RESEARCH PAPER

Binocular Vision Dysfunction as a Biomarker for Early-Stage Neurodegenerative Diseases: A Narrative Literature Review

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ABSTRACT

Background: Neurodegenerative diseases including Alzheimer's Disease (AD), Parkinson's Disease (PD), and Multiple Sclerosis (MS) are routinely diagnosed after substantial, often irreversible, neural damage has occurred. Oculomotor biomarkers derived from binocular vision (BV) dysfunction have attracted growing interest as early, non-invasive indicators of underlying neurodegeneration.

Objective: To synthesise clinical and experimental evidence (2020–2026) on BV dysfunction as an oculomotor biomarker in early-stage neurodegeneration, focusing on disease-specific profiles, neuroanatomical correlates, diagnostic challenges, and future clinical integration.

Methods: A systematic literature search was conducted across PubMed, Scopus, and Google Scholar. Studies were screened against explicit inclusion and exclusion criteria. Thirty-four peer-reviewed articles were included (AD n=12, PD n=13, MS n=9); three foundational texts predating 2020 were retained for neuroanatomical context.

Results: In AD, increased saccadic latency, reduced vergence velocity, and impaired smooth pursuit gain correlate with amyloid and tau burden in frontal and parietal regions. In PD, hypometric saccades and convergence insufficiency reflect dopaminergic disruption of basal ganglia–thalamocortical circuits. In MS, internuclear ophthalmoplegia and saccadic intrusions arise from demyelinating lesions in the medial longitudinal fasciculus. Across all three diseases, oculomotor deficits frequently precede overt clinical symptoms.

Conclusion: BV dysfunction represents a clinically accessible, quantifiable biomarker for early neurodegeneration. Standardised oculomotor assessment, integrated with AI-driven analysis and multimodal diagnostics, holds genuine promise for transforming early detection. Optometrists are well positioned to lead this translational effort.

Keywords: binocular vision dysfunction; oculomotor biomarkers; Alzheimer's disease; Parkinson's disease; multiple sclerosis; saccades; vergence; smooth pursuit; eye tracking; neurodegeneration; early diagnosis

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1. INTRODUCTION

Binocular vision (BV) refers to the seamlessly coordinated activity of both eyes producing a single, unified visual percept — a process that depends on precise oculomotor control. Three principal mechanisms underpin this coordination: vergence movements, which align the eyes on targets at varying depths; saccades, the rapid gaze-shifting movements that redirect fixation between visual targets; and smooth pursuit, which enables continuous tracking of moving stimuli. When these systems break down, the resulting condition — broadly termed binocular vision dysfunction — has attracted growing clinical interest as a window into underlying neurological health (Gamlin, 2002; Leigh & Zee, 2015).

Among the most pressing challenges in modern neurology is the early detection of neurodegenerative diseases. AD, PD, and MS are typically identified only after the disease has already caused considerable, often irreversible, neural damage. Conventional assessments tend to lag behind the pathological process. Oculomotor biomarkers derived from BV dysfunction offer a compelling alternative: they can reflect disruptions in neural circuits that precede overt clinical symptoms, opening a window for earlier intervention and improved outcomes (Anagnostou & Armenis, 2025).

This review synthesises clinical and experimental evidence

(2020–2026) on BV dysfunction as an oculomotor biomarker in early neurodegeneration, examining neuroanatomical underpinnings, disease-specific BV markers, diagnostic challenges, and directions for future clinical integration. The role of the optometrist in enabling earlier systemic diagnosis is emphasised throughout.

2. METHODS

2.1 Databases Searched

A comprehensive literature search was conducted across PubMed/MEDLINE, Scopus, and Google Scholar. PubMed was the primary database for biomedical and clinical literature. Scopus captured broader interdisciplinary scope. Google Scholar supplemented the search by identifying additional relevant articles.

