ANNUAL REVIEWS

Annual Review of Vision Science

Machine Learning for Noninvasive Diagnosis of Neurodegenerative Diseases Using Retinal and Optic Nerve Imaging: A Comprehensive Review

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Annu. Rev. Vis. Sci. 2026. 12:155–86

The *Annual Review of Vision Science* is online at vision.annualreviews.org

https://doi.org/10.1146/annurev-vision-110423-025837

Keywords

neurodegenerative disorders, multiple sclerosis, retina, optic nerve, optical coherence tomography, machine learning

Abstract

Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis, encompass a wide range of chronic conditions with irreversible damage to the central nervous system. Current diagnostic workups of these disorders rely on invasive, time-consuming, and costly tests, such as magnetic resonance imaging and cerebrospinal fluid analysis, preventing accurate decision-making and timely therapeutic interventions. The retina is an extension of the central nervous system; thus, retinal imaging, which is a noninvasive and easily accessible tool, provides a unique window to study brain pathologies. There is a great body of evidence suggesting that neurodegenerative disorders are associated with various structural and vascular problems within the retina. Notably, training machine learning models with retinal images has yielded high levels of accuracy in

classifying neurodegenerative diseases, encouraging a new era for early and automated diagnosis of these disorders. This article reviews studies that use such models for classifying these disorders.

INTRODUCTION

The term "neurodegeneration" can broadly refer to any condition that causes progressive loss of function and/or structure of neurons and/or associated glial support tissues. Neurodegenerative diseases are therefore largely heterogeneous, presenting with a wide variety of clinical signs and symptoms, which are typically progressive and irreversible (Przedborski et al. 2003). The diagnosis of many neurodegenerative diseases is not straightforward, relying on typical and sometimes atypical clinical presentations, in addition to batteries of cognitive tests; brain imaging studies, including magnetic resonance imaging (MRI), positron emission tomography (PET), and dopamine transporter scans; and serum and/or cerebrospinal fluid (CSF) biomarkers, such as neurofilament light chain and glial fibrillary acidic protein (Hansson 2021, Schindler et al. 2022). Furthermore, even after the completion of batteries of expensive, invasive, and time-consuming tests, an accurate diagnosis is not assured when compared with postmortem pathological assessments. Indeed, Alzheimer's disease (AD) and Parkinson's disease (PD) misdiagnosis rates in clinics are reported to be as high as 25–30% and 20%, respectively; the numbers may be even higher for other forms of dementing disorders (Beach et al. 2012; Hansson 2021; Knopman et al. 2001; Rizzo et al. 2016, 2018). Given the high prevalence, diagnosis complexity and high associated cost, and unavailability of effective therapies at advanced stages, there is a great need for the development of early biomarkers with acceptable diagnostic performance for neurodegenerative diseases.

Neurodegenerative Diseases and the Retina

Being a direct extension of brain tissue, the retina and optic nerve head share many characteristics of brain tissue in terms of embryological origin, structure, vascular physiology, and an unusual relationship to the immune system, as both the brain and eye are considered immune-privileged sites. Given that the function of the eye is to transmit light, processes affecting the retina and the optic nerve can be readily assessed in vivo by studying the optic nerve and the retina. As brain tissue within the cranium cannot be directly observed in this way, its analogous extension, the eye, is often referred to as a window to the brain (London et al. 2013).

Supplemental Material >

Optical coherence tomography (OCT) systems (for a brief explanation of these technologies, see Section 1 of the **Supplemental Text**) currently in routine use in eye clinics and optometry practices enable the observation of subtle changes in retinal and optic nerve structure, which can be difficult, if not impossible, to detect by clinical examination of the eye using a biomicroscope. Decreased thickness of retinal layers, most commonly the retinal nerve fiber layer (RNFL) and the ganglion cell layer, has been observed in a wide range of neurogenerative and/or neuroinflammatory conditions using OCT (Alber et al. 2020; Aly et al. 2020; Britze & Frederiksen 2018; Di Maio et al. 2021; Mendoza-Santiesteban et al. 2017; Nepal et al. 2022; Oberwahrenbrock et al. 2013; Oertel et al. 2021, 2022; Woo et al. 2022; Zhang et al. 2022). Damage to ganglion cells and their axons may happen concurrently with brain pathology and/or as a secondary phenomenon, with inflammation and neurodegeneration spreading from the brain to the retina in a retrograde manner (Kashani et al. 2021). While less widely accepted, some authors have proposed that neurodegeneration may begin in the retina and then advance toward the brain (Gupta et al. 2021). You et al. (2019) provided evidence for this in glaucoma; they observed pathological changes in higher visual

areas, including increased water diffusion in optic radiations and calcarine cortex thinning, with topographic correlations with optic nerve deficits. Further evidence comes from findings of amyloid beta and tau protein (p-tau) aggregates in the retina, which appear even earlier than their manifestations in the brain (Koronyo-Hamaoui et al. 2011). However, this hypothesis certainly needs to be further investigated (Gupta et al. 2021). Importantly, OCT changes have been shown to correlate with patients' clinical status and other disease biomarkers found in MRI, PET, laboratory, and electrophysiological studies (Alber et al. 2020; Britze & Frederiksen 2018; Graves et al. 2022; Kersten et al. 2015; Mendoza-Santiesteban et al. 2017; Oertel et al. 2018, 2023; Puthenparampil et al. 2017; Rzepiński et al. 2021; Soldatov et al. 2021; Vural et al. 2018; Woo et al. 2022; Zhang et al. 2022). Furthermore, analogous to cerebral microvascular changes, retinal blood vessels, which can be easily visualized in vivo, may also become affected in neurodegenerative diseases. Vascular density, assessed by OCT angiography (OCT-A), has been shown to be lower in patients with AD (Alber et al. 2020), PD (Zhang et al. 2022), multiple sclerosis (MS) (Kleerekooper et al. 2020), neuromyelitis optica spectrum disorder (NMOSD) (Kleerekooper et al. 2020), and clinically isolated syndrome (CIS) (Cennamo et al. 2020, Feucht et al. 2018) compared to healthy controls.

These findings suggest great potential for the use of OCT technologies to exploit changes in retinal and optic nerve structure for the development of powerful biomarkers to aid the accurate and timely diagnosis of a range of neurodegenerative diseases. However, OCT imaging generates vast volumes of data, which are difficult and time-consuming for human observers to meaningfully process. Statistical methods used in conventional clinical studies offer useful insights where data volumes and variables are limited, but they meet severe limitations as the volume and complexity of data are scaled. Advanced computational techniques encompassing machine learning (ML) appear to offer an attractive solution to this problem. A brief introduction to artificial intelligence, ML, and deep learning is provided in Section 2 of the **Supplemental Text**. A schematic illustrating several prevalent retinal imaging modalities, their interrelationships, retinal layers, and the construction of retinal thickness maps and mean value fundus images is presented in **Figure 1**.

Supplemental Material >

Neurodegenerative Diseases and Machine Learning

ML models have already been proven to be valuable tools augmenting diagnosis and prognosis in numerous neurodegenerative conditions, including AD (E. Lin et al. 2021, Jo et al. 2019, Narasimhan et al. 2021), MS (Afzal et al. 2020; Nabizadeh et al. 2022a,b; Shoeibi et al. 2021), PD and atypical parkinsonian disorders (Giannakopoulou et al. 2022, Mei et al. 2021, Rana et al. 2022), amyotrophic lateral sclerosis (Fernandes et al. 2021), and Huntington's disease (Myszczynska et al. 2020, Tăuţan et al. 2021). These models were trained on different types of high-quality data, including clinical information extracted from medical case notes; serum and/or CSF biomarkers; neuroimaging parameters such as MRI, PET, and single-photon emission computed tomography variables; electroencephalography and electromyography measurements; and signals from wearable and nonwearable sensors that primarily detect movement-related data, such as gait, posture, voice, handwriting, and even drawing patterns (Giannakopoulou et al. 2022, Myszczynska et al. 2020, Tăuţan et al. 2021). However, although training ML models with data from imaging technologies such as MRI and PET or serum and/or CSF investigations have yielded high diagnostic accuracies, these methods are very time-consuming, costly, invasive, and inaccessible in many clinical centers, especially in less-developed regions. Notably, studies have highlighted that retinal biomarkers—detected using modalities such as OCT or fundus

