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The Retina–Brain Axis: Optical Coherence Tomography and OCT Angiography Biomarkers of Neurodegeneration

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Abstract: *The neural retina is an accessible extension of the central nervous system, and optical coherence tomography (OCT) and OCT angiography (OCTA) permit repeatable measurement of retinal neuroaxonal tissue and microvasculature. This critical narrative review examines the strength, limitations, and clinical readiness of retinal imaging biomarkers in multiple sclerosis (MS), Alzheimer disease (AD), mild cognitive impairment (MCI), Parkinson disease (PD), cerebral small-vessel disease (CSVD), and ischemic stroke. PubMed/MEDLINE and reference lists of recent systematic reviews were searched through July 2026, with emphasis on meta-analyses, longitudinal cohorts, studies using biomarker-defined disease, and work correlating retinal findings with magnetic resonance imaging or cognition. Peripapillary retinal nerve fibre layer and macular ganglion cell–inner plexiform layer thinning are most reproducible in MS, particularly after optic neuritis, and have established research and supportive clinical roles. In AD/MCI and PD, average group differences in inner retinal thickness and OCTA vessel-density metrics are frequently reported but remain heterogeneous, overlapping with normal ageing and ocular or vascular comorbidity. CSVD and stroke studies support a retina–brain microvascular association, although specificity and prognostic thresholds are unresolved. Across conditions, device dependence, segmentation error, motion and projection artefacts, scan-quality selection, eye-level statistical errors, and inconsistent adjustment for confounders limit translation. OCT and OCTA should therefore be considered adjunctive research biomarkers rather than stand-alone diagnostic tests outside selected MS applications. Progress requires harmonised acquisition, disease-specific reference standards, longitudinal multimodal validation, and transparent reporting of image quality and confounding.*

Keywords: *retina–brain axis; optical coherence tomography; OCT angiography; retinal nerve fibre layer; neurodegeneration; retinal biomarkers*

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I. INTRODUCTION

The retina shares embryological, anatomical, and physiological features with the brain. Retinal ganglion-cell axons form the optic nerve; retinal neurons and glia participate in neuroinflammatory and degenerative responses; and the retinal microcirculation is protected by a blood–retinal barrier with functional similarities to the blood–brain barrier. These features underlie the concept of the retina as a measurable "window" into central nervous system disease [1].

OCT provides micrometre-scale cross-sectional measurements of retinal layers, while OCTA derives motion contrast from repeated scans to map perfused retinal capillaries without intravenous dye [2,3]. The technologies are rapid, non-contact, and suitable for serial assessment. Common structural metrics include peripapillary retinal nerve fibre layer (pRNFL), macular ganglion cell–inner plexiform layer (GCIPL), ganglion cell complex, total macular thickness, and selected outer-retinal layers. Common OCTA metrics include vessel density, perfusion density, foveal avascular zone (FAZ) area, and capillary-complexity measures.

Accessibility does not automatically confer biomarker validity. A clinically useful biomarker must be analytically reliable, biologically interpretable, associated with a meaningful disease state or outcome, and validated against an appropriate reference standard. This review therefore focuses not only on reported retinal differences but also on their reproducibility, specificity, confounding, and readiness for use in clinical decision-making.

II. REVIEW METHODS

A critical narrative search of PubMed/MEDLINE was performed through July 2026 using combinations of "optical coherence tomography," "OCT angiography," "retina," "multiple sclerosis," "Alzheimer disease," "mild cognitive impairment," "Parkinson disease," "cerebral small-vessel disease," "stroke," "magnetic resonance imaging," and "biomarker." Reference lists of recent systematic reviews and meta-analyses were also examined. Priority was given to systematic reviews, longitudinal studies, biomarker-

defined cohorts, multimodal retina–brain studies, and representative primary investigations that illustrated major findings or methodological limitations. This was a narrative synthesis; formal risk-of-bias scoring and quantitative meta-analysis were not undertaken.

III. BIOLOGICAL AND TECHNICAL BASIS

Structural OCT markers

The pRNFL largely represents unmyelinated retinal ganglion-cell axons, whereas macular GCIPL combines ganglion-cell bodies and dendritic layers. Thinning may reflect primary retinal neurodegeneration, retrograde degeneration after optic-nerve or posterior visual-pathway injury, trans-synaptic degeneration, or a mixture of these mechanisms. Swelling, gliosis, microcystic macular change, and segmentation failure can produce apparent thickening or mask atrophy. Consequently, layer-specific interpretation and clinical context are essential.

OCTA markers

OCTA visualises perfused vessels rather than vascular anatomy independent of flow. Slow flow may fall below a device's detection threshold, whereas motion, projection, blink, and segmentation artefacts can create or erase capillary signal [3]. Vessel-density values are not interchangeable across manufacturers, scan sizes, slabs, software versions, or thresholding methods. OCTA may capture neurovascular injury, vascular risk, reduced metabolic demand after neuronal loss, or all three; cross-sectional association alone cannot identify causal direction.