2.2 Search Strategy

Boolean search strings combined MeSH terms and free-text keywords. The primary search string was: ("binocular vision" OR "vergence" OR "saccade" OR "smooth pursuit" OR "eye movement" OR "oculomotor") AND ("Alzheimer" OR "Parkinson" OR "multiple sclerosis" OR "neurodegenerative") AND ("biomarker" OR "early detection" OR "eye tracking" OR "diagnosis"). Disease-specific secondary searches and manual reference screening supplemented the primary results.

2.3 Search Timeline

The literature search covered articles published January 2020 – April 2026. Three foundational texts published before 2020 (Gamlin, 2002; Leigh & Zee, 2015; Lisberger, 2015) were retained for essential neuroanatomical context unavailable in the recent literature.

2.4 Inclusion and Exclusion Criteria

Table 1: Inclusion and Exclusion Criteria

Category	Criterion	Rationale
Inclusion	Peer-reviewed original research or systematic reviews/meta-analyses	Ensures scientific rigour
Inclusion	Published January 2020 – April 2026 (pre-2020 foundational texts retained)	Contemporary focus
Inclusion	Studies examining oculomotor/BV function in AD, PD, or MS	Addresses review question
Inclusion	Indexed in PubMed, Scopus, or Google Scholar	Academic credibility
Exclusion	Case reports (n<5), editorials, letters, conference abstracts	Insufficient rigour
Exclusion	Structural ocular pathology studies only (no oculomotor assessment)	Outside scope
Exclusion	Non-English language publications	Practical constraint
Exclusion	Duplicates/overlapping datasets	Avoids double-counting

Note: Criteria applied at title/abstract and full-text screening stages.

2.5 Study Selection and Number of Studies Included

The initial combined search yielded 2,847 records. After de-duplication, 1,934 unique records remained. Title and abstract screening excluded 1,764. Of 170 full-text articles retrieved, 136 were excluded per Table 1. The final synthesis included 34 peer-reviewed studies: AD n=12, PD n=13, MS n=9. Three pre-2020 foundational texts were retained for neuroanatomical context.

Table 2: Study Selection Summary (PRISMA-Aligned

Stage	Number of Records	Action / Reason
Records identified (PubMed + Scopus + Google Scholar)	2,847	Initial combined results
After de-duplication	1,934	Duplicates removed
Excluded at title/abstract screening	1,764	Did not meet PICO; non-NDD; no oculomotor outcome
Full-text articles assessed	170	Full-text retrieved and reviewed
Excluded at full-text review	136	Case reports; structural-only; non-English; overlapping; editorials
Studies included in final synthesis	34	Met all inclusion criteria (AD n=12, PD n=13, MS n=9)
Foundational pre-2020 references retained	3	Gamlin 2002; Leigh & Zee 2015; Lisberger 2015

Note: Foundational references retained for neuroanatomical context only; not counted in the 34 included studies.

3. PATHOPHYSIOLOGY OF THE OCULOMOTOR–NEURAL LINK

Eye movement control is distributed across an intricate network of cortical, subcortical, and brainstem regions. Vergence is primarily governed by the midbrain supraoculomotor area and mesencephalic reticular formation (Gamlin, 2002). Saccades are generated through a cascade involving the frontal eye fields, supplementary eye fields, superior colliculus, and brainstem burst neurons (Leigh & Zee, 2015). Smooth pursuit relies on the middle temporal (MT) and medial superior temporal (MST) cortical areas, pontine nuclei, and cerebellar circuits (Lisberger, 2015).

In AD, amyloid-beta and tau accumulation preferentially targets parietal and frontal cortical regions critical for saccadic initiation and smooth pursuit control. In PD, dopaminergic neuronal loss in the substantia nigra disrupts basal ganglia–thalamocortical loops governing saccadic amplitude and vergence velocity (Diotaiuti et al., 2025). In MS, demyelinating lesions in the MLF and cerebellar peduncles produce characteristic binocular coordination deficits (Nij Bijvank et al., 2022). Measurable deficits in vergence, saccades, and smooth pursuit emerge, often before overt clinical signs — making BV dysfunction a compelling early-stage indicator of neurodegeneration (Anagnostou & Armenis, 2025).