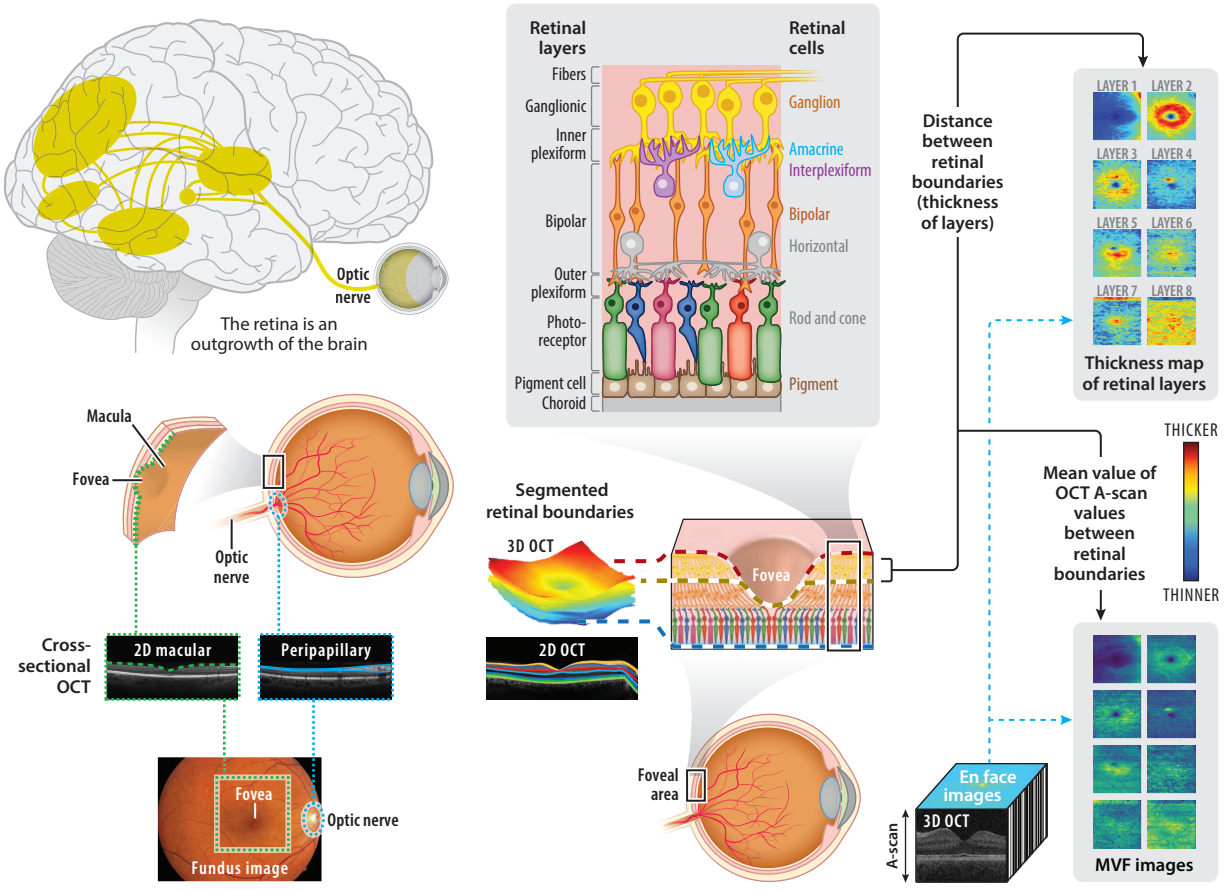


Figure 1

(*Left*) The retina, an extension of the brain, is depicted alongside ocular imaging modalities such as optical coherence tomography (OCT) and fundus imaging, highlighting their spatial relationships with the eye. (*Middle*) The segmentation of OCT images in both 2D and 3D is illustrated, along with a cross-sectional schematic detailing retinal layers and cellular structures. (*Right*) The process of constructing retinal thickness maps (by measuring the distance between retinal boundaries) and mean value fundus (MVF) images (by calculating the brightness values of OCT angiography scans between two boundaries) is demonstrated. Thickness map, MVF, en face cube, and cross-sectional OCT scan images reproduced from He et al. (2019) (CC BY 4.0). Fovea cross-section image provided by Posit Science (**https://www.brainhq.com/resources/image-gallery/vision-image-gallery/**). Color OCT image reproduced with permission from Kafieh et al. (2013). Fundus image reproduced from Hajeb Mohammad Alipour et al. (2012) (CC BY 4.0).

photography—potentially provide a more straightforward, affordable, and accessible means of diagnosing neurodegenerative diseases.

Neurodegenerative Diseases, Machine Learning, and the Retina

Recent advances in ML have driven impressive performance improvements in classification, segmentation, and quality control of ocular images captured via different modalities, including fundus photography, OCT, and, more recently, OCT-A (Ting et al. 2019, Yang et al. 2023). Suitably trained algorithms have demonstrated the ability to successfully screen for diabetic retinopathy, glaucoma, and age-related macular degeneration, the leading causes of blindness in the elderly

population (Deng et al. 2022, Stein et al. 2021, Teo et al. 2021), with performance comparable to that of human ophthalmologists (Gulshan et al. 2016, Ting et al. 2019).

Interestingly, human and animal studies have shown that neurodegenerative diseases can also be identified using features extracted from retinal images. For instance, ML models using fundus camera (Cheung et al. 2022, Gao et al. 2023, Kim et al. 2022, Shi et al. 2024, Tian et al. 2021, Zhang et al. 2021), OCT (Ferreira et al. 2022; Gao et al. 2023; Lemmens et al. 2020; Nunes et al. 2019; Shi et al. 2024; Trindade 2021; Wang et al. 2022; Wisely et al. 2022, 2024), and OCT-A (Wisely et al. 2022, 2024) images are able to detect AD or mild cognitive impairment (MCI) with high accuracies. A 2022 meta-analysis showed that when using OCT findings alone or combined with demographic and clinical data, ML algorithms have a pooled sensitivity and specificity of 92% and 93%, respectively, for automated detection of MS (Nabizadeh et al. 2022b). Promising results have also been reported for diagnosing PD (Ahn et al. 2023, Nunes et al. 2019, Richardson et al. 2024, Tran et al. 2024).

Overview

In this article, we review human and animal studies that have taken advantage of ML classifiers to identify neurodegenerative diseases using retinal imaging data, with exclusive focus on MS (**Supplemental Table 1**), AD (**Supplemental Table 2**), and PD, in descending order of number of studies identified. The remainder of this article is structured as follows: The section titled Method of Literature Search describes the search strategies employed for identifying the relevant studies to be reviewed. In the sections titled Multiple Sclerosis, Alzheimer's Disease, and Parkinson's Disease, we review in detail specific studies on MS, AD, and PD, respectively. In the section titled Discussion, we present our recommendations for future avenues of research. Then we offer our conclusions on the topic. As most of this article's authors are nonnative English speakers, we took advantage of large language models to rephrase some of the sentences we initially crafted while maintaining their intended meaning. The final text was further edited and adapted for clarity by William Innes, a native English speaker.

Supplemental Material >

METHOD OF LITERATURE SEARCH

We performed a literature search on the PubMed database using the following keywords: (machine learning [title/abstract] OR deep learning [title/abstract] OR artificial intelligence [title/abstract] OR neural network* [title/abstract]) AND (retina* [title/abstract] OR optical coherence tomography* [title/abstract] OR fund* [title/abstract]) AND (neurodegenerative disease* OR neurodegenerative disorder* OR neurodegeneration OR multiple sclerosis OR clinically isolated syndrome OR radiologically isolated syndrome OR Alzheimer* OR mild cognitive impairment OR cogniti* OR Parkinson* OR Huntington* OR amyotrophic lateral sclerosis OR multiple system atrophy [title/abstract]). Additionally, we reviewed the reference lists of all identified studies to capture any relevant works missed during the primary search. All full-text articles written in English were included. During a secondary evaluation, studies were excluded if they used artificial intelligence models for purposes other than classifying (i.e., diagnosing) the diseases, for example, applying the models only to segment retinal images.

MULTIPLE SCLEROSIS

MS, an autoimmune neurodegenerative disease of the central nervous system (CNS), affects more than 2 million individuals globally. The disease is characterized by chronic inflammation, demyelination, gliosis, and axonal loss. MS presents with a wide range of clinical signs and symptoms,

with motor difficulties, sensory impairments, and visual disturbances as the most common manifestations. Diagnosis of MS is a time-consuming, challenging task, primarily relying on clinical assessments and radiologic findings obtained through MRI. Other diagnostic tests (e.g., CSF analysis, visual evoked potential, OCT) may provide further evidence to support the diagnosis (Thompson et al. 2018).

