in Pubmed: [18718352](https://pubmed.ncbi.nlm.nih.gov/18718352/).
26. Ali FR, Michell AW, Barker RA, et al. The use of quantitative oculometry in the assessment of Huntington's disease. *Exp Brain Res*. 2006; 169(2): 237–245, doi: [10.1007/s00221-005-0143-6](https://doi.org/10.1007/s00221-005-0143-6), indexed in Pubmed: [16273398](https://pubmed.ncbi.nlm.nih.gov/16273398/).
27. Golding CVP, Danchavijitr C, Hodgson TL, et al. Identification of an oculomotor biomarker of preclinical Huntington disease. *Neurology*. 2006; 67(3): 485–487, doi: [10.1212/01.wnl.0000218215.43328.88](https://doi.org/10.1212/01.wnl.0000218215.43328.88), indexed in Pubmed: [16625001](https://pubmed.ncbi.nlm.nih.gov/16625001/).
28. Lasker AG, Zee DS. Ocular motor abnormalities in Huntington's disease. *Vision Res*. 1997; 37(24): 3639–3645, doi: [10.1016/S0042-6989\(96\)00169-1](https://doi.org/10.1016/S0042-6989(96)00169-1), indexed in Pubmed: [9425536](https://pubmed.ncbi.nlm.nih.gov/9425536/).
29. Ober JK, Przedpelska-Ober E, et al. Hand-held system for ambulatory measurement of saccadic durations of neurological patients. In: Gadjia J (ed) *Modelling and Measurement in Medicine* Komitet Biocybernetyki i Inżynierii Biomedycznej. PAN, Warsaw, 2003: 187–198.
30. Ali FR, Michell AW, Barker RA, et al. The use of quantitative oculometry in the assessment of Huntington's disease. *Exp Brain Res*. 2006; 169(2): 237–245, doi: [10.1007/s00221-005-0143-6](https://doi.org/10.1007/s00221-005-0143-6), indexed in Pubmed: [16273398](https://pubmed.ncbi.nlm.nih.gov/16273398/).
31. Przytuła F, Sławek J. Hyperkinetic movement disorders following SARS-CoV-2 infection and vaccination - an update. *Neurol Neurochir Pol*. 2023; 57(1): 63–76, doi: [10.5603/PJNNS.a2023.0012](https://doi.org/10.5603/PJNNS.a2023.0012), indexed in Pubmed: [36799521](https://pubmed.ncbi.nlm.nih.gov/36799521/).
32. Semnol I, Ristic T, Koprivsek K. PNKP mutation in a child: is there a firm line between MCSZ and AOA4 phenotype? *Neurol Neurochir Pol*. 2024; 58(2): 207–209, doi: [10.5603/pjnns.97269](https://doi.org/10.5603/pjnns.97269), indexed in Pubmed: [38230758](https://pubmed.ncbi.nlm.nih.gov/38230758/).
33. Alster P, Madetko-Alster N, Migda A, et al. Sleep disturbances in progressive supranuclear palsy syndrome (PSPS) and corticobasal syndrome (CBS). *Neurol Neurochir Pol*. 2023; 57(3): 229–234, doi: [10.5603/PJNNS.a2023.0019](https://doi.org/10.5603/PJNNS.a2023.0019), indexed in Pubmed: [36928793](https://pubmed.ncbi.nlm.nih.gov/36928793/).
34. Grabska N, Wójcik-Pędziwiatr M, Sławek J, et al. Reflexive and voluntary saccadic eye movements as biomarker of Huntington's Disease. *Neurol Neurochir Pol*. 2024; 58(3): 323–330, doi: [10.5603/pjnns.95190](https://doi.org/10.5603/pjnns.95190), indexed in Pubmed: [38818957](https://pubmed.ncbi.nlm.nih.gov/38818957/).