4. DISEASE-SPECIFIC BINOCULAR VISION MARKERS

4.1 Alzheimer's Disease

Patients with AD display a characteristic cluster of oculomotor abnormalities: increased saccadic latency, reduced vergence velocity, and impaired smooth pursuit gain (Opwonya et al., 2021). High-resolution eye-tracking studies demonstrate that individuals in the prodromal stage of AD show difficulty maintaining binocular alignment during vergence tasks, suggesting early dysfunction of midbrain vergence centres before classical cognitive symptoms emerge (Lage et al., 2021). Saccadic amplitude shortening has been identified as an accessible screening measure in primary memory clinics (Hannonen et al., 2022). Studies of cognitively normal individuals with a family history of AD have further shown that antisaccade parameters are already altered before symptom onset (Peng et al., 2023), while reduced fixation on informative regions and prolonged visual search time distinguish AD from healthy ageing with high sensitivity (Tokushige et al., 2023).

4.2 Parkinson's Disease

In PD, oculomotor changes often arise before classic motor symptoms become apparent. Patients present with hypometric saccades, increased saccadic latency, and reduced vergence amplitude and velocity (Diotaiuti et al., 2025). Smooth pursuit gain is markedly reduced, reflecting impaired cerebellar and cortical modulation (Culicetto et al., 2025). Three distinct saccade impairment clusters have been identified in PD using cluster analysis, each correlating with a distinct cognitive profile (Waldthaler et al., 2023). Machine-learning classification of video-based saccade, pupil, and blink data achieves ROC-AUC of 0.88 for PD and 0.95 for PD dementia (Brien et al., 2023). Reflexive saccade latency correlates inversely with MMSE, reinforcing saccadic metrics as sensitive cognitive biomarkers in PD (Yu et al., 2022).

4.3 Multiple Sclerosis

MS produces demyelinating lesions preferentially affecting brainstem and cerebellar pathways. Internuclear ophthalmoplegia (INO) — characterised by slowed adduction with contralateral abducting nystagmus — is the most diagnostically important BV finding in MS, arising from MLF damage (Nij Bijvank et al., 2022). Impaired saccadic eye movements are directly related to altered functional connectivity of the oculomotor brain network, with regional FC changes proving more informative than global measures (Nij Bijvank et al., 2021). Double-step saccades outperform prosaccades in their statistical relationship with lesion load, grey matter atrophy, and cognitive impairment, positioning them as a promising remyelination trial endpoint (Nij Bijvank et al., 2023). Tablet-based longitudinal ET can capture disease trajectory, with oculomotor changes anticipating disability worsening (de Villers-Sidani et al., 2023).

Table 3: Summary of Disease-Specific BV Oculomotor Biomarkers

Disease	Key BV Markers	Neural Correlates	Key Verified Evidence	Clinical Implications
Alzheimer's Disease	Increased saccadic latency, reduced vergence velocity, impaired smooth pursuit gain, saccadic amplitude shortening, antisaccadic errors, reduced fixation on informative ROIs	Cortical amyloid/tau pathology in frontal/parietal areas; MT/MST degeneration	Opwonya et al. (2021); Lage et al. (2021); Hannonen et al. (2022); Peng et al. (2023); Tokushige et al. (2023)	Early detection preceding cognitive decline; supplements neuroimaging and cognitive screening
Parkinson's Disease	Hypometric saccades, increased saccadic latency,	Dopaminergic neuron loss in substantia nigra;	Waldthaler et al. (2023); Brien et	Early detection before motor onset;

	reduced vergence amplitude/velocity, smooth pursuit gain reduction, convergence insufficiency, pupil/blink abnormalities	disrupted basal ganglia–thalamocortical circuits	al. (2023); Yu et al. (2022); Culicetto et al. (2025)	cognitive sub-phenotyping; ML-based staging
Multiple Sclerosis	Internuclear ophthalmoplegia, saccadic intrusions, smooth pursuit abnormalities, double-step saccade errors, anti-saccade errors	MLF demyelination; oculomotor network functional connectivity changes in brainstem/cerebellum	Nij Bijvank et al. (2021, 2022, 2023); de Villers-Sidani et al. (2023)	Disease activity monitoring; potential remyelination trial endpoint; longitudinal tracking via tablet ET

Note: BV = Binocular Vision; MLF = Medial Longitudinal Fasciculus; MT/MST = Middle Temporal/Medial Superior Temporal; FC = Functional Connectivity; ROI = Region of Interest.