Optic neuritis is among the most common presentations of MS. About 25% of patients suffer from optic neuritis as the onset symptom, and up to 70% eventually experience it during the disease course (Lambe et al. 2019, Petzold et al. 2014). Furthermore, autopsy studies have shown that almost all MS individuals have variable degrees of optic nerve damage, even without any clinical manifestation (Ikuta & Zimmerman 1976, Toussaint et al. 1983). OCT investigations in MS were initiated by Parisi et al. (1999), who revealed a reduction in peripapillary RNFL (pRNFL) thickness using a time-domain OCT device. To date, numerous studies have demonstrated that inner retinal layers [i.e., pRNFL, macular ganglion cell–inner plexiform layer (mGCIPL)] have lower thickness values in MS patients who have a prior history of optic neuritis compared to healthy controls (Petzold et al. 2017). This observation has been attributed to retrograde neuroaxonal loss following the acute phase of inflammation. The pRNFL and mGCIPL become thinner in MS patients even without any history of optic neuritis. Hypothetically, in this subpopulation of MS patients, several subclinical episodes of optic neuritis may occur throughout the disease course. Otherwise, transsynaptic degeneration originating from lesions in optic radiations could be the responsible pathomechanism. Finally, ganglion cell degeneration itself might be a primary event, not secondary to prior inflammatory episodes in the optic nerve or other CNS regions (Britze & Frederiksen 2018). Interestingly, RNFL and ganglion cell–inner plexiform layer (GCIPL) thinning has also been observed in very early stages of the disease course (e.g., among CIS patients) (Oberwahrenbrock et al. 2013, Oreja-Guevara et al. 2012) and even in individuals with no clinical presentation of MS [i.e., radiologically isolated syndrome (RIS)] (Aly et al. 2020, Filippatou et al. 2018, Knier et al. 2015, Vural et al. 2018). The thickness of these layers has been associated with disease duration, physical disability, visual acuity, contrast sensitivity, cognitive decline, MS subtype, visual evoked potential measurements, and MRI parameters such as total brain, gray matter, and white matter volumes (Alonso et al. 2018, Britze & Frederiksen 2018, Cennamo et al. 2020, Mehmood et al. 2021). Longitudinal works revealed that such OCT variables could also be used for predicting disability worsening, visual function, and risk of conversion from RIS to MS (Alonso et al. 2018; Aly et al. 2020; Britze & Frederiksen 2018; Chalkias et al. 2022; Lambe et al. 2019, 2021; Mehmood et al. 2021). Such studies also showed that the rate of GCIPL thickness reduction correlated with that of brain atrophy (Saidha et al. 2015) and new T2 or contrast-enhancing lesions suggesting active disease (Ratchford et al. 2013). Furthermore, disorders such as NMOSD (Ciftci Kavaklioglu et al. 2022, T.-Y. Lin et al. 2021) can be differentiated from MS based on OCT thickness data (Bennett et al. 2015). OCT-A investigations also showed lower vessel density among MS patients, with a clear association with RNFL, GCIPL, and total retinal thickness values (Cennamo et al. 2022, Chalkias et al. 2022, Kleerekooper et al. 2020). Vessel density measurements correlated with patients' disability, visual acuity, and visual evoked potential latency. Therefore, retinal imaging, which is much less costly, invasive, and time-consuming than MRI and CSF investigations, provides promising biomarkers for aiding in the diagnosis of MS, even in its earlier stages.

Aside from two studies that employed infrared reflectance scanning laser ophthalmoscopy (IR-SLO) (Aghababaei et al. 2024, Arian et al. 2024), automatic diagnosis of MS based on retinal images has focused on OCT parameters, mainly pRNFL and mGCIPL thickness, alone or combined with demographic and clinical data. While spectral-domain devices are used in the majority of OCT works [with accuracy ranging from 80% (Ciftci Kavaklioglu et al. 2022) to 96% (Montolío et al. 2022)], four studies (Cavaliere et al. 2019, Garcia-Martin et al. 2021, López-Dorado et al.

2022, Pérez del Palomar et al. 2019), three of which employed the same datasets (Cavaliere et al. 2019, Garcia-Martin et al. 2021, López-Dorado et al. 2022), are based on swept-source OCT findings [with accuracy ranging from 91% (Cavaliere et al. 2019) to 100% (López-Dorado et al. 2022)]. Very recently, two studies employed IR-SLO images for classifying MS, yielding favorable results [88% accuracy in Aghababaei et al. (2024) and 92% accuracy in Arian et al. (2024)]. Details of all studies are shown in **Table 1**, Section 3 of the **Supplemental Text**, and **Supplemental Table 2**.

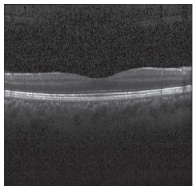
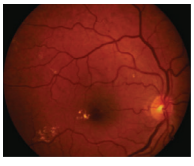
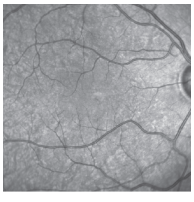
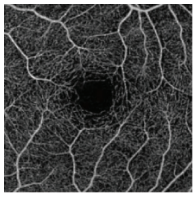
Supplemental Material >

ALZHEIMER'S DISEASE

Dementia presents one of the most significant challenges to modern healthcare systems. In 2018, ~50 million people worldwide were living with dementia (Patterson 2018), with the number estimated to double every 20 years. According to the 2018 World Alzheimer Report, the global cost of dementia is expected to rise to USD 2 trillion by 2030 (Patterson 2018). AD is the leading cause of dementia, responsible for 50–75% of cases. Its hallmark pathological features include the extracellular accumulation of amyloid beta plaques and the intracellular aggregation of neurofibrillary tangles composed of hyperphosphorylated p-tau (Gupta et al. 2021). Interestingly, research has revealed that amyloid beta deposits start forming in the CNS years to decades before the clinical signs and symptoms of AD become evident enough for a physician diagnosis (Koronyo-Hamaoui et al. 2011). These early pathological changes can be detected using advanced imaging technologies, such as PET scans, or CSF analysis (Gupta et al. 2021). The diagnosis of AD in its preclinical stage is crucial, as it provides an opportunity to initiate treatment while neural connections are still intact and neurons are functioning optimally. Early intervention can help minimize the catastrophic progression of the disease to its later, more debilitating stages (Dubois et al. 2016). Beyond diagnosis, accurately monitoring the progression of AD is crucial for determining suitable treatment strategies. However, using PET and CSF investigations for identifying preclinical AD patients or monitoring disease progression is expensive, inaccessible in many centers, and invasive.

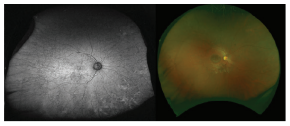
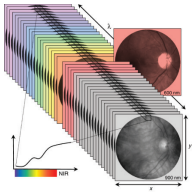
Thus far, a range of changes in the structure, function, and microvascular system of the retina, along with retinal buildup of amyloid beta and p-tau, has been identified in patients with AD, MCI, and even preclinical AD (Alber et al. 2020, Gupta et al. 2021, Kashani et al. 2021). Since the introduction of OCT into clinical practice in the mid-1990s, numerous studies have demonstrated that compared to healthy controls, the RNFL, GCIPL, and choroid become thinner in AD, MCI, and preclinical AD subjects (Alber et al. 2020, Gupta et al. 2021, Kashani et al. 2021). Two large longitudinal studies showed that macular RNFL thinning is associated with an increased risk of developing cognitive deterioration at 3-year (Ko et al. 2018, Mutlu et al. 2018) and up to 8-year (Mutlu et al. 2018) follow-ups. Other works also showed a correlation between cognitive function and RNFL and/or GCIPL thickness (Alber et al. 2020). The superior and inferior areas of the pRNFL have been reported to be more affected than the nasal and temporal quadrants; however, there is inconsistency between the studies (Kashani et al. 2021). Low thickness of inner retinal layers has also been linked with MRI measurements (Haan et al. 2019, Tao et al. 2019) or cerebral amyloid beta deposition detected by PET and CSF investigations (Alber et al. 2020, Haan et al. 2019, Santos et al. 2018). Furthermore, amyloid beta and p-tau aggregation has been found within retinal tissue and in connection with the retinal blood vessels (Koronyo et al. 2017) of animal models (Jiang et al. 2016) and less consistently of human subjects (Alber et al. 2020) with AD, even before cerebral deposits occur (Chiasseu et al. 2017, Koronyo-Hamaoui et al. 2011). In vivo tracking of amyloid beta in the retina has been made possible by novel imaging technologies, including fluorescence imaging using curcumin (Koronyo et al. 2017), a fluorochrome with binding affinity for amyloid beta; fluorescence lifetime imaging ophthalmoscopy (Sadda et al. 2019); and hyperspectral imaging (Hadoux et al. 2019, Sharafi et al. 2019). Studies have shown that the

Table 1 Summary of machine learning studies that employed retinal images for discriminating neurodegenerative diseases

Modality	Multiple sclerosis	Alzheimer's disease	Parkinson's disease
Optical coherence tomography 	RNFL and GCIPL thickness: Cavaliere et al. 2019; Ciftci Kavaklioglu et al. 2022; Garcia-Martin et al. 2013, 2015, 2021; Hernandez et al. 2023; Kenney et al. 2022; Khodabandeh et al. 2023; López-Dorado et al. 2022; Montolío et al. 2021, 2022, 2024; Ortiz et al. 2023; Pérez del Palomar et al. 2019; Zhang et al. 2020 Thickness of other retinal layers: Arian et al. 2024, Cavaliere et al. 2019, Khodabandeh et al. 2023, Ortiz et al. 2023	RNFL and GCIPL thickness: Wang et al. 2022 RNFL thickness: Lemmens et al. 2020 B-scans: Gao et al. 2023, Shi et al. 2024 Mean value fundus images: Ferreira et al. 2022, Nunes et al. 2019, Trindade 2021	GCIPL thickness: Richardson et al. 2024 Mean value fundus images: Nunes et al. 2019
Fundus photograph[a] 	None	Cheung et al. 2022, Gao et al. 2023, Kim et al. 2022, Shi et al. 2024, Tian et al. 2021, Zhang et al. 2021	Ahn et al. 2023, Tran et al. 2024
Infrared reflectance scanning laser ophthalmoscopy 	Aghababaei et al. 2024, Arian et al. 2024	None	None
Optical coherence tomography angiography[b] 	None	Wisely et al. 2022, 2024	Richardson et al. 2024

(*Continued*)

Table 1 (*Continued*)

Modality	Multiple sclerosis	Alzheimer's disease	Parkinson's disease
Ultra-widefield color and fundus autofluorescence scanning laser ophthalmoscopy[c] 	None	Wisely et al. 2022	Richardson et al. 2024
Hyperspectral images[d] 	None	Hadoux et al. 2019, Lemmens et al. 2020, Sharafi et al. 2019	None