IV. DISEASE-SPECIFIC EVIDENCE

Multiple sclerosis

MS provides the strongest example of a clinically interpretable retinal neuroaxonal biomarker. A large meta-analysis found marked pRNFL and GCIPL loss after MS-associated optic neuritis and smaller but significant thinning in eyes without a recognised optic-neuritis history [4]. These layers correlate with visual function, disability, and aspects of brain atrophy, and OCT has a mature role as an outcome measure in neuro-ophthalmic practice and clinical research [5,6]. The distinction between eyes with and without previous optic neuritis is crucial because focal optic-nerve injury can dominate the retinal signal.

OCTA meta-analysis suggests lower retinal vessel-density measures in MS, but effect estimates vary across plexuses and devices and may be influenced by prior optic neuritis, structural loss, disease duration, and vascular risk [7]. At present, OCTA is best viewed as a complementary research measure rather than a replacement for structural OCT, magnetic resonance imaging (MRI), visual evoked potentials, or neurological assessment.

Alzheimer disease and mild cognitive impairment

Studies of AD and MCI frequently report thinner pRNFL, GCIPL, ganglion cell complex, or total macula at the group level [8]. OCTA studies have described reduced superficial or deep capillary density, altered peripapillary perfusion, and FAZ differences [9–14]. Recent reviews, however, emphasise heterogeneity in disease definition, retinal layer selection, device platform, scan quality, and adjustment for glaucoma, axial length, diabetes, hypertension, and age [15,16]. Studies enrolling biomarker-confirmed preclinical AD remain fewer than clinically diagnosed case–control studies.

The retina–brain relationship is biologically plausible but not disease-specific. In a small amyloid-characterised early-onset cohort, total macular thickness correlated with parietal cortical atrophy but did not clearly discriminate AD from controls [17]. A 2025 systematic review of OCT/OCTA–MRI correlations concluded that associations with brain structure occur across disorders but are not yet sufficiently standardised for individual diagnosis [18]. Thus, retinal imaging may contribute to multimodal risk stratification or longitudinal research, but an isolated thin RNFL or low vessel density should not be interpreted as evidence of AD.

Parkinson disease

In PD, structural studies have reported thinning of the pRNFL, macular ganglion-cell measures, and selected outer-retinal layers, with some associations with disease severity, duration, or visual dysfunction [19,20]. Meta-analysis of OCTA studies also suggests lower macular or peripapillary perfusion metrics, but between-study heterogeneity is substantial and the direction or location of abnormalities is not fully consistent [21]. A recent clinical study and contemporary reviews support continued investigation while highlighting overlap with ageing, dopaminergic retinal physiology, ocular disease, medication exposure, and variable PD phenotyping [22]. No OCT or OCTA threshold currently establishes or excludes PD.

Cerebral small-vessel disease and ischemic stroke

The retinal and cerebral microcirculations share small-vessel architecture and vulnerability to hypertension, diabetes, and endothelial dysfunction. A systematic review of retinal biomarkers in CSVD found associations involving microvascular abnormalities and RNFL thickness, but noted small samples, inconsistent imaging definitions, and limited specificity [23]. Cross-sectional OCTA studies in ischemic stroke have reported reduced superficial, deep, and peripapillary vessel density [24]. In early-onset dementia, retinal microvascular measures have also correlated with MRI markers, supporting a cross-system association but not proving diagnostic equivalence [25]. Retinal imaging in vascular neurological disease should therefore be interpreted alongside conventional vascular-risk assessment and neuroimaging.

Table 1. ***Summary of retinal OCT/OCTA findings and current evidentiary maturity***

Condition	Most reproducible structural signal	Reported OCTA signal	Current maturity	Principal interpretive caveat
Multiple sclerosis	pRNFL and GCIPL thinning; strongest after optic neuritis	Lower macular or peripapillary vessel-density metrics in some cohorts	Established research marker; supportive clinical use for optic-nerve involvement and monitoring	Prior optic neuritis, acute swelling, inter-eye asymmetry, and scan quality
AD / MCI	Group-level thinning of pRNFL, GCIPL/GCC, or total macula	Reduced vessel density and variable FAZ/perfusion changes	Promising multimodal research marker; not a stand-alone diagnostic test	Ageing, glaucoma, vascular disease, inconsistent AD biomarker confirmation
Parkinson disease	Variable inner-retinal and occasional outer-retinal thinning	Reduced vessel density reported across differing slabs	Exploratory / early validation	Small cross-sectional cohorts, medication and phenotype heterogeneity
CSVD / ischemic stroke	RNFL or ganglion-cell changes in selected cohorts	Reduced capillary density and altered microvascular geometry	Association and risk-stratification research	Shared vascular risk factors and low disease specificity

V. RETINA–BRAIN AND FUNCTIONAL CORRELATIONS

Retinal measures have been correlated with brain volume, regional cortical atrophy, white-matter disease, cognition, vision, and neurological disability. These associations strengthen biological plausibility but do not by themselves establish clinical utility. Correlation magnitudes are affected by age range, disease stage, sample size, multiple testing, and whether both eyes are analysed as independent observations. Reverse causation is also possible: neuronal loss may reduce metabolic demand and retinal perfusion, while systemic microvascular disease may affect the retina and brain in parallel.

Multimodal models that combine OCT structure, OCTA perfusion, clinical variables, and established biomarkers may outperform a single retinal measure. A 2026 study reported improved discrimination of MCI and probable AD when structural and vascular retinal features were combined [28]. Such results are encouraging, but performance in enriched case–control samples must not be equated with population screening accuracy. External validation, calibration, and clinically relevant positive and negative predictive values are required.

VI. LIMITATIONS AND SOURCES OF BIAS

Acquisition and segmentation

Low signal strength, defocus, media opacity, blink or motion, poor fixation, and segmentation error can bias thickness and perfusion measures. OCTA is additionally vulnerable to projection artefact, decorrelation tails, threshold effects, and slab displacement [26]. Images should be reviewed rather than accepted solely because an automated quality score passes. Studies should report device, software version, scan size, averaging, segmentation corrections, and prespecified exclusion criteria.

Confounding and spectrum bias

Age, sex, ethnicity, refractive error, axial length, disc size, glaucoma, retinal disease, cataract, diabetes, blood pressure, smoking, renal disease, and vasoactive medication may influence retinal measures. Neurological case–control studies often compare highly selected patients with unusually healthy controls, exaggerating apparent diagnostic separation. Disease severity and treatment status should be described, and ocular examination should be sufficiently detailed to identify competing explanations.

Statistical design

Both eyes from one participant are correlated and require eye-level modelling, averaging, or a prespecified eye-selection strategy. Extensive testing of sectors, layers, and vascular slabs increases false-positive risk. A methodological review of 134 neurodegeneration OCT publications found that most studies were cross-sectional and identified recurring weaknesses in design and statistical analysis [27]. Pre-registration, primary-outcome specification, correction for multiple comparisons, effect sizes with confidence intervals, and external validation would improve credibility.

Table 2. ***Minimum reporting and validation elements for retina–brain biomarker studies***

Domain	Minimum information to report	Why it matters
Participants	Diagnostic criteria; disease stage; treatment; vascular and ocular comorbidity; recruitment setting	Defines the clinical spectrum and limits selection bias
Ocular assessment	Visual acuity; refraction/axial length when relevant; intraocular pressure; lens, optic disc, and macular status	Separates neurological signal from common ocular causes
Imaging	Device and software; scan size; signal threshold; segmentation review; artefact exclusions; repeatability	Enables analytical comparison and reproducibility
Analysis	Eye-selection or correlated-eye method; prespecified primary metric; covariates; multiplicity control; missing-data handling	Reduces unit-of-analysis errors and false-positive findings
Validation	Independent cohort; established clinical/imaging/fluid reference standard; longitudinal outcome; calibration	Determines whether a group association can support individual decisions

VII. CLINICAL READINESS AND FUTURE DIRECTIONS

The most defensible current use of retinal OCT in neurology is as a quantitative adjunct in MS and optic-nerve assessment, integrated with history, examination, MRI, and visual testing. In AD/MCI, PD, CSVD, and stroke, OCT and OCTA remain research or supportive phenotyping tools. Contemporary reviews similarly conclude that retinal imaging is promising but not ready to function as an independent diagnostic gateway [16,18,29].

Translation requires vendor-neutral harmonisation, disease- and age-appropriate normative data, longitudinal estimates of within-person change, and prospective studies in intended-use populations. Disease-specific reference standards are essential: amyloid or tau biomarkers for AD research, rigorous movement-disorder phenotyping for PD, and standard MRI markers for CSVD. Multimodal algorithms should be reported with transparent training and validation, clinically interpretable performance, and safeguards against confounding by ocular disease [28,30].

A useful near-term objective is not to ask whether the retina can "diagnose neurodegeneration," but to define the incremental information a retinal measure adds to an existing pathway. Examples include monitoring neuroaxonal loss after optic neuritis, enriching a research cohort for multimodal testing, or identifying a retinal microvascular phenotype associated with cerebral vascular burden. This narrower framing produces testable clinical questions and reduces premature claims.

VIII. CONCLUSION

OCT and OCTA provide uniquely accessible measures of retinal neural tissue and microvasculature. Evidence is strongest and most clinically interpretable in MS, whereas findings in AD/MCI, PD, CSVD, and stroke are promising but heterogeneous and insufficiently specific for stand-alone diagnosis. The next phase of the field should prioritise harmonised acquisition, rigorous ocular and systemic confounder control, appropriate eye-level statistics, longitudinal multimodal validation, and clear intended-use claims. Used within these boundaries, retinal imaging can become a valuable component of neurodegeneration research and selected clinical pathways without being overextended beyond the evidence.

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