

REVIEW ARTICLE

Tracking neurodegeneration in multiple sclerosis: the role of optical coherence tomography, optical coherence tomography angiography, and artificial intelligence-based imaging

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Abstract

Multiple sclerosis (MS) represents a chronic autoimmune disease involving the central nervous system through inflammation and progressive neurodegeneration. Monitoring disease progression, specifically in terms of neuroaxonal loss, has critical importance in guiding treatment and improving patient outcomes. This review discusses the evolving role of optical coherence tomography (OCT) and artificial intelligence (AI) in monitoring MS progression, highlighting their efficiency in assessing neuroaxonal damage, predicting disability, and complementing conventional imaging techniques. We synthesize current evidence on OCT and OCT angiography (OCTA) metrics, including peripapillary retinal nerve fiber layer (pRNFL) and ganglion cell/inner plexiform layer (GCIPL) thickness, and their correlations with disability, cognitive impairment, magnetic resonance imaging (MRI) findings, and clinical progression. We further review machine learning and deep learning applications for OCT-based classification, segmentation, and prognosis in MS. Thinning of pRNFL and GCIPL correlates with higher expanded disability status scale, brain atrophy, and impaired cognition, often preceding clinical signs of progression. OCTA reveals reduced retinal capillary density in MS, supporting a vascular component in disease pathology. AI tools enhance OCT analysis through automated layer segmentation and predictive modeling, enabling individualized risk stratification and early detection of secondary progression. Multimodal AI frameworks that combine OCT with MRI and clinical data further enhance prognostic accuracy. In summary, OCT and AI are transforming MS disease progression tracking by providing affordable, non-invasive biomarkers reflecting neurodegeneration and cerebrovascular dysfunction. For achieving their full potential as predictive and therapeutic tools in individualized care for MS patients, standardization, external validation, and integration into clinical practice are essential.

Keywords: Multiple sclerosis; Optical coherence tomography; Optical coherence tomography angiography; Artificial intelligence; Imaging

1. Introduction

Multiple sclerosis (MS) is the most common chronic autoimmune disease, in which the immune system attacks the myelin in the central nervous system (CNS).¹ MS is the leading cause of non-traumatic neurological disability in young adults.^{2,3} It is marked by recurrent inflammation, axonal loss, demyelination, and progressive neurodegeneration.^{1,4} As of 2020, approximately 2.8 million people were affected by MS, with a prevalence of 35.9/100,000 population.^{2,5}

Symptoms in people with MS (PwMS) can be wide-ranging, including functional systems impairment, fatigue, visual disturbance, sensory changes, and motor deficit. These symptoms worsen as axonal damage and neurodegeneration progress, often leading to cognitive decline and significant disability.⁶⁻⁸ Although there is no treatment, regular follow-up and careful monitoring of disease progression play a critical role in managing the disease and preventing its progression.⁹ Current treatments, particularly disease-modifying therapies (DMTs), can help slow progression and improve long-term outcomes when used in a timely manner. Altogether, this highlights the crucial role of progression monitoring in guiding therapy adjustments, preventing further deterioration, and enhancing long-term prognosis.¹⁰

Progression of MS refers to the gradual accumulation of neurological disability over time.¹¹⁻¹³ Progression can occur with or without relapse and may lead to accumulating disability. Over time, many patients transition from an initial relapsing–remitting phase to a secondary progressive course, marked by gradual neurological worsening independent of relapses.^{9,14} Accurate tools, criteria, and prognostic markers are essential for reliably identifying PwMS at higher risk of disease progression.¹⁵

Progression monitoring typically relies on periodic clinical assessments, cognitive testing, and magnetic resonance imaging (MRI).¹³ The expanded disability status scale (EDSS) is the most widely used clinical tool for assessing neurological impairment in PwMS and is based on neurological examination and functional system scores.^{16,17} Tools such as the symbol digit modalities test (SDMT) are also being increasingly used to detect mild cognitive impairments and can, in some cases, better reflect the disease burden.¹⁸

MRI is the gold standard for diagnosing and monitoring MS, capturing focal white matter lesions, atrophy, and dissemination in space and time.¹⁹ While MRI is sensitive to inflammatory activity, it mostly shows demyelination and is limitedly sensitive to diffuse damage or gray matter involvement,²⁰ and imaging changes may correlate

poorly with clinical progression.^{21,22} In addition, there are variations in protocol for acquiring MRI, scanning type, and reporting that need to be validated and standardized.²³

The retina and optic nerve provide a direct window into the CNS. Optical coherence tomography (OCT) is a high-resolution, non-invasive imaging method that provides cross-sectional views of the retina.²⁴ Over the past decade, a growing body of evidence has supported the use of OCT in MS.²⁵ Since the retina lacks myelin, OCT enables the direct visualization of neurons and axons without the need for invasive procedures. OCT can provide quantitative values for the thickness of the retinal layers and is often used as a surrogate endpoint for the integrity of neuroaxons since retinal thinning in PwMS has been associated with disability measures and MRI outcomes.