Abbreviations: B-scan, brightness scan; GCIPL, ganglion cell–inner plexiform layer; RNFL, retinal nerve fiber layer.
[a]Image reproduced from Hajeb Mohammad Alipour et al. (2012) (CC BY 4.0).
[b]Image reproduced from Spaide et al. (2018) (CC BY 4.0).
[c]Image adapted from Oishi et al. (2019) (CC BY 4.0).
[d]Image reproduced from Hadoux et al. (2019) (CC BY 4.0).

retinal vascular system is affected by AD. Parameters such as vessel caliber, tortuosity, branching angle, and fractal dimension, obtained from fundus photography and OCT-A investigations, have been noted to have lower values in different stages of AD, including the presymptomatic phase (Alber et al. 2020, Gupta et al. 2021, Kashani et al. 2021). OCT-A studies also revealed reduced vessel density and an enlarged foveal avascular zone. Moreover, dynamic vascular biomarkers, such as reduced blood flow rate (Feke et al. 2015), velocity (Jiang et al. 2018), and pulsatility (Golzan et al. 2017), have been demonstrated to possess higher specificity for AD. Systemic vascular variables such as arterial stiffness, endothelial cell dysfunction, pulse pressure, and pulse wave velocity also undergo changes in association with cognitive decline (Elias et al. 2009, Hazzouri et al. 2013, Pase et al. 2012, Waldstein et al. 2008). In addition, various retinopathies have been associated with AD (Heringa et al. 2013), and these are characterized by microaneurysms or microhemorrhages, hard and/or soft exudates, optic disc edema, and neovascularization, to name a few. Similar to structural changes, vessel damage and retinopathy have also been linked to cerebral amyloid beta burden (Golzan et al. 2017), MRI abnormalities (Heringa et al. 2013), and cognitive scores (Bulut et al. 2018). Therefore, retinal biomarkers could serve as a valuable supplement to or even a substitute for the currently established biomarkers for AD, including clinical, imaging, CSF, and blood biomarkers.

To date, different animal and human studies have been performed for automated diagnosis of AD or MCI using fundus photography (Cheung et al. 2022, Gao et al. 2023, Kim et al. 2022, Shi et al. 2024, Tian et al. 2021, Zhang et al. 2021), with accuracy ranging from 63% (Shi et al. 2024) to 92% (Cheung et al. 2022); OCT (Ferreira et al. 2022; Gao et al. 2023; Lemmens et al. 2020; Nunes et al. 2019; Shi et al. 2024; Trindade 2021; Wang et al. 2022; Wisely et al. 2022, 2024), with accuracy ranging from 69% (Shi et al. 2024) to 89% (Trindade 2021); OCT-A (Wisely et al.

2022, 2024), with the area under the curve (AUC) ranging from 0.58 (Wisely et al. 2022) to 0.63 (Wisely et al. 2024) (the studies reported only the AUCs); and hyperspectral images (Hadoux et al. 2019, Lemmens et al. 2020, Sharafi et al. 2019), with 85% accuracy by Sharafi et al. (2019) and an AUC of 0.87 by Hadoux et al. (2019) (the latter work reported only the AUC). Several studies also took advantage of multiple retinal imaging modalities, including fundus camera and OCT brightness scan (B-scan) images [with accuracies of 91.6% (Gao et al. 2023) and 71.0% (Shi et al. 2024)]; OCT thickness values and hyperspectral imaging [with an AUC of 0.74 (Lemmens et al. 2020) (the study reported only the AUC)]; and OCT thickness measurements, OCT-A en face images, ultra-widefield color and fundus autofluorescence SLO images, and patients' demographic and clinical data [with AUCs of 0.84 (Wisely et al. 2022) and 0.81 (Wisely et al. 2024) (no accuracy was reported)]. Fundus camera–based studies have trained models using either original fundus images (Cheung et al. 2022, Gao et al. 2023, Kim et al. 2022, Shi et al. 2024, Zhang et al. 2021) or vessel maps derived from these images (Tian et al. 2021, Zhang et al. 2021). The use of vessel maps is well-supported by clinical evidence, which indicates that individuals with cognitive impairment exhibit various retinal vascular changes (Alber et al. 2020, Gupta et al. 2021). As discussed above, the retinal changes associated with cognitive impairment are not limited to vascular abnormalities; rather, structural pathologies (e.g., reduced thickness of inner retinal layers) that can be detected in detail by OCT also occur. Except for the study by Gao et al. (2023), who used swept-source OCT, OCT-based works have relied on spectral-domain devices. Four studies used RNFL and GCIPL thickness measurements in numerical (Lemmens et al. 2020, Wang et al. 2022) or image (Wisely et al. 2022, 2024) formats for classifying AD and MCI. Three works also generated mean value fundus images from OCT scans, and the models were then trained with either the resulting images (Ferreira et al. 2022, Trindade 2021) or the texture features obtained from them (Nunes et al. 2019). Mean value fundus images are created by averaging the amplitude scan (A-scan) intensities between adjacent retinal layers and giving them an appearance similar to fundus camera photographs. Interestingly, the most recent studies (Gao et al. 2023, Shi et al. 2024) used OCT B-scans for identifying cognitive impairment and yielded promising results. This is noteworthy since neurodegenerative diseases are not typically associated with B-scan changes discernable to human physicians. However, these studies showed that ML may be capable of uncovering such subtle alterations. The details of all studies are shown in **Table 1**, Section 4 the **Supplemental Text**, and **Supplemental Table 2**.

Supplemental Material >

PARKINSON'S DISEASE

PD, the second most common neurodegenerative disease, is characterized by the loss of dopaminergic neurons in the midbrain substantia nigra and the accumulation of abnormal alpha-synuclein in cytoplasmic inclusions known as Lewy bodies (Balestrino & Schapira 2020). More than 6 million people suffer from PD worldwide, with an estimated annual incidence rate of 160 per 100,000 people over the age of 65 years in developed countries (Ascherio & Schwarzschild 2016). PD is mainly recognized by its motor signs and symptoms, with bradykinesia, resting tremor, and rigidity being the most cardinal clinical presentations included in the diagnostic criteria (Postuma et al. 2015). It is also common for individuals with PD to experience nonmotor symptoms, which are probably associated with pathologies in other regions, such as the olfactory and autonomic nervous systems, rather than solely the basal ganglia (Tolosa et al. 2021). Exclusion of other similar disorders, such as essential tremor and multiple system atrophy, is crucial; this can be facilitated by findings from neuroimaging studies, such as MRI and PET (Balestrino & Schapira 2020). Like AD, early diagnosis of PD is of paramount importance since the disease is often identified at its advanced stage, when neuronal tissue and synaptic connections have been disrupted, leading to

therapeutic interventions being much less effective compared to when they are initiated at the early, asymptomatic phase. In recent years, several imaging (i.e., molecular imaging and MRI), biochemical (i.e., blood and CSF), and genetic markers have been studied to aid early diagnosis of PD, before clinically discernable presentations occur (Mahlknecht et al. 2015). However, the use of such biomarkers is limited in routine clinical practice due to their invasiveness, high cost, and unavailability in many centers.

As an extension of the CNS, the retina is damaged in up to 70% of PD patients (Zhang et al. 2022), resulting in problems such as disturbances in visual acuity, contrast sensitivity, and color discrimination, as well as visual hallucinations and changes in motion perception (Zhang et al. 2022). The first evidence for the loss of retinal dopaminergic neurons in PD was found in 1988. Nguyen-Legros (1988) observed that tyrosine hydroxylase, a rate-limiting enzyme in the dopamine synthesis pathway, showed reduced immunoreactivity in retina specimens from PD patients. OCT investigations have shown that the RNFL, GCIPL, and outer retinal layers become thinner in PD patients compared to healthy controls (Kashani et al. 2021, Zhang et al. 2022, Zhou et al. 2021); the thickness of such layers has been associated with a number of visual problems, including visual acuity, contrast sensitivity, and color vision disturbances as well as visual hallucinations (Zhang et al. 2022). The level of RNFL thinning has also been linked to the severity, duration, and progression of PD (Hasanov et al. 2019, Ma et al. 2018). Additionally, several works using OCT-A have reported retinal microvascular changes in PD, including reduced vessel density, perfusion density, and fractal dimension (Kwapong et al. 2018, Robbins et al. 2021, Shi et al. 2020). Therefore, as various retinal changes occur in PD, imaging the retina through currently available noninvasive, cheap, and accessible technologies, such as fundus camera photography or OCT, offers promising biomarkers for timely detection of this disorder.