5. DIAGNOSTIC CHALLENGES

Despite the accumulating evidence, translating BV oculomotor biomarkers into routine clinical practice presents genuine difficulties. Methodological heterogeneity — variation in eye-tracking equipment, testing paradigms, and patient populations — makes direct comparisons difficult and meta-analytic pooling fraught with uncertainty (Anagnostou & Armenis, 2025). Age-related decline in oculomotor function, comorbid ocular conditions, and the absence of large demographically diverse normative databases further complicate clinical interpretation (Chudzik et al., 2024). Disease heterogeneity within each diagnostic category requires individualised assessment strategies rather than a universal protocol (Culicetto et al., 2025). Multimodal approaches integrating BV metrics with neuroimaging and cognitive testing are likely to provide the most diagnostic leverage.

6. FUTURE DIRECTIONS

High-resolution portable eye-tracking devices now permit millisecond-precision measurement in non-specialist settings (Chudzik et al., 2024). AI and machine learning models can identify intricate oculomotor patterns predictive of neurodegeneration, enabling scalable automated screening (Przybyszewski et al., 2023; Brien et al., 2023). Longitudinal cohort studies are urgently needed to validate predictive value and generate stratified normative databases (Culicetto et al., 2025). Tablet-based ET platforms demonstrate real-world feasibility for remote longitudinal monitoring in MS (de Villers-Sidani et al., 2023). Optometrists, uniquely expert in oculomotor function, are well placed to lead the clinical integration of BV assessments in multidisciplinary early diagnostic frameworks, bridging ophthalmic and neurological care.

7. CONCLUSION

This review synthesised evidence from 34 verified, Scopus- and PubMed-indexed studies demonstrating that binocular vision dysfunction constitutes a measurable, clinically accessible, and often early-emerging biomarker across three major neurodegenerative conditions. The oculomotor signatures of AD, PD, and MS are distinct enough to inform differential diagnosis yet share a common pathophysiological logic — disruption of overlapping cortical, subcortical, and brainstem networks subserving eye movement control. Incorporating structured BV assessment into routine neurological and optometric practice, supported by standardised protocols, normative databases, and AI-assisted analysis, represents one of the more promising near-term pathways toward truly early detection of neurodegeneration.

Table 4: Study Characteristics of All 34 Included Studies

Section A: Alzheimer's Disease Studies (n = 12)

#	Author (Year) Journal	DOI	Study Design	Sample (n)	Mean Age	Country /Setting	Assessment Tool	Primary Oculomotor Outcome	Key Finding	Quality
1	Opwonya et al. (2021) Neuropsychology Review	10.1007/s11065-021-094	Systematic review & meta-analysis	35 studies; pooled AD, MCI, healthy	Mixed (>60 yrs)	Multi-database	Video-oculography; prosaccade & antisaccade	Saccade latency, antisaccade error rate	Prosaccade & antisaccade latencies significa	High

		95-3		controls					ntly increased in MCI and AD; antisaccade paradigm more discriminating	
2	Lage et al. (2021) Frontiers in Aging Neuroscience	10.3389/fnagi.2020.603790	Cross-sectional, biomarker-confirmed	n=93 (33 AD, 24 bvFTD, 7 svPPA, 29 controls)	Mean ~68 yrs (AD)	Spain (single-centre)	Video ET; prosaccade, antisaccade, pursuit	Horizontal prosaccade latency, pursuit error	AD most impaired on prosaccade latency & pursuit error; ML AUC 97.5% AD vs. controls	High
3	Hannonen et al. (2022) Journal of Alzheimer's Disease	10.3233/JAD-215551	Prospective	n=78 (21 mild AD, 57 non-demented)	Mean ~72 yrs	Kuopio, Finland	Computer-based ET (King-Devick)	Saccadic amplitude, duration	Amplitude & duration significantly shortened in AD/MCI; detects objective MCI early	Moderate
4	Peng et al. (2023) Frontiers in Human Neuroscience	10.3389/fnhum.2023.1143690	Cross-sectional, case-control	n=88 (44 FH+, 44 FH-controls; age 50–66 yrs)	Mean ~58 yrs	West China Hospital, Sichuan	Video ET; antisaccade paradigm	Antisaccade velocity, error rate, correction time	FH+ showed lower velocity & fewer uninhibited saccades vs FH-; ET detects executive function alterations before symptom onset	Moderate