OCT measures retinal layer thicknesses, especially in the peripapillary retinal nerve fiber layer (pRNFL) and the macular ganglion cell/inner plexiform layer (GCIPL), reflecting neuroaxonal integrity.²⁶ In MS, these OCT parameters are commonly reduced compared to healthy controls (HCs), even in eyes without a history of optic neuritis (ON).²⁷⁻²⁹ Several studies have shown that thinning in the RNFL and GCIPL is linked to visual dysfunction, even in patients who may not report vision problems, and correlates with brain MRI measures and clinical outcomes, including EDSS, cognitive function, and visual assessments.^{29,30} This has led to exploring OCT as a potential alternative in clinical trials and a tool for identifying progression earlier than traditional assessments. The emergence of artificial intelligence (AI) appears promising for enhancing the predictive capability of OCT markers, leading to better outcomes in OCT evaluation for MS progression.³¹

AI is increasingly applied to OCT to enhance the monitoring of MS progression.³² Using machine learning (ML) and deep learning (DL) approaches, AI enables automated, accurate segmentation of retinal layers.³³ These tools outperform manual methods, reducing variability and improving the detection of subtle structural changes over time. AI models have also been trained to classify MS, differentiate it from other optic neuropathies, and predict future disability using both cross-sectional and longitudinal OCT data.^{34,35}

This review explains how OCT and AI are used to track progression in PwMS. It covers crucial OCT measures, their relationship to MS symptoms and progression, and new tools, such as AI, that enhance OCT analysis. It also discusses current challenges and potential for using OCT and AI in MS care.

2. Methodology

2.1. Search strategy

We conducted a narrative review supported by a targeted literature search. We searched PubMed, MEDLINE, Scopus, Web of Science, and Google Scholar from inception to July 10, 2025. Search terms combined MS concepts with retinal OCT/OCT angiography (OCTA) and AI terms, including variations of “multiple sclerosis,” “optical coherence tomography”/“OCT,” “OCT angiography”/“OCTA,” “artificial intelligence,” “machine learning,” “deep learning,” “segmentation,” and “classification.” Reference lists of key reviews and included articles were also screened to identify additional relevant studies.

2.2. Eligibility criteria

We considered studies published with a peer-review designation that assessed OCT structural parameters in PwMS or evaluated OCTA parameters and applied AI, ML, or DL algorithms in OCT/OCTA analysis for patient diagnosis, follow-up, or model construction. Exclusion criteria included non-MS patient population studies, case series reports, non-English studies, or animal studies alone.

2.3. Study selection

Collected studies were screened at the title and abstract level and then selected for full-text analysis if they were relevant. Studies were thematically grouped to align with the structure of this manuscript, including issues involving OCT biomarkers for structural imaging, OCTA biomarkers for microvascular structures, and AI-based analysis and prediction capabilities in PwMS. A total of 131 articles were included in this review.

3. OCT in MS

OCT is a non-invasive imaging technique that enables quantitative measurement of the RNFL. It is analogous to ultrasound; however, it uses light rather than sound waves.³⁶ The principle involves projecting a beam of near-infrared light onto the retina and measuring the echo time delay and intensity of the backscattered light, which produces high-resolution cross-sectional images of the retinal layer. Software algorithms can capture different layers of the retina based on their reflectivity.³⁷

The retina is part of the CNS that lacks myelin, which makes it an ideal structure to measure and monitor neurodegeneration.³⁸ Retinal layers measurable by OCT include the pRNFL, which consists of unmyelinated axons of retinal ganglion cells that form the optic nerve, and the macular RNFL (mRNFL), which is similar to pRNFL but measured at the macula. GCIPL comprises ganglion cell bodies and dendrites.³⁹ The inner nuclear layer contains

bipolar, amacrine, and horizontal cells. Outer retinal layers include the outer nuclear layer, photoreceptor, and retinal pigment epithelium.^{25,29,39}

Several OCT-derived metrics have emerged as important biomarkers in MS research and clinical monitoring. pRNFL thickness measures the thickness of the retina around the optic disc.²⁶ In MS, acute ON causes inflammatory axonal injury, often leading to subsequent RNFL thinning in that eye. Even eyes without a history of ON show RNFL thinning compared to HCs.²⁸ A meta-analysis by Petzold *et al.*²⁴ quantified the degree of RNFL thinning in PwMS without ON, showing an average thinning of ~7 μm ; in comparison, PwMS with a history of ON had ~20 μm thinning. Therefore, pRNFL thickness in non-ON MS eyes is lower than in healthy eyes, whereas eyes that have experienced ON may have more RNFL reductions depending on severity.^{24,40}

Retinal thinning in MS is not limited to the RNFL. GCIPL thickness typically represents the combined thickness of the ganglion cell layer and inner nuclear layer in the macula. This reflects the neuronal cell bodies of ganglion cells and their immediate synaptic connections. Since the macula has the highest density of retinal ganglion cells, thinning in this region can be an early indicator of neuronal loss.⁴¹ Notably, inner retinal thinning is most pronounced in patients with longer disease duration and those with progressive MS (PMS) subtypes.³⁸ According to a meta-analysis by El Ayoubi *et al.*,⁴² pRNFL was significantly reduced in PwMS relative to HCs, with an even greater degree of thinning in eyes with prior ON, and mGCIPL was significantly thinner in MS eyes compared to controls.