Compared to MS and AD studies, a smaller number of ML works have explored the utility of retinal biomarkers for diagnosing PD. Overall, these studies achieved high levels of accuracy, from 71% (Tran et al. 2024) to 90% (Richardson et al. 2024), using mean value fundus images obtained from OCT [with an accuracy of 82% (Nunes et al. 2019)], fundus camera images [with accuracies of 71% (Tran et al. 2024) and 77% (Ahn et al. 2023)], and a combination of OCT thickness measurements in numerical or image formats, OCT-A en face images, and ultra-widefield color and fundus autofluorescence SLO images [with an accuracy of 90% (Richardson et al. 2024)]. Two studies used OCT for classifying PD (Nunes et al. 2019, Richardson et al. 2024). The work by Nunes et al. (2019) created mean value fundus images from OCT and trained ML models with the texture features of these images, finally reaching a sensitivity of 78% and a specificity of 98% for discriminating between AD, PD, and healthy controls. Distinguishing between neurodegenerative disorders such as AD and PD is sometimes critical; patients with PD dementia may have signs and symptoms that overlap with other causes of dementia, such as dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, and AD (Poewe & Wenning 2002). The only study that used OCT thickness measurements was the multimodal study by Richardson et al. (2024), who focused on the GCIPL, which is in line with statistical studies suggesting the reduction in RNFL and GCIPL thickness in PD (Kashani et al. 2021, Zhang et al. 2022, Zhou et al. 2021); however, these values led to inferior model performance compared to ultra-widefield color SLO images. Given that previous studies showed that color SLO images yield unfavorable results for classifying AD (Wisely et al. 2022) and MCI (Wisely et al. 2024), there may be some retinal changes unique to PD that can be better identified using color SLO images. This necessitates future studies to further explore the discriminant capacity of retinal images and especially color SLO images for differentiating PD from healthy controls and even other neurodegenerative disorders. Two studies used fundus camera images to distinguish between PD patients and individuals with non-PD atypical motor symptoms (Ahn et al. 2023) or between established PD,

preclinical PD, and healthy control subjects (Tran et al. 2024). Ahn et al. (2023) also used fundus camera images to predict the neurological disability state of PD patients. Tran et al. (2024) achieved satisfactory performance, yielding an AUC of 0.8, for detecting preclinical or prodromal PD. This critical finding shows the great potential of retinal imaging for early diagnosis of PD. As discussed above, the currently available options for detecting early biomarkers of PD are based on molecular imaging and MRI as well as blood and CSF investigations, along with genetic variables (Mahlknecht et al. 2015), which, compared to retinal imaging, are high cost, time-consuming, invasive, and unavailable in many clinical centers. The details of all studies are shown in **Table 1** and Section 5 of the **Supplemental Text**.

Supplemental Material >

DISCUSSION

In this article, we have provided a thorough summary of the recent endeavors aimed at automatically identifying neurodegenerative disorders based on features extracted from retinal images. Within the overall field of research, the outcomes appear to be encouraging, with classification accuracies of 80% (Ciftci Kavaklioglu et al. 2022) to 100% (López-Dorado et al. 2022) for MS, 63% (Shi et al. 2024) to 92% (Cheung et al. 2022, Gao et al. 2023) for AD, and 71% (Tran et al. 2024) to 90% (Richardson et al. 2024) for PD.

Of note, these results are comparable to those achieved in studies using other types of input data. Regarding MS, a meta-analysis showed that the diagnostic accuracy of ML models is 96% with MRI scans, 93% with laboratory findings, and 88% with movement-related measurements; OCT data, with an accuracy of 92%, ranked as the second most effective input source (Nabizadeh et al. 2022b). The accuracy range of MS classification models in the current review was 80% (Ciftci Kavaklioglu et al. 2022) to 100% (López-Dorado et al. 2022). Regarding AD and PD, however, there is lack of meta-analyses that provide a comprehensive and unbiased comparison of models employing different input data types. Most studies on AD detection have relied on neuroimaging data, including MRI, functional MRI, and PET, leading to median accuracies of 94.1% (mean = 94.0%) for distinguishing between AD and healthy controls and 88.5% (mean = 86.9%) for distinguishing between MCI and healthy controls, according to a systematic review (not a meta-analysis) by Fathi et al. (2022). As shown here, retinal imaging data have yielded relatively comparable results, with an accuracy range of 64% (Shi et al. 2024) to 92% (Cheung et al. 2022, Gao et al. 2023). An AUC of 0.97 was achieved in Gao et al.'s (2023) study for identifying AD and MCI individuals. In addition to neuroimaging technologies, various wearable and nonwearable sensors, including inertial, pressure, image, depth, audio, and voice sensors, have provided input data for detecting PD (Giannakopoulou et al. 2022); the average accuracy for the most commonly used data types has been reported to be 91% for voice recordings, 89% for movement-related parameters, and 88% for MRI data (Mei et al. 2021), apparently outperforming the results obtained in studies using retinal images (Nunes et al. 2019, Tran et al. 2024). In a very recent study, however, relatively higher performance compared to Nunes et al.'s (2019) and Tran et al.'s (2024) studies (i.e., an AUC of 0.92) was reported for classifying PD when multiple retinal imaging modalities (i.e., OCT thickness maps, OCT-A en face images, ultra-widefield color and fundus autofluorescence SLO images) were incorporated (Richardson et al. 2024). Indeed, more studies with larger datasets are required to establish a clear conclusion on the diagnostic value of retinal images for neurodegenerative diseases, especially PD. In addition, studies have shown that retinal changes (e.g., RNFL and inner nuclear layer thinning detected using OCT) occur in other neurodegenerative diseases, such as amyotrophic lateral sclerosis, multiple system atrophy, and Huntington's disease (Gouravani et al. 2024, Mendoza-Santiesteban et al. 2017, Nepal et al. 2022). Nonetheless, ML studies have not yet used retinal images for automatic diagnosis of these disorders, necessitating future research to also include patients with these less common but disabling brain pathologies.

Problems

Although ML-based analysis of retinal images shows great promise for automated classification of neurodegenerative diseases, several challenges must be addressed before it can be widely adopted in clinical practice. Overfitting, a common problem in ML leading to poor performance and inaccurate predictions, is a situation in which a model learns the noise or idiosyncrasies of the training data instead of learning the underlying patterns (Ying 2019). This is also a major challenge in studies of fundus camera images or OCT scans, as these datasets are obtained from populations with different demographic and clinical characteristics through a variety of imaging devices and scanning protocols. To mitigate the risk of overfitting, a range of approaches have been suggested, falling into two primary categories: strategies aimed at restricting model complexity and strategies aimed at addressing the challenge of limited data. To fulfill the first strategy, in the studies discussed here, methods such as feature selection (the majority of studies listed in **Supplemental Tables 1 and 2**) or simply using a smaller model with fewer parameters (López-Dorado et al. 2022, Ortiz et al. 2023) were employed. In addition, L1/L2 regularization (Wisely et al. 2022), dropout (Aghababaei et al. 2024; Arian et al. 2024; Montolío et al. 2024; Richardson et al. 2024; Wisely et al. 2022, 2024), batch normalization (Aghababaei et al. 2024; Arian et al. 2024; Gao et al. 2023; Kim et al. 2022; López-Dorado et al. 2022; Ortiz et al. 2023; Richardson et al. 2024; Trindade, 2021; Wisely et al. 2022, 2024), and early stopping (Aghababaei et al. 2024, Arian et al. 2024, Gao et al. 2023, Tran et al. 2024, Trindade 2021) were regularization techniques aimed at tuning the values of model parameters. To fulfill the second strategy for overcoming model overfitting, many authors have employed techniques such as rotation, vertical or horizontal flip, affine, color jitter, zoom, crop, and shift transformation or even used generative adversarial neural networks (López-Dorado et al. 2022) to artificially augment their datasets. In several studies (Arian et al. 2024; Gao et al. 2023; Richardson et al. 2024; Shi et al. 2024; Wisely et al. 2022, 2024), retinal images from different modalities were incorporated and given to a single convolutional neural network–based architecture; this could be viewed as an intriguing way to enlarge and diversify the input data, which prevents overfitting to images of a specific modality. In addition, some fundus camera studies took advantage of a larger dataset by using multiple fundus images for each participant (i.e., macula-centered and optic disc–centered images of one or both eyes) (Cheung et al. 2022, Shi et al. 2024, Zhang et al. 2021).

Supplemental Material >

The challenge of model overfitting continues to be a significant concern, given the extremely small datasets typically available ($N \approx 100$). With overfitting, a model can perform well on in-distribution data, and even previously unseen test data that are similar to those used during training (sometimes even from the same patient; see the **Supplemental Text**), but fail when deployed on external datasets (e.g., scans from a different hospital). Simpler models with fewer parameters have less ability to overfit and can thus outperform large, complex models on external datasets, even if they appear worse when assessed on withheld data from the same source as used during training. Therefore, future studies are highly encouraged to use multicenter datasets to improve the generalization ability of their models as much as possible, thereby paving the way for wider impact within the neurologist and ophthalmologist community. Another important area for future research should be the development of large, labeled retinal image datasets captured using different devices and scanning protocols from patients with diverse demographic and clinical backgrounds. Drawing inspiration from large and accessible databases such as the UK Biobank that have been effectively used in classifying AD (Kim et al. 2022, Tian et al. 2021) and PD (Tran et al. 2024), it is crucial to collect open-source image datasets to serve as input data for MS models as well. In studies by Aghababaei et al. (2024) and Arian et al. (2024), an open-source dataset was used

(He et al. 2019) as an external dataset; however, it has a very low size (14 healthy controls and 21 MS subjects).