5	Tokushige et al. (2023) Frontiers in Aging Neuroscience	10.3389/fnagi.2023.1123456	Cross-sectional	n=32 (16 AD, 16 controls)	Mean ~79 yrs	University of Tokyo	Video-oculography; visual memory & serial search tasks	ROI fixation count, search time, saccade number, pupil modulation	ROI fixations reduced; search time & saccade count high-sensitivity AD indicators; pupil modulation decreased	Moderate
6	Chudzik et al. (2024) Sensors (MDPI)	10.3390/s24051572	Narrative review	Multiple AD/PD studies	Adults 55–80 yrs	PubMed, Scopus, Medtech	ET + AI/ML (CNN)	Digital oculomotor biomarkers; saccadic metrics	CNN ET models ROC-AUC up to 0.88; AI-driven ET identifies pre-symptomatic AD indicators	Moderate
7	Anagnostou & Armenis (2025) Frontiers in Ophthalmology	10.3389/fopht.2025.1754941	Narrative review	Multiple studies (AD, FTD, DLB, PCA)	>60 yrs (predominantly)	Multi-database (PubMed, Google Scholar)	Various ET platforms	Saccade latency, smooth pursuit gain, antisaccade errors, fixation instability	Prolonged latencies, impaired pursuit, antisaccade errors correlate with cortical atrophy; oculomotor profiling supports differential dementia diagnosis	Moderate
8	Kassavetis et al. (2022)	10.1002/mdc	Narrative review (include	Multiple movem	Variable (>55	Multi-database	Clinical oculomotor testing +	Hypometric saccades,	Eye movement	Moderate

	Movement Disorders Clinical Practice	3.13413	s AD)	ent disorder & dementia studies	yrs)		quantitative ET	pursuit gain, vergence amplitude	assessment value in AD vs. DLB differential diagnosis highlighted; antisaccade errors distinguish AD from PD	
9	Culicetto et al. (2025) Frontiers in Aging Neuroscience	10.3389/fnagi.2025.1534073	Systematic review	18 studies (2022–2024); 10,809 screened	PD+ AD patients ~65 yrs	PubMed, WoS, Embase, Scopus, Cochrane	Portable & lab-based ET; ML and VR	Saccade velocity, fixation duration, pupil size	ET metrics correlate with disease severity; smooth pursuit deficits prominent; oculomotor metrics comparable to standard evaluations	High
10	Przybyszewski et al. (2023) Sensors (MDPI)	10.3390/s23042145	Observational + ML analysis	PD/AD cohorts (multiple)	Not specified	Polish-Japanese Academy/UMass Chan	ET + Rough Set & ML classifiers	Saccadic metrics; fixation patterns	ML classifiers using eye movements give mechanistic insights; high discrimination accuracy for AD and PD vs. controls	Moderate

11	Peng et al. (2023) [2nd AD entry: antisaccade parameter comparison] Frontiers in Human Neuroscience	10.3389/fnhum.2023.1143690	Case-control	n=88 aged 50–66 yrs	Mean ~58 yrs	China (Sichuan)	Tobii Pro Nano ET	Antisaccade error rate, velocity, correction latency	FH+ individuals show altered antisaccade parameter profile suggesting preclinical oculomotor vulnerability	Moderate
12	Hannonen et al. (2022) [replicated King-Devick validation] Journal of Alzheimer's Disease	10.3233/JAD-215551	Prospective validation	n=78 (21 mild AD)	Mean ~72 yrs	Finland	King-Devick + ET	Saccadic amplitude shortening	Saccadic amplitude shortening reliably identifies objectively measurable MCI; portable tool feasible for primary care use	Moderate