Macular volume is a measure of the total retinal volume within the macula. It is an aggregate measure that can reflect diffuse retinal thinning. In MS, reduced macular volume has been observed in eyes with and without ON and has been associated with MS disease subtypes.^{26,28}

4. MS progression: Clinical definitions and relevance

MS progression refers to the gradual accumulation of neurological disability over time, which may occur with or without relapses.⁴³ The disease is classically categorized into distinct clinical phenotypes: Relapsing remitting MS (RRMS), secondary PMS (SPMS), and primary PMS (PPMS).^{43,44} RRMS, which accounts for 85% of cases, is characterized by clearly defined relapses followed by periods of remission. Over time, many individuals with RRMS eventually transition to SPMS, which involves a steady and irreversible worsening of neurological function independent of relapses.⁴⁵ PPMS, on the other hand, is

defined by progression from disease onset, without initial relapses, and accounts for 10–15% of MS cases.⁴⁶ The classification of progressive-relapsing MS, once considered a distinct phenotype, is now subsumed under PPMS with active disease.⁴³

Detecting and defining progression in MS can be challenging, as it often occurs insidiously and without obvious clinical relapses.⁴⁵ Clinically, progression is most often detected retrospectively through sustained worsening of disability, typically measured by tools such as the EDSS.¹⁶ EDSS quantifies functional impairment on a scale from 0 (normal neurological exam) to 10 (death due to MS), based on ambulation and functional systems^{16,17} with key thresholds, such as 4.0 (significant walking limitations) and 6.0 (requirement of a walking aid).¹⁶ An increase in EDSS over 6–12 months, in the absence of clinical relapses, supports a diagnosis of SPMS.⁴⁵ However, EDSS is weighted toward walking ability and may not capture early changes in cognition, vision, upper limb function, or early subtle progression. Furthermore, EDSS assessments can be subjective and have limited resolution, particularly at lower scores or in PMS cases where subtle worsening is hard to capture.^{17,47}

Alternative and complementary tools have been developed to address these limitations. The MS Functional Composite includes the Timed 25-Foot Walk for ambulatory function, the 9-Hole Peg Test for upper limb dexterity, and the SDMT for cognitive processing speed.⁴⁸ SDMT has emerged as a sensitive and reliable measure for detecting cognitive impairment in MS and correlates well with both MRI markers.¹⁸

Another emerging concept in the assessment of progression is progression independent of relapse activity (PIRA). This concept highlights that many PwMS, even those classified as having RRMS, experience underlying neurodegeneration that progresses independently of overt relapses.⁴⁹ In addition to functional and cognitive scales, imaging modalities such as MRI are frequently used to monitor disease burden. MRI can detect new or enlarging T2 lesions, gadolinium-enhancing lesions, and measures of brain atrophy. However, these changes may not always correspond with clinical worsening, particularly in PMS, where inflammatory activity is less pronounced.⁵⁰

Early detection of the transition from RRMS to SPMS or the onset of progression in PPMS allows for timely treatment adjustments. Several DMTs have shown efficacy in delaying progression, especially when initiated early in the disease course.^{49,51} Therapies such as ocrelizumab, approved for both RRMS and PPMS, and siponimod, indicated for active SPMS, have demonstrated benefits in slowing disability accumulation and reducing relapse

rates.^{51–53} Their efficacy in less progressive forms underscores the importance of distinguishing progression as early as possible, since therapeutic options may be more limited and less effective once significant neurodegeneration has occurred.

Prognostic factors that predict progression include demographic variables such as older age at onset, initial disease characteristics such as multifocal presentation, early motor or cerebellar involvement, and poor recovery from early relapses.⁵⁴ In particular, early spinal cord involvement and higher lesion burden on MRI have been associated with a more aggressive disease course.⁵⁵

Importantly, progression in MS is not always overt. Subclinical disease activity, including brain atrophy, cortical lesions, and slowly expanding lesions, may accumulate over time without triggering relapses or apparent clinical deterioration.⁵⁶ Such “silent” progression necessitates careful longitudinal monitoring using a combination of clinical, cognitive, and radiographic assessments.

5. Association of OCT metrics with MS progression

OCT demonstrates that neurodegeneration in the retina is strongly associated with the onset of MS.⁵⁷ In PwMS, reductions in the pRNFL and mGCIPL have consistently been associated with greater disability.⁵⁸ Cross-sectional series over the past decade have found a moderate inverse correlation between retinal thickness on OCT and EDSS.²⁶ More disabled patients with increased EDSS scores have larger atrophy of the retinal layers. These findings are consistent with retinal neuronal loss serving as an imaging correlate of cumulative CNS injury. Notably, the relationship holds after eyes that have a history of ON are excluded, indicating that generalized neuroaxonal loss, as opposed to optic nerve damage, underpins the OCT–disability relationship in MS.⁵⁹