Another concern with using ML models in health care is their lack of interpretability. Medical decision-making requires a high degree of caution and should be based on solid evidence to ensure accuracy, effectiveness, and safety. Although many ML models have achieved astonishing performance levels comparable to those of human physicians, the limited transparency in how they make decisions has been a major barrier to their adoption in clinical practice. This problem is particularly prominent in deep learning models, which consist of numerous hidden neurons and layers and are frequently described as black boxes because they do not reveal the internal processes leading to a prediction (Hakkoum et al. 2022). To address this challenge, several interpretability methods have been developed and are categorized in different ways, such as local versus global, model-specific versus model-agnostic, and intrinsic versus post hoc interpretability methods. Local interpretability methods focus on identifying which elements of an individual input contributed most to the model's decision, while global methods aim to explain the overall behavior of the model (Bhattacharya 2022). Regarding the studies that used retinal images to classify neurodegenerative diseases, both global and local methods were used to interpret the predictions made by ML (Hernandez et al. 2023, Khodabandeh et al. 2023, Tian et al. 2021) and deep learning (Aghababaei et al. 2024, Ahn et al. 2023, Arian et al. 2024, Cheung et al. 2022, Gao et al. 2023, Richardson et al. 2024, Shi et al. 2024, Tran et al. 2024, Trindade 2021, Wisely et al. 2022) models. More details are provided in Sections 6 and 7 of the **Supplemental Text** and **Supplemental Table 3**.

Supplemental Material >

Future Potential

Using retinal images holds potential for noninvasive and early diagnosis of neurodegenerative diseases. The studies reviewed in this article focused on classifying MS, AD, and PD using retinal images from patients whose diagnoses were already confirmed at the time of imaging by expert physicians through conventional diagnostic methods (mainly using MRI and CSF investigations). Retinal imaging technologies, such as OCT, offer significant advantages over conventional approaches due to their noninvasive nature, accessibility, and lower cost. Nonetheless, while these attributes are beneficial, they are not sufficient; early diagnosis remains a critical and highly sought-after goal. This is because current diagnostic workups often identify neurodegenerative diseases at advanced stages, when treatment options are less effective than they might be with earlier detection. Notably, three studies (Tran et al. 2024, Wisely et al. 2024, Zhang et al. 2021) aimed to address this by leveraging retinal images for early diagnosis: Wisely et al. (2024) and Zhang et al. (2021) trained their models with image datasets of patients with MCI, and Tran et al. (2024) included individuals in the preclinical phase of PD. The potential of retinal imaging for early diagnosis of neurodegenerative diseases is further explored in this section.

Multiple sclerosis. The degree to which OCT may help in the diagnosis of MS has been a matter of debate. To confirm an MS diagnosis, current guidelines require evidence of dissemination in time and space, meaning lesions must occur in separate anatomical regions of the CNS and develop or resolve over time (Thompson et al. 2018). Recent studies propose that the optic nerve, with involvement verified by MRI, visual evoked potentials, or OCT imaging, could be included as an additional region for establishing dissemination in space (Bsteh et al. 2023, Vidal-Jordana et al. 2021). Although the 2017 McDonald criteria did not incorporate OCT due to insufficient evidence at the time (Thompson et al. 2018), the 2024 revision has changed this. OCT evidence of optic nerve damage is now acknowledged as fulfilling one region for dissemination in space, provided the intereye difference in pRNFL thickness is >6 μm or the intereye difference in GCIPL thickness is >4 μm (Barkhof et al. 2025, Montalban et al. 2025, Saidha et al. 2025). It

is important to note that two ML studies reviewed here (Kenney et al. 2022, Ortiz et al. 2023) used these two OCT indicators of dissemination in space (RNFL and GCIPL intereye thickness difference measurements) to train their models and achieved satisfactory results for classifying MS [with an AUC of 0.89 (Kenney et al. 2022) and accuracy of 87% (Ortiz et al. 2023)].

Despite promising results, nearly all ML-based studies for the diagnosis of MS using retinal images have included MS patients with an already-established diagnosis of the disease. Additionally, an exact duration of disease was not clarified in many studies; an exception could be three swept-source OCT studies (Cavaliere et al. 2019, Garcia-Martin et al. 2021, López-Dorado et al. 2022), which stated that they specifically included individuals for whom MS was recently (<9 months) diagnosed. The inclusion of patients with prolonged disease duration presents a problem, as these patients are likely to have greater optic nerve damage than those diagnosed at an earlier stage. Therefore, although the studies have shown remarkable diagnostic accuracies, their results cannot be reliably generalized to patients with early diagnoses, limiting their utility in routine clinical practice. This is because automated diagnosis of MS is most valuable to the neurology community when it can identify the disease in its early phase, as well as conditions such as CIS and RIS, and distinguish it from similar disorders during initial presentations, enabling timely initiation of disease-modifying therapies and ultimately improving the disease prognosis (Filippi et al. 2022).

Before a definite diagnosis of MS is made, two conditions can develop, CIS and RIS (Niino & Miyazaki 2017). In CIS, a single episode of neurological presentations indicative of MS occurs, but MRI lesions do not satisfy the McDonald criteria (Thompson et al. 2018) for dissemination in time and/or space required for a definite diagnosis of MS; however, most individuals eventually develop MS. RIS individuals show no MS symptoms but have lesions discovered incidentally on MRI scans (Thompson et al. 2018). Nearly one-third of RIS individuals convert to clinically discernable MS within 5 years (Okuda et al. 2014); the condition is therefore sometimes called preclinical MS. Studies have shown that RNFL and GCIPL thickness decreases in individuals with RIS (Aly et al. 2020, Knier et al. 2015, Vural et al. 2018) or CIS (Knier et al. 2015, Oberwahrenbrock et al. 2013, Oreja-Guevara et al. 2012). Knier et al. (2015) and Zimmermann et al. (2018) also reported an increase in inner nuclear layer thickness among these patients. Such OCT changes have been related to MRI findings, including newly formed lesions indicative of disease activity (Knier et al. 2015) or the presence of infratentorial and subcortical lesions (Filippatou et al. 2018). Reduction in GCIPL and RNFL thickness has been introduced as a risk factor for predicting the progression to MS (Aly et al. 2020, Knier et al. 2015, Vural et al. 2018, Zimmermann et al. 2018), helping to solve a key problem in the clinical practice of neurologists. Indeed, there is evidence that MS patients may benefit from initiating disease-modifying therapies at earlier stages (Förster et al. 2019); thus, an intriguing research endeavor would be to predict the risk of conversion from CIS and/or RIS to definite MS by applying ML algorithms to retinal images. Beyond assessing the risk of conversion to MS, retinal imaging holds promise as a vital supplementary diagnostic modality for identifying CIS and/or RIS as standalone conditions. Thus far, ML-based works have tried to predict the outcome of CIS based on MRI parameters, both with (Bendfeldt et al. 2019; Wottschel et al. 2015, 2019) and without (Pareto et al. 2022, Zhang et al. 2019) adding demographic and clinical characteristics, which have not consistently led to high levels of accuracy (Pareto et al. 2022). As mentioned above, patients with CIS are known to progress to MS more often than those with RIS. Therefore, identifying RIS patients at higher risk of conversion to MS may be a more clinically important goal than focusing on CIS patients. Nevertheless, currently no ML studies aim to classify these high-risk RIS individuals, even using MRI data. This may be partly due to the challenges of generating large-scale datasets that track RIS subjects over time through prospective longitudinal studies.

Using IR-SLO images to differentiate between individuals with MS and healthy controls (Aghababaei et al. 2024, Arian et al. 2024) is particularly intriguing because en face retinal images, such as those captured by IR-SLO or fundus cameras, have not been associated with significant changes that are reliably detectable by human physicians, especially in the early stages of MS. It has been demonstrated that RNFL changes are not visible on an ophthalmoscopic examination until the layer thickness has decreased by at least 50% (Quigley et al. 1982). As detailed in the following sections, ultra-widefield color and fundus autofluorescence SLO images have been employed to detect AD (Wisely et al. 2022), leading to unfavorable outcomes; however, the same imaging modalities have demonstrated high performance in classifying PD (Richardson et al. 2024). Therefore, it is possible that retinal changes, such as reduced retinal layer thickness, deposits of misfolded proteins, or alterations in retinal blood vessels, can be identified in MS and PD using SLO technology. However, the evidence supporting this approach is currently very weak, underscoring the need for future studies to thoroughly investigate the potential of SLO imaging in classifying different neurodegenerative diseases.

Additionally, novel imaging technologies, such as adaptive optics, offer promising prospects for early diagnosis of MS and other neurodegenerative disorders (Hammer et al. 2023, McIlwaine et al. 2023). Adaptive optics was first used in astronomy for correcting wavefront distortions that occur when light is passed through the atmosphere to reach the optical telescope (Jayabalan & Bille 2019). Applying adaptive optics in retinal imaging can enhance lateral resolution in a way that cellular and subcellular objects can be visualized (Jayabalan & Bille 2019). McIlwaine et al. (2023) employed OCT for measuring the macular and peripapillary thickness of different retinal layers as well as adaptive optics for calculating cone photoreceptor density and spacing. The authors showed that patients without a history of optic neuritis have lower cone densities, but no thinning of the inner retina can be detected using OCT. Therefore, compared to conventional OCT investigations, adaptive optics may serve as a more sensitive imaging modality that can reveal subtle pathological changes and be more beneficial for early detection of neurodegenerative diseases. However, there is huge lack of evidence in this regard, as adaptive optics technology is now used only for research applications and is not accessible in most clinical centers.