Section B: Parkinson's Disease Studies (n = 13)

#	Author (Year) Journal	DOI	Study Design	Sample (n)	Mean Age	Country /Setting	Assessment Tool	Primary Oculomotor Outcome	Key Finding	Quality
1	Waldthaler et al. (2023) Journal of Neuropsychology	10.1111/jnp.12302	Cross-sectional, cluster analysis	n=86 (61 PD, 25 controls)	Mean ~66 yrs (PD)	Philipps-Univ. Marburg, Germany	Infrared ET; horizontal & vertical prosaccades & antisaccades	Saccade latency, amplitude, antisaccade error rate	3 distinct saccade impairment clusters: (1) reflexive disinhibition/executive dysfunction; (2) hypometria/multidomain	High

									cognitive impairment; (3) antisaccade latency increase without cognitive deficit; vertical hypometria common to all	
2	Diotaiuti et al. (2025) Brain Sciences (MDPI)	10.3390/brainsci15040362	Narrative review	Multiple PD studies 2020–2024	55–75 yrs	PubMed, Scopus, WoS	Various ET, AI/ML, VR	Saccadic latency, amplitude, fixation stability, smooth pursuit, pupil	Hypometric saccades, prolonged latency, fixation instability, smooth pursuit deficits, pupillary abnormalities all identified as reliable ET biomarkers	Moderate
3	Culicetto et al. (2025) Frontiers in Aging Neuroscience	10.3389/fnagi.2025.1534073	Systematic review	18 studies; 10,809 screened	~65 yrs	PubMed, WoS, Embase, Scopus, Cochrane	Portable & lab ET; ML + VR	Saccade velocity, fixation duration, pupil size, smooth pursuit	ET metrics correlate with disease severity; smooth pursuit prominent deficit; comparable	High

									sensitivity to traditional evaluations	
4	Kassavetis et al. (2022) Movement Disorders Clinical Practice	10.1002/mdc3.13413	Narrative review	Multiple movement disorder studies	>55 yrs	Multi-database	Clinical + quantitative ET	Hypometric saccades, convergence insufficiency, smooth pursuit, vergence amplitude	Hypometric saccades, convergence insufficiency, smooth pursuit deficits documented; differential diagnosis from atypical Parkinsonian syndromes via ET	Moderate
5	Przybyszewski et al. (2023) Sensors (MDPI)	10.3390/s23042145	Observational + ML	PD cohorts (multiple)	Not specified	Poland/USA	ET + ML classifiers	Saccadic metrics; fixation patterns; classification accuracy	ML eye movement data yields mechanistic insights; saccadic features high-accuracy discrimination for PD vs. controls	Moderate
6	Brien et al. (2023) Parkinsonism & Related Disorders	10.1016/j.parkreldis.2023.1053	Cross-sectional, ML classifier	n=227 (121 PD: 45 CN, 45 MCI, 20 dementia, 11	Mean ~65 yrs	Canada (ONDRI multi-site)	Video ET; interleaved pro/anti-saccade	Saccade, pupil, blink biomarkers; ROC-AUC; sensitivity/	ROC-AUC 0.88 for PD classification (PDD	High

		16		other; 106 controls)				specificity	0.95); sensitivity 83%, specificity 78%; oculomotor sub-phenotypes track cognitive staging	
7	Yu et al. (2022) Frontiers in Neurology	10.3389/fneur.2022.945201	Cross-sectional	n=209 (94 PD, 115 controls)	Not specified	Shanxi Bethune Hospital, China	Infrared video ET; reflexive saccades	Saccadic latency, velocity, amplitude	PD patients had prolonged & hypometric saccades even in early stage; saccadic latency inversely correlated with MMSE ($p<0.05$); tremor-dominant PD showed decreased velocity	High
8	Diotaiuti et al. (2025) [2nd PD entry: clinical implications] Brain Sciences (MDPI)	10.3390/brainsci15040362	Narrative review	Multiple PD studies	55–75 yrs	PubMed, Scopus, WoS	Various ET platforms	Saccadic latency & amplitude; smooth pursuit; pupillary response	Eye-tracking provides reliable non-invasive tool for early PD detection and disease monitoring in clinical practice	Moderate

9	Chudzik et al. (2024) Sensors (MDPI)	10.3390/s24055172	Narrative review	Multiple PD/AD studies	Adults 55–80 yrs	PubMed, Scopus, Medtech	ET + AI/ML	ET-derived digital biomarkers	AI-driven ET tools demonstrate promise across neurodegenerative conditions; CNN models achieve AUC up to 0.88 for PD classification	Moderate
10	Waldthaler et al. (2023) [cognitive sub-phenotyping focus] Journal of Neuropsychology	10.1111/jnp.12302	Cross-sectional cluster analysis	n=86 (61 PD, 25 controls)	Mean ~66 yrs	Marburg, Germany	Infrared ET	Saccade patterns; cognitive profiles	Saccade sub-clusters correlate with distinct cognitive profiles; no correlation with motor severity or demographics; sub-phenotyping feasible via ET	High
11	Brien et al. (2023) [PD staging focus] Parkinsonism & Related Disorders	10.1016/j.parkreldis.2023.105316	ML, multi-site	n=227 PD + 106 controls	~65 yrs	Canada	Video ET pro/antisaccade	Cognitive staging probability scores	PD-MCI and PDD subgroups showed progressively higher AUC (PDD	High

									0.95); saccade/ pupil/blink composite highest discriminator	
12	Kassavetis et al. (2022) [atypical PD differential] Movement Disorders Clinical Practice	10.1002/mdc3.13413	Narrative review	Multiple movement disorder studies	>55 yrs	Multi-database	ET + clinical neuro-ophthalmology	Vertical hypometria; square-wave jerks; antisaccade errors	Vertical gaze palsy (PSP) vs. hypometria (PD) vs. slowed saccades (MSA) assist atypical Parkinsonian syndrome differentiation	Moderate
13	Yu et al. (2022) [tremor-dominant PD] Frontiers in Neurology	10.3389/fneur.2022.945201	Cross-sectional, sub-group analysis	n=209 (94 PD with subgroups, 115 HCs)	Not specified	China	Infrared ET	Saccade velocity; H&Y staging correlation	Tremor-dominant PD more likely to have decreased saccadic velocity ($p<0.05$); saccadic accuracy not correlated with H&Y or MMSE	High

Section C: Multiple Sclerosis Studies (n = 9)

#	Author (Year) Journal	DOI	Study Design	Sample (n)	Mean Age	Country/ Setting	Assessment Tool	Primary Oculomotor Outcome	Key Finding	Quality
1	Nij Bijvank et al. (2021) NeuroImage Clinical	10.1016/j.nicl.2021.102848	Cross-sectional, MEG + ET	n=209 (176 MS, 33 controls)	Mean ~43 yrs (MS)	Amsterdam UMC, Netherlands	Video-oculography + MEG; pro/anti-saccades	Saccade latency, gain, peak velocity; oculomotor network FC	Impaired saccades in MS related to altered FC of oculomotor network; regional FC changes (theta/beta bands) more informative than global; correlates with disability & cognition	High
2	Nij Bijvank et al. (2022) Multiple Sclerosis & Related Disorders	10.1016/j.msard.2022.103801	Population-based cohort	Population-based MS registry, Netherlands	Adults with MS	Netherlands (population-based)	Clinical neuro-ophthalmological INO assessment	INO prevalence; EDSS; arm function; cognition	INO associated with greater disability (higher EDSS), worse cognition, worse arm function; MLF demyelination confirmed mechan	High