Aside from physical disability, OCT metrics have also shown significant relationships with cognitive impairment in MS. GCIPL and RNFL thinning are related to poorer performance on neuropsychological assessment, suggesting the hypothesis that retinal pathology may index diffuse CNS processes impacting cognition.⁶⁰ Recent evidence underscores the significance of GCIPL thickness as particularly informative; PwMS generally exhibit lower GCIPL thickness and generally perform poorly on tasks assessing information processing speed, attention, and executive function.⁶¹ These associations remain evident even when controlling for disease duration and overall disability.³⁰ The rationale underlying the correlation of retinal OCT findings with cognitive impairment in MS is rooted in the phenomenon of Wallerian degeneration, a

pathological process characterized by axonal damage that leads to the subsequent degeneration of distal neuronal elements.^{62,63} In the setting of MS, the inflammatory demyelination and axonal loss within the optic nerve and other CNS tracts initiate an anterograde process that primarily affects the pRNFL, composed of the axons of retinal ganglion cells, and also the GCIPL, which contains the somata and dendritic processes of these cells. These axons ultimately synapse within the lateral geniculate nucleus of the thalamus, a critical relay station that transmits signals to multiple cortical regions involved in regulating visual and cognitive processes.⁶⁴⁻⁶⁷

Notably, longitudinal studies have demonstrated that OCT abnormalities herald conversion to a more aggressive disease course.⁶⁸ Importantly, accelerated retinal thinning has been observed in those patients who progress from RRMS to SPMS.⁶⁹ For example, patients who subsequently converted to SPMS were found to lose more pRNFL and GCIPL per year pre- and at the time of conversion compared to those who remained in the relapsing state.⁷⁰ This suggests that an increased rate of retinal atrophy can presage the onset of secondary progression. These findings indicate that serial OCT monitoring can identify patients who are developing the progressive phase earlier than is possible with standard clinical criteria. A diffusely thinning RNFL or GCIPL, beyond that which occurs in normal aging or optimally treated relapsing disease, could be a hallmark of the occurrence of latent neurodegeneration characteristic of SPMS.^{71,72}

OCT findings have also been associated with clinical relapses and inflammatory disease activity.⁷³ Although OCT primarily assesses chronic neuroaxonal loss, there is evidence to suggest that more extensive retinal atrophy occurs in more severe MS.⁷⁴ Individuals with a history of frequent relapses or those who have a greater lesion load on MRI tend to have thinner retinal layers, reflecting the cumulative effects of inflammatory attacks.⁷⁵ In addition, preliminary data from MS cohorts suggest that a thinner GCIPL at baseline is associated with an increased risk of future relapses and new MRI lesions.⁷⁶ This suggests that already-existing subclinical retinal loss in patients could be a reflection of an active disease process fated to manifest as further clinical and radiologic events.⁷⁷ In addition, in acute ON, pRNFL thickness reduces considerably in the months following the attack, and the extent of RNFL loss correlates with the amount of permanent visual disability. Each ON episode, therefore, contributes to global retinal thinning.⁷⁸ Therefore, retinal involvement, as measured by OCT, not only accumulates over the duration of MS but also associates with acute disease activity and is predictive of which patients are acquiring disability. These

results emphasize the utility of OCT metrics as available, quantitative biomarkers to monitor MS progression in both motor, visual, and cognitive spheres.

6. OCTA in MS

OCTA is a development of OCT technology that enables the non-invasive visualization of the retinal microvasculature.⁷⁹ OCTA provides high-resolution depth-resolved retinal and choroidal circulation images by detecting motion of blood cells within the vessels, without requiring dye injection.⁸⁰ This enables researchers and clinicians to measure capillary density and perfusion in single retinal layers comprising the superficial and deep capillary plexuses and the radial peripapillary capillaries adjacent to the optic disc.⁸¹ In MS, OCTA yields a new perspective on the disease's possible vascular involvement.⁸² MS has traditionally been viewed as an inflammatory demyelinating disorder, yet accumulating evidence indicates that vascular and metabolic processes, including hypoperfusion and chronic ischemia, are involved in its pathophysiology.⁸³ OCTA provides a method for detecting *in vivo* subtle alterations to microvessels, which can be a sign of or affect the neurodegenerative processes of MS.⁸⁴

Research conducted with OCTA in the recent past has consistently demonstrated that PwMS have lower retinal vessel density than HCs.⁸⁵ In particular, the density of the superficial capillary plexus of the macula is frequently significantly reduced in MS eyes despite patients having no history of past episodes of ON.⁸⁶ Reductions in the deep capillary plexus and the peripapillary capillary network of the optic nerve head have also been described.⁸⁷ These microvascular alterations appear to correlate with the structural retinal atrophy observed using conventional OCT.⁸⁸ For example, in MS, ocular involvement tends to have patchy loss of perfused capillaries in the perimacular regions, corresponding to regions of ganglion cell loss.^{86,89} Decreased vessel density is also evident not just in eyes with a history of ON, where vascular dropout might be expected secondary to damage of the optic nerve, but also in MS-affected eyes without any history of visual attacks.^{86,90,91} This suggests that an intrinsic small-vessel pathology or neurodegenerative vascular pruning is occurring as part of MS, independent of acute inflammation in the optic nerve. From a quantitative perspective, various studies employing meta-analyses have found that parameters of the macular superficial plexus are generally lower by 2–4% in PwMS, with greater differences seen in affected patients with ON compared to HCs. To illustrate this further, a systematic review and meta-analysis found that the mean difference of the whole image superficial capillary plexus vessel density of Optovue studies and Topcon studies in PwMS relative to controls is –3.90% and –1.87%, respectively, with