Alzheimer's disease. Unlike definite AD, MCI is defined as a condition in which dementing symptoms do not interfere with daily routine activities, and preclinical AD may be considered an even earlier phase where the individual is asymptomatic and it is diagnosed based only on the presence of AD biomarkers, that is, amyloid beta and p-tau, in PET and CSF investigations (Dubois et al. 2016). Notably, OCT changes associated with AD, that is, reduction in pRNFL and mGCIPL thickness, have also been reported in individuals with MCI (Chan et al. 2019, Haan et al. 2017) or preclinical AD (Garcia-Martin et al. 2016, Santos et al. 2018), although this has not been confirmed by all studies (Kashani et al. 2021). Furthermore, histopathological investigations in mice have revealed that amyloid beta aggregation can be detected within the retina, even before it becomes evident in the brain (Koronyo-Hamaoui et al. 2011, Mirzaei et al. 2019). Due to inconsistency between the studies, however, an umbrella review of the meta-analyses was performed in 2023, reporting that based on the current knowledge, only pRNFL thinness and increased fovea avascular zone measurements can be considered the most reliably confirmed retinal changes in AD.

Diagnosing preclinical AD is an attractive topic for neurologists, as it facilitates the early initiation of effective therapies. Nevertheless, the majority of the studies reviewed here focused on symptomatic patients, making it difficult to apply their findings to asymptomatic populations. Given the high prevalence and significant burden of dementia, community-level screening for this disorder appears justified. Although ML-assisted retinal image analysis, with its noninvasive

nature, low cost, and accessibility, shows promise as a potential screening tool, the studies conducted so far have not fully aligned with the goals of screening asymptomatic individuals, as their models were trained with data from symptomatic patients. A few studies, however, have shown that retinal imaging holds great potential for detecting amyloid beta and p-tau deposits within the brain (biomarkers that may precede clinical AD) based on fundus camera (Cheung et al. 2022) and hyperspectral (Hadoux et al. 2019, Lemmens et al. 2020, Sharafi et al. 2019) images, necessitating future research on larger scales to focus on classifying individuals with preclinical AD (confirmed through PET or CSF investigations) using retinal features.

Since MCI does not significantly disrupt daily activities, patients often do not seek neurological evaluation until the condition progresses to its advanced stage, dementia. Considering the high prevalence of conditions such as glaucoma, age-related macular degeneration, and diabetic retinopathy among the elderly, we propose integrating an ML-equipped system into retinal imaging devices such as OCT and fundus cameras in eye clinics. This tool could then analyze retinal images for signs of MCI or preclinical AD and direct patients, who initially sought care for ocular disease, to neurologists for additional assessment and follow-up. In this regard, studies (Cheung et al. 2022, Shi et al. 2024) have shown that ML models can successfully be used to detect cognitive dysfunction even in the presence of common ocular disorders (see the section titled Specificity and the **Supplemental Text**).

Supplemental Material >

Parkinson's disease. Early diagnosis of PD is of critical importance, especially as its growth rate now exceeds that of AD (Dorsey & Bloem 2018). Timely detection paves the way for disease-modifying therapies and preventive interventions that focus on alpha-synuclein aggregation and other pathogenic processes, offering a window of opportunity to act before extensive neuronal damage occurs. PD patients may experience a range of nonmotor symptoms, including hyposmia, rapid eye movement sleep disorders, and constipation years or even decades before the initial occurrence of cardinal motor presentations. These early manifestations are thought to result from neurodegenerative changes occurring in extranigral regions, such as the olfactory or peripheral autonomic nervous systems (Tolosa et al. 2021). While this phase is referred to as the prodromal stage of PD, the term "preclinical PD" is used when neither nonmotor nor subtle motor symptoms are present but biomarker evidence indicates the onset of PD-related pathology. Prodromal PD has been linked to some advanced imaging findings, including neuromelanin-sensitive MRI (Ehrminger et al. 2016, Ohtsuka et al. 2013) and visual assessment of dorsal nigral hyperintensity (De Marzi et al. 2016, Mahlknecht et al. 2017). Additionally, single-photon emission computed tomography and PET scans have shown the potential to detect alpha-synuclein deposits in the brain and peripheral autonomic nervous system (Dauvilliers et al. 2018, Meles et al. 2018, Tolosa et al. 2021). Alpha-synuclein aggregations have also been identified in CSF (Fairfoul et al. 2016, Tolosa et al. 2021) and tissue biopsy samples from autonomic nerves in the salivary glands (Vilas et al. 2016) and skin (Donadio et al. 2014) of individuals with prodromal PD (Tolosa et al. 2021). Some researchers have introduced the term "prephysiologic PD" to describe a stage where even biomarkers for PD are undetectable with current technologies. At this stage, individuals may possess genetic and/or environmental risk factors that predispose them to developing PD (Siderowf & Lang 2012).

Although promising, the previously mentioned biomarkers for PD have not consistently provided reliable results in identifying its prodromal or preclinical stages (Tolosa et al. 2021). Their high cost, invasiveness, and limited accessibility further hinder their application for community-level screening. In contrast, the structural and vascular changes in the retina seen in PD present an opportunity to leverage retinal imaging, a noninvasive, affordable, and widely available technology, as an early diagnostic tool.

Most ML studies using retinal imaging for PD classification have focused on individuals with an already-confirmed diagnosis. Consequently, their results, though promising, are not applicable to individuals in prodromal or preclinical stages. An exception is the study by Tran et al. (2024), which used fundus camera images from individuals in the preclinical or prodromal stages and achieved diagnostic accuracy (71%) comparable to that for established PD. Their results suggest that retinal imaging could play a key role in community-level screening for PD. In addition to early detection, reliable disease monitoring is crucial for determining the appropriate time to begin or modify treatment. Distinguishing PD from other neurodegenerative diseases with similar parkinsonism symptoms, such as multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration, is also an area that requires further attention (Tolosa et al. 2021). In this regard, Richardson et al. (2024) were able to classify PD using multiple retinal imaging modalities, with ultra-widefield color SLO images showing the highest discriminative capacity. Interestingly, the same image type (i.e., ultra-widefield color SLO images) yielded unsatisfactory results when used for AD classification (Wisely et al. 2022). This suggests that ultra-widefield SLO images may be effective for distinguishing between PD and AD eyes. Novel retinal imaging technologies, such as hyperspectral imaging, that have been applied in several AD studies (Hadoux et al. 2019, Lemmens et al. 2020, Sharafi et al. 2019) have only recently been explored for human PD detection. Ueda et al. (2024) found that reflectance spectra measurements, especially at shorter wavelengths, are reduced in the PD retina, likely due to alpha-synuclein deposition. Upcoming research should further focus on applying ML algorithms to hyperspectral images of PD individuals.

Different Machine Learning Approaches

It is interesting to note that certain strategies implemented for a specific neurodegenerative disease can potentially be adopted for other conditions in future research. For instance, methods such as wavelet transform (Zhang et al. 2020) or Cohen's d technique (Garcia-Martin et al. 2021, López-Dorado et al. 2022) for extracting OCT thickness map features in MS studies can also be used for classifying AD and PD. Other promising techniques for feature extraction include sparse, stacked, and convolutional autoencoders; restricted (Hinton & Salakhutdinov 2006) and deep (Salakhutdinov & Hinton 2009) Boltzmann machines; and the vision transformer (Khan et al. 2022). The vision transformer and some other architectures based on attention mechanisms were used to classify AD and MCI in the study by Gao et al. (2023). While several state-of-the-art convolutional neural network models have been employed for PD and AD classification, most works in MS have not taken advantage of DL, except for studies conducted recently (Aghababaei et al. 2024, Arian et al. 2024, López-Dorado et al. 2022, Ortiz et al. 2023). Moreover, exploring retinal images with different modalities, such as fundus photographs, ultra-widefield color and fundus autofluorescence or IR-SLO images, or OCT-A en face images, have not been tested for automated classification of MS and may possibly yield encouraging results. Regarding fundus photographs, for example, retinal vessel maps can first be segmented, and then the extracted features from these maps can be used for classification, similar to Tian et al.'s (2021) and Zhang et al.'s (2021) studies on dementia and MCI patients. Furthermore, mean value fundus images, previously used for identifying AD (Ferreira et al. 2022, Nunes et al. 2019, Trindade 2021) and PD (Nunes et al. 2019), may hold potential for MS classification. Generation of fundus-like images from OCT is not necessarily limited to averaging A-scan intensities; wavelet-based fusion methods are alternative options (Jalili et al. 2020).

In addition, similar to the studies on AD and MCI classification (Gao et al. 2023; Lemmens et al. 2020; Shi et al. 2024; Wisely et al. 2022, 2024), the integration of multimodal retinal images can

aid in distinguishing between individuals with MS (Arian et al. 2024) and/or PD (Richardson et al. 2024) and healthy controls. Future studies are recommended to go beyond using retinal images as the sole input in these models. Some authors (Ahn et al. 2023; Cheung et al. 2022; Kenney et al. 2022; Montolío et al. 2021, 2022, 2024; Wisely et al. 2022, 2024) have taken a step in this direction using demographic and clinical information along with retinal images; however, the diversity of such input data is still not optimal. In this regard, brain imaging findings from MRI studies and laboratory parameters can also be added and would likely lead to higher performance on the test dataset since in this case the models would be trained with more heterogeneous features. Retinal biomarkers can also be used for predicting the course of AD and MCI (Hua et al. 2022) and PD, similar to the approach employed by Montolío et al. (2021, 2022, 2024) in MS studies.