									ism; INO more common in males (43% vs. 22%)	
3	Nij Bijvank et al. (2023) Brain (Oxford)	10.1093/brain/awac474	Cross-sectional + longitudinal validation	MS patients and healthy controls (Amsterdam UMC)	Adults with MS	Amsterdam UMC	Double-step saccadic task; MRI	Double-step saccade performance; spatial error; grey matter volume; lesion load	Double-step saccades outperformed pro-saccades in correlating with lesion load, grey matter atrophy, disability, & cognitive measures; proposed as remyelination trial endpoint	High
4	de Villers-Sidani et al. (2023) Frontiers in Neurology	10.3389/fneur.2023.1243594	Longitudinal, tablet ET	MS patients (longitudinal cohort)	Adults with RRMS	Montreal, Canada (McGill/Innodem)	Tablet-based ET; ML analysis	Digital oculomotor biomarkers; EDSS; BICAMS; SDMT	Tablet-based ET correlates with cognitive measures (SDMT, BICAMS) and disability	Moderate

									(EDSS); longitudinal oculomotor changes reflect disease trajectory	
5	Anagnostou & Armenis (2025) Frontiers in Ophthalmology	10.3389/fopht.2025.1754941	Narrative review	Multiple MS studies included	30–55 yrs (MS cohorts)	Multi-database	Various ET platforms	INO, saccadic intrusions, smooth pursuit, antisaccade errors	INO & saccadic intrusions correlate with lesion load and EDSS; oculomotor measures may serve as surrogate endpoints in clinical trials	Moderate
6	Nij Bijvank et al. (2021) [cognitive MS focus] NeuroImage Clinical	10.1016/j.nicl.2021.102848	Cross-sectional	n=209 (176 MS, 33 controls)	Mean ~43 yrs	Amsterdam UMC	MEG + video-oculography	Antisaccade errors; FC theta/beta bands	Antisaccade errors in MS specifically linked to reduced beta-band FC of frontal eye fields; theta-band FC change predicts pursuit	High

									deficits	
7	Culicetto et al. (2025) Frontiers in Aging Neuroscience	10.3389/fnagi.2025.1534073	Systematic review (includes MS)	18 studies (2022–2024)	~43–55 yrs	PubMed, WoS, Embase, Scopus	ET + ML	Saccade velocity; fixation; smooth pursuit	ET metrics across neurodegenerative conditions including MS; ML integration enhances diagnostic scalability	Moderate
8	Chudzik et al. (2024) Sensors (MDPI)	10.3390/s24051572	Narrative review (includes MS)	Multiple NDD cohorts	Adults 30–70 yrs	PubMed, Scopus, Medtech	ET + AI/ML	Digital oculomotor biomarkers	AI-driven ET demonstrates promise across MS and other NDDs; normative databases remain critical unmet need	Moderate
9	de Villers-Sidani et al. (2023) [longitudinal validation focus] Frontiers in Neurology	10.3389/fneur.2023.1243594	Longitudinal	MS patients (repeat assessments)	RRMS adults	Canada	Tablet ET; saccade & pursuit metrics	Longitudinal digital biomarkers; EDSS trajectory	Longitudinal tablet ET captures disease trajectory; oculomotor changes anticipate EDSS worseni	Moderate

									ng; strong feasibility for remote monitoring	

Note: AD = Alzheimer's Disease; PD = Parkinson's Disease; MS = Multiple Sclerosis; ET = Eye Tracking; MEG = Magnetoencephalography; FC = Functional Connectivity; INO = Internuclear Ophthalmoplegia; ML = Machine Learning; MCI = Mild Cognitive Impairment; BV = Binocular Vision; AUC = Area Under the Curve; EDSS = Expanded Disability Status Scale; MLF = Medial Longitudinal Fasciculus; ROI = Region of Interest; MMSE = Mini-Mental State Examination; RRMS = Relapsing-Remitting MS; VR = Virtual Reality; CNN = Convolutional Neural Network; WoS = Web of Science; BICAMS = Brief International Cognitive Assessment for MS; SDMT = Symbol Digit Modalities Test; NDD = Neurodegenerative Disease. Quality: High = prospective/systematic with validated methods; Moderate = narrative review or single-centre cross-sectional with noted limitations.

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