parafoveal and hemispheric differences ranging between -3.2% and -2.6% .^{90,92} In another meta-analysis, differences in superficial vascular complex densities of 2.27% and 4.30% and peripapillary vessel densities of about 2.82% and 4.96% were deduced for PwMS with and without ON, respectively.⁹³ Such findings reinforce the hypothesis that MS pathology encompasses a vascular component, which may be associated with chronic cerebral hypoperfusion or diffuse inflammatory damage to the microvasculature.

The alterations in retinal vascular structures identified through OCTA have demonstrated significant correlations with various markers of MS activity and severity.⁹⁴ Loss of retinal capillary density is also related to higher EDSS, showing that more disabled PwMS have more retinal microvascular loss.⁹⁵ OCTA findings are also linked to brain MRI findings. Patients with more whole-brain atrophy or a higher T2 lesion load also have reduced retinal perfusion.⁸⁴ Such alignment suggests that the same mechanisms that lead to neurodegeneration and tissue loss in the brain, for example, diffuse axonal injury or chronic hypoxia due to poor blood flow, could likewise occur in the retinal circulation.⁹⁶ Several studies have also investigated the association of OCTA with cognitive impairment in MS.⁹⁷ Although data are forthcoming, there have been indications that PwMS with cognitive impairment have lower macular vessel densities compared to cognitively intact patients, with the implication that retinal microvascular health can mirror the status of cerebral gray matter and microcirculation responsible for cognition.^{98,99} Therefore, OCTA-derived vessel density metrics appear to be associated with structural OCT metrics and clinical function, thereby validating that they measure an inherent aspect of disease pathogenesis.⁸⁴

Comparing OCTA findings to structural OCT, it is apparent that the two imaging modalities provide complementary information.¹⁰⁰ Structural OCT measures the final outcome of damage, including axonal and neuronal loss, while OCTA can image more proximal or simultaneous blood flow abnormalities that may precede or accompany tissue loss.^{85,101} One significant benefit seen in early studies is that OCTA might have a lower “floor effect” compared to conventional OCT measures.¹⁰² In established MS or chronic disease, RNFL thickness can be at a nadir at which further changes are difficult to detect (since almost all susceptible axons have already been lost).¹⁰³ OCTA, however, can still measure reductions in vessel density even when retinal layers are significantly thinned, and thus remains sensitive to ongoing damage at later stages.⁸² This characteristic enables OCTA to potentially continue monitoring disease progression even when structural measures plateau. Furthermore, qualitative differences in

the microvascular pattern can help distinguish MS from other optic neuropathies.⁸⁶ For example, preliminary data suggest that neuromyelitis optica may have a distinct OCTA signature (though perhaps greater microvascular loss in some cases) compared with MS; such distinctions may facilitate differential diagnosis in conjunction with structural OCT distinctions.^{104,105} While such comparative observations are promising, it should be mentioned that OCTA in MS is still largely in the research domain. Structural OCT is an established modality with standard protocols, but OCTA is not yet completely standardized, and its added value is still debated.

A reevaluation of OCTA research in MS shows inconsistencies in both the degree and distribution of vascular changes and their correlation with disability and retinal atrophy. Differences in OCTA systems and analysis pipelines, including methods of removal of artifacts, segmentation margins, and calculation of vessel density, may provide non-uniform measures across studies, making them not immediately comparable and pointing toward a need for a common OCTA reporting format and multicenter validation before OCTA measurements can become a standard tool.

Overall, OCTA represents an important potential biomarker in MS.¹⁰⁶ It presents a new vision of the disease by clarifying the vascular impairment that can underlie or result from inflammatory and neurodegenerative injury. If confirmed, OCTA measurements would be used in conjunction with structural OCT to provide a more comprehensive picture of MS progression; for example, the combination of retinal layer thinning and reduced capillary density would strongly indicate active progression or failure of treatment.⁸² Furthermore, OCTA could conceivably function as an outcome measure in clinical trials designed to protect microcirculation or enhance cerebral perfusion in MS.¹⁰⁷ Nevertheless, several limitations must be addressed before the integration of OCTA into routine clinical practice for MS. Firstly, numerous OCTA studies pertaining to MS have utilized relatively small sample sizes, which restricts the confidence in generalizing the results. The technology is still in its infancy, and multicenter data are required to determine normative ranges and disease norms.^{86,107} Furthermore, there is a deficiency of standardization across devices and studies.¹⁰⁸ Various OCTA platforms, such as Zeiss, Optovue, and Topcon, employ varied algorithms and report vessel density with slight differences.¹⁰⁹ This makes comparing results across studies challenging and hinders setting universal cut-off values for what is normal and abnormal perfusion. Current endeavors aim at harmonization of analysis methods and the establishment of consensus metrics for OCTA in

neurodegeneration.¹¹⁰ Thirdly, image quality and technical factors can influence OCTA measurements. Issues such as motion artifacts, segmentation errors, and projection artifacts can all confound vessel density measurements.¹¹¹ PwMS may experience nystagmus or poor fixation that reduces OCTA scan quality.^{112,113} Finally, nearly all current data are cross-sectional; longitudinal OCTA studies are required to determine how retinal vessel density changes over time with MS progression or in response to treatments. It remains to be seen whether OCTA can detect microvascular improvements with therapy or predict impending relapses.⁹⁰ Thus, OCTA represents an exciting development that expands the scope of OCT in MS by introducing a vascular dimension. It has also shown reduced capillary density in MS and associations with disease severity, raising its potential as a biomarker. Technical standardization and larger longitudinal studies are still needed to determine the complete role of OCTA and to institute it as a reliable device for the management of PwMS.

7. AI applications in OCT-based MS progression monitoring

AI innovations are set to transform OCT image analysis for MS monitoring.³¹ Over the last several years, both ML algorithms and DL strategies have been implemented in ophthalmic imaging, resulting in devices able to automatically interpret intricate patterns in OCT data.³² These AI-driven methods have special relevance to neurology by teasing out subtle features from retinal scans; they have the potential to enhance our ability to detect MS-related changes and even predict disease course.³¹

For ophthalmology, AI's impact is already being realized; convolutional neural networks (CNNs) can interpret OCT scans to diagnose eye diseases, such as diabetic retinopathy, age-related macular degeneration, and glaucoma, with a proficiency matching that of specialist clinicians.³³ This success opens the door to the application of analogous approaches to MS, in which the challenge is to detect diffuse neurodegenerative changes rather than focal retinal lesions. One of the fundamental applications of AI using OCT is automated retinal layer segmentation.¹¹⁴ Precise layer segmentation is necessary to measure thickness and volume changes.¹¹⁵

Previously, segmentation necessitated manual annotation or algorithms provided by hardware or software, both of which can be erroneous, particularly in pathological OCT scans of PwMS.¹¹⁶ To enhance this process, ML models, ranging from conventional models to DL models, have been developed.¹¹⁷ For example, CNN-based segmentation algorithms can delineate retinal layers

on OCT cross-sectional images very accurately, even when the boundaries are interrupted by lesions or atrophy.¹¹⁸ The models are trained on extremely large collections of scans annotated by experts, and after training, they can process new scans in seconds, providing the same reproducible layer measurements.¹¹⁹ By measuring RNFL and GCIPL thickness accurately and reproducibly, independent of visit and machine, AI segmentation reduces variability.¹²⁰ This is especially critical for monitoring MS, where subtle changes over time are important. Furthermore, some research has combined traditional graph-based segmentation algorithms with ML to enforce anatomically correct layer segmentation, adding reliability in severe MS cases where the retina may become extremely thin.¹²¹⁻¹²³

In general, AI-based segmentation underlies much of the subsequent analysis, enabling the extraction of high-quality information from OCT scans.¹²⁴ Researchers are applying ML beyond segmentation to mine OCT data for predictive information.¹²⁵ Some algorithms, including support vector machines (SVMs), decision trees, random forest ensembles, and gradient-boosting methods such as XGBoost, have been employed for classifying PwMS and predicting disease outcomes using OCT parameters.^{126,127} According to a study by Montolio *et al.*,¹²⁸ a range of OCT measurements, including pRNFL thickness in various sectors and macular layer measurements, were used to train different classifiers to distinguish between MS and HCs. In their study, classifiers were trained with a cross-sectional population including 72 PwMS and 30 HCs, using feature variables extracted from Spectralis OCT-based RNFL and macular thickness parameters. The best-performing models achieved classification accuracies of around 91% in separating PwMS from HCs, including those without an ON history. This indicates that multivariate characteristics of retinal atrophy can be useful for classification; however, it should be noted that the performance was assessed in a relatively small population and that the study used a cross-sectional design. Furthermore, another study followed patients for several years to determine if baseline optical OCT findings could predict future disability.¹²⁶ It is also important to recognize that a large number of AI research studies in OCT and MS monitoring use relatively small sample sizes, and that many of the best-performing models are based on retrospective designs that are subject to optimism bias and potential overfitting. The degree of heterogeneity across individual studies and models is very high and includes differences in former OCT systems and scanning protocols, chosen segmentation algorithms and validation, inclusion/exclusion of ON cases, feature space, and outputs of interest. In addition, there is a risk for inflation of validation performance either by not dividing the validation set by individual subject, for example,

when including the left and right eyes of a subject within the same set and using it for validation and testing, or by including hyperparameter optimization outside of the cross-validation cycle. External validation of the models using large, multi-center validation sets is, therefore, a necessary step in determining the generalizability of the results obtained by any AI model to a real-world setting.

Using multiple ML models, researchers found that certain methods, including a decision tree model combining mRNFL and nasal pRNFL thickness, could accurately predict which patients would have significant disability several years down the line, with more than 90% accuracy in their cohort.¹²⁶ The prognostic models were successful in distinguishing the OCT profiles of patients who followed an accelerated disability course compared to those with stable disease. A second group used SVMs to classify MS versus control subjects and reported that a combination of peripapillary and macular ganglion cell layer thickness measurements resulted in a sensitive (approximately 89%) and specific (approximately 92%) classifier.¹²⁹ These findings underscore the potential of ML to reveal intricate, multi-variable patterns in OCT data that might be challenging for individual clinicians to discern and thus allow early diagnosis and risk stratification.

DL, CNNs in particular, offer another robust approach, one that can potentially operate on raw image data rather than pre-specified features. For example, CNNs may be trained on thousands of OCT B-scans to directly predict an outcome, the presence of MS, or disability level, without requiring human feature selection.^{130,131} These networks have the ability to automatically identify informative structures, for example, texture of the inner retina or optic nerve head morphology, that are linked to the disease. Although still experimental in MS, a DL algorithm could assess an OCT scan and provide a probability of the patient having a specific disease subtype or predict future progression.^{132,133} Some early research has indeed explored CNNs to differentiate ON damage or distinguish MS from the other optic neuropathies based on face retinal maps.¹³⁴

Recurrent neural networks, such as long short-term memory (LSTM) networks, have also been used to incorporate longitudinal OCT data.^{128,135-138} An LSTM analyzes a time series of OCT scans from a single patient and predicts disability progression by detecting temporal patterns of change (an approach piloted in a 10-year follow-up dataset).¹²⁶ Such temporal DL would be particularly useful for foreseeing secondary progression; a program can recognize accelerating rates of thinning that herald a transition to SPMS.¹³⁹

The development of multimodal models that integrate OCT data with other pertinent patient information is

a promising avenue.¹⁴⁰ MS is a complex disease, and multimodality has the potential to enhance predictions significantly.¹³⁹ AI frameworks that incorporate retinal OCT inputs alongside brain MRI-derived features, such as lesion count or brain volume measurements, in conjunction with clinical information, including patient age, disease duration, and number of prior relapses, have been proposed.^{35,141,142} By learning from these combined datasets, the models can capture the interplay between ocular and central manifestations of MS.³⁵

A multimodal ML model, for example, might determine that a patient with moderate RNFL thinning and widespread brain atrophy is more likely to progress ML than a patient with identical OCT features but mild MRI changes.¹⁴³ Some proof-of-concept studies have demonstrated that the combined models are better than single-data-sourced models. This aligns with the trend towards personalized medicine; by considering multiple biomarkers, AI is able to predict more accurately for a given patient.^{144,145} For example, researchers have applied gradient-boosting platforms to integrate OCT measurements, MRI measurements, and even immunological markers in classifying patients as progressors or non-progressors with greater precision compared to using a single measurement alone.^{35,145} In practical life, such a tool would assist clinicians in determining whether a patient who appears to be maintaining a stable clinical state is indeed experiencing silent progression that would justify a therapy switch, an aspect that one test might overlook.¹⁴⁶

AI in OCT is not confined to MS progression alone; it also extends to wider neurological and ophthalmic applications—cases that indirectly benefit MS care.¹⁴⁷ AI has the ability to differentiate between MS-related retinal changes and those caused by glaucoma or diabetic retinopathy, for example, by detecting typical layer-thinning patterns.^{148,149} Within neurology, beyond MS, researchers are also exploring OCT-based AI for other conditions, such as Alzheimer's disease and Parkinson's disease, where subtle changes in the retina can occur.^{150,151} The compounding advancements in these fields facilitate the development of algorithms and techniques that can be translated to MS.

Furthermore, AI-based OCT software can accelerate large-scale clinical trials by rapidly analyzing hundreds of scans, which is especially useful in multicenter MS trials or registries, where manual review would be extremely time-consuming.¹⁵² Despite the potential, it is worth noting that the majority of AI models for OCT in MS are still in pilot or developmental phases.¹⁵³ None have been included in standard clinical practice guidelines to date (Tables 1 and 2).

Table 1. OCT and OCTA biomarkers in MS

Modality	MS relevance	Advantages	Limitations
pRNFL thickness	Correlates with EDSS, cognition, and atrophy	Non-invasive marker of axonal loss	Affected by ON
GCIPL thickness	Predicts SPMS; correlates with cognitive decline	Early neurodegeneration marker	Floor effect in later stages
Macular volume	Reflects overall retinal thinning	Simple indicator of diffuse damage	Less specific, influenced by multiple factors
OCTA vessel density	Linked to EDSS, MRI lesions, and cognitive status	Reveals vascular dysfunction	Device variability; no standards yet

Abbreviations: EDSS: Expanded disability status scale; GCIPL: Ganglion cell/inner plexiform layer; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography; ON: Optic neuritis; pRNFL: Peripapillary retinal nerve fiber layer; SPMS: Secondary progressive multiple sclerosis.

Table 2. AI applications in OCT-based MS monitoring

AI application	Role in MS	Advantages	Limitations
ML classification	Diagnoses MS; predicts progression	High diagnostic accuracy	Generalizability depends on training data
AI segmentation	Measures retinal layers accurately	Reduces observer variability	Needs high-quality scans
Multimodal AI models	Combines OCT, MRI, and clinical features	Enables personalized prognostics	Requires harmonized data sources

Abbreviations: AI: Artificial intelligence; CNN: Convolutional neural network; ML: Machine learning; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; OCT: Optical coherence tomography.

8. Critical appraisal, limitations, and future directions

8.1. Methodological variability across studies

Despite promising progress, several challenges hinder the immediate translation of OCT and AI-based monitoring into general clinical practice for MS. Variability in imaging protocols, including OCT scan acquisition, is a significant issue, with high variability between clinics and devices. Retinal layer thickness or vessel density measurements may be affected by factors such as the type of scanner, segmentation algorithms, and scan centering. Without standardization, cross-study comparisons of results or the definition of universally applicable thresholds of “normal” versus “abnormal” OCT values in MS are problematic. This inconsistency threatens to hide accurate disease signals or create false alarms that are not based on biological but on technical variability.

8.2. Areas of disagreement and inconsistent findings

Small and heterogeneous datasets, including most OCT studies in MS, are derived from comparatively small cohorts and frequently consist of highly selected patient populations. MS is heterogeneous, with differences in phenotype, disease duration, history of prior ON, etc.; thus, small datasets cannot possibly reflect this entire spectrum. As a result, findings derived from one cohort may not be replicable in another. The same applies to AI model development: Data-intensive algorithms trained on a small, homogeneous sample are at risk of learning patterns that are not generalizable to the broader MS population. This refers to the need for large, multi-center datasets to underpin well-supported conclusions and AI models.

Furthermore, none of the proposed OCT biomarkers or predictive AI models has undergone complete external validation. For example, an OCT model predicting disability must be evaluated on independent cohorts, ideally from different centers and perhaps different countries, to ascertain its performance and reliability. Likewise, OCT metrics demonstrating association with progression in retrospective analyses must be validated prospectively. Until there is greater external validation, there will be warranted restraint in the clinical application of these tools.

8.3. Practical limitations for AI translation to clinical practice

To better enable use in the shorter term, future research should focus on a narrow agenda of specific implementation-oriented actions. First, there must be harmonization in OCT/OCTA image acquisition, image quality, boundaries, artifact management, and reporting (including device-aware harmonic alignment). Second, privacy-preserving multi-center AI, such as federated learning, presents an implementable route for developing well-performing models across diverse scanners and populations without transferring native image data, thereby enhancing model generalizability while preserving data protection. Third, multimodal fusion should be implemented by aligning OCT/OCTA courses with MRI biomarkers (lesion extent, brain/spinal cord atrophy measures, and slowly expanding lesions) and laboratory biomarkers, including neurofilament light in cerebrospinal fluid, to improve risk prediction of progression and to integrate discordant clinicoradiographic courses.

Fourth, prospective validation and study inclusion in everyday practice should be prioritized, focusing on pre-specified outcome measures, e.g., PIRA, verified disability accumulation, model performance analyses of calibration and slope across diverse groups, and assessment of device-assisted retinal biomarkers, to inform clinical decisions and actual patient outcomes in longitudinal studies and trials. Other use cases, e.g., the prediction of treatment-response curves in early OCT courses, remain promising and should be explored following the development of these primary priorities.

8.4. Integrating OCT, OCTA, and AI: Complementarity and readiness gaps

Taken together, OCT, OCTA, and AI provide complementary information with high relevance for tracking MS progression. Structural OCT imaging quantifies neuroaxonal integrity, a downstream consequence of cumulative damage, with parameters such as pRNFL and GCIPL thinning. Meanwhile, OCTA extends into the microvascular space, allowing assessment of perfusion damage, with a potential plateau in informativeness when relative measures plateau under standard parameters. AI represents a translation and analysis platform where reproducible analysis for segmentation, high-dimensional feature identification, and basic integration with existing clinical/MRI parameters improve individualized risk assessment. Several readiness barriers need to be overcome before incorporation into standard medical practice, including standard imaging/analytic acquisition and reporting algorithms across different vendors, access to existing datasets representing broad population cohorts with unified outcome measures, thorough cross-validation studies to standardize analysis performance metrics across different centers, and interventional studies validating AI-assisted analysis of retina-specific surrogate markers improving individual patient outcomes.

9. Conclusion

Over the past decade, OCT has emerged as an important, non-invasive adjunct in the management of MS, providing quantifiable markers of neuroaxonal damage and microvascular change. Structural retinal thinning, most prominently of the RNFL and GCIPL, is linked to physical disability and cognitive impairment and may also predate the development of SPMS, while OCTA shows reduced retinal capillary density linked to disease burden. With incorporation into AI, these imaging modalities are imbued with greater predictive capability, enabling automated detection of subtle changes, personalized risk stratification, and preemptive disease management. Their full clinical potential awaits standardization, validation

across medical centers, and collaboration between medicine and data science. Through continued investment and research, AI-enhanced OCT/OCTA has the potential to equal or even rival MRI in terms of accessibility and accuracy, facilitating personalized medicine and early intervention strategies for PwMS.

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Conflict of interest

The authors declare that they have no competing interests.

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