Specificity

It is essential that ML models learn retinal features that are unique to neurodegenerative disorders, not those for other conditions that lead to similar retinal changes. This could be achieved by controlling the potential confounding parameters that may confuse the model and contribute to misclassification errors. In this regard, most previous studies have excluded patients with concomitant eye disorders, and some adjusted for age (Tian et al. 2021, Wisely et al. 2024) and sex (Tian et al. 2021) between training and test datasets. In AD and MCI studies, however, excluding patients with ophthalmologic conditions such as diabetic retinopathy, age-related macular degeneration, and glaucoma may yield unrealistic results not applicable to routine clinical care. This is because these eye disorders are very prevalent among the elderly population, which also happens to have the highest proportion of individuals with AD and MCI. Apart from concomitant ocular diseases, it is broadly accepted that retinal thickness decreases during the normal process of healthy aging (Jorge et al. 2020). Even without excluding patients with such concomitant eye diseases, Cheung et al. (2022) and Shi et al. (2024) achieved impressive accuracy in discriminating individuals with cognitive dysfunction from those without, suggesting the existence of unique markers for cognitive impairment within OCT scans and fundus camera images that can be uncovered using ML. Thus, although it is of relevance to employ strict exclusion criteria for initial research, future studies should develop models that are able to detect AD and MCI even in the presence of common ophthalmologic disorders, as Cheung et al.'s (2022) and Shi et al.'s (2024) studies did.

Furthermore, ML models based on retinal imaging data can be trained in a way that allows them to differentiate between neurodegenerative diseases, moving beyond the conventional comparison between patients and healthy controls. This is critical since different disorders have varying prognoses and require specific treatment approaches. Misdiagnosis can have serious consequences, as a treatment suitable for one condition might worsen another. For example, while NMOSD and MS are associated with inflammation and demyelination in the CNS leading to many overlapping symptoms, the disease-modifying therapies that work well for MS could exacerbate NMOSD (Etemadifar et al. 2024, Kümpfel et al. 2024). Another example is the various types of dementia, including AD dementia, vascular dementia, dementia with Lewy bodies, PD dementia, frontotemporal lobe dementia, and so forth. These conditions share many similar clinical features, necessitating a detailed evaluation for accurate differential diagnosis. Therefore, it is not unusual for different types of dementia to be misdiagnosed; for example, most individuals with dementia with Lewy bodies are mistakenly identified as having AD (Palmqvist et al. 2009). The importance of distinguishing between dementia disorders in a timely manner cannot be overstated, as it plays a key role in clinical decision-making. For instance, patients with dementia with Lewy bodies face a more progressive disease course (van de Beek et al. 2020) and show more

severe sensitivity reactions to antipsychotic medications compared to AD patients (Ballard et al. 1998), and they have decreased responsivity to levodopa for parkinsonism symptoms compared to PD patients (Molloy et al. 2005). Advancements in neuroimaging technologies such as MRI, PET, single-photon emission computed tomography, and CSF investigations have brought us closer to accurately distinguishing neurodegenerative diseases (Bousiges & Blanc 2022); despite their effectiveness, these methods are costly, unavailable in many healthcare centers, and somewhat invasive. Retinal imaging, on the other hand, holds significant promise as a less invasive and potentially more accessible alternative for distinguishing these conditions.

Several studies have indicated that there may be distinct patterns of pRNFL thickness decrease in neurodegenerative diseases; that is, the superior and inferior quadrants in AD (Kashani et al. 2021), the inferior and temporal quadrants in PD (Kashani et al. 2021), and the temporal quadrant in MS (Birkeldh et al. 2017, Garcia-Martin et al. 2023, Schneider et al. 2013) are primarily involved. This difference might stem from the predominance of magnocellular ganglion cells, which are largely affected in diseases such as glaucoma, multiple system atrophy, and AD, in the superior and inferior sectors; in contrast, parvocellular ganglion cells, which are typically damaged in PD, Huntington's disease, and MS, are located in the temporal quadrant, corresponding to the papillomacular bundle (La Morgia et al. 2017). In NMOSD, RNFL and GCIPL thickness is more markedly reduced compared to MS. In addition, thickness decline is equally distributed in NMOSD (T.-Y. Lin et al. 2021), and more external layers such as the inner nuclear layer and outer nuclear layer may be affected as well. Nonetheless, a recent study found that outer retinal layers such as the cone photoreceptor layer are also involved in MS (McIlwaine et al. 2023). Moreover, in a recent work by Garcia-Martin et al. (2023), outer nuclear layer thickness was shown to act as a suitable measure for discriminating between MS and AD eyes. However, there is inconsistency between these statistical studies (Kashani et al. 2021), and the patterns of retinal loss, in a way discernable to humans, cannot reliably indicate a specific neurodegenerative disorder or even normal aging.

To date, Nunes et al. (2019) and Ciftci Kavaklioglu et al. (2022) have applied ML models to differentiate between neurodegenerative diseases using retinal images, specifically to solve AD versus PD (82% accuracy for discriminating between three classes, i.e., AD, PD, and healthy controls) and MS versus other demyelinating disorders {68% accuracy [other demyelinating diseases included myelin oligodendrocyte glycoprotein antibody–associated disease (Banwell et al. 2023), NMOSD, and monophasic acquired demyelinating syndromes]} classification problems, respectively. However, there is a major lack of research in this field when compared to studies that used input data other than retinal images for discriminating between neurodegenerative diseases; many of these studies yielded more favorable outcomes. For instance, an accuracy of 82% (sensitivity = 83%, specificity = 80%) has been achieved for discriminating MS from NMOSD (Etemadifar et al. 2024) using MRI features. Furthermore, different subtypes of dementia syndromes have been classified using data from MRI, single-photon emission computed tomography, electroencephalography, clinical assessments, and laboratory investigations (such as lipidomic profiles or infrared microscopic measurements of blood cells) with high levels of accuracy; some classification problems include dementia with Lewy bodies versus AD [accuracy of 79% (Nemoto et al. 2021), AUC of 0.77 (Shen et al. 2024), accuracy of 80% (Suzuki et al. 2022), accuracy of 87% (Yamada et al. 2022), accuracy of 89% (Iizuka et al. 2019), accuracy of 93% (Salman et al. 2020), accuracy of 100% (Garn et al. 2017)], PD dementia versus dementia with Lewy bodies [accuracy of 91% (Bougea et al. 2022)], and frontotemporal dementia versus AD [accuracy of 86% (Nguyen et al. 2023), accuracy of 99% (Hu et al. 2021), accuracy of 100% (Garn et al. 2017)]. To our knowledge, no ML study has focused on differentiating between dementia disorders based on retinal images, and only one has paid attention to differential diagnoses of MS (Ciftci Kavaklioglu et al.

2022). To draw a more reliable conclusion regarding the effectiveness of retinal images for distinguishing between different neurodegenerative diseases, more studies on larger scales are needed.

CONCLUSION

The use of ML models brings us closer to early and precise diagnosis of MS, AD, and PD, although we are still in the early stages of this promising era. Notably, the use of retinal images has yielded excellent results in automatically classifying these conditions, performing similarly to when other forms of input data are used to train models, such as MRI scans for MS (Nabizadeh et al. 2022b) and AD (Jo et al. 2019) or kinematic parameters for PD (Rana et al. 2022). Current diagnostic workflows for many neurodegenerative disorders rely heavily on imaging modalities such as MRI and investigations that require serum or CSF sampling; these approaches are typically invasive, expensive, and not readily accessible in regions with limited resources. Therefore, imaging the retina through noninvasive, low-cost, and feasible technologies such as fundus photography, OCT, and OCT-A, as well as more novel ones such as adaptive optics, can provide ML models with invaluable input features possessing high discriminating capacity. Future studies should focus on training models with multimodal retinal images, incorporated with other readily available input data types such as clinical parameters, obtained from large multicenter datasets. Additionally, it is highly encouraged to explore ML-based methods for differentiating neurodegenerative diseases from each other and from healthy aging using retinal images. Future researchers should also delve into novel feature extraction and interpretability algorithms to further advance the field.

SUMMARY POINTS

1. Machine learning (ML) offers an innovative approach to analyzing retinal imaging data for noninvasive diagnosis of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis.
2. Structural changes in retinal layers (e.g., thinning of the papillary retinal nerve fiber layer and the macular ganglion cell–inner plexiform layer) serve as promising biomarkers for identifying neurodegenerative conditions at early stages.
3. Retinal imaging is more accessible, cost-effective, and noninvasive compared to magnetic resonance imaging and cerebrospinal fluid analysis for diagnosing neurodegenerative disorders.
4. Studies demonstrate classification accuracies between 60% and 100% for neurodegenerative diseases using ML techniques.
5. Retinal imaging could be integrated into routine eye examinations to screen for asymptomatic or early-stage neurodegenerative diseases.
6. Novel imaging modalities such as hyperspectral imaging and adaptive optics may improve early detection and diagnosis capabilities.
7. Combining data from optical coherence tomography, fundus photography, and demographic and clinical information enhances the diagnostic performance of ML models.
8. Barriers such as data overfitting, lack of interpretability in ML models, and limited multicenter datasets must be addressed for clinical implementation.

FUTURE ISSUES

1. Research should focus on leveraging retinal imaging for diagnosing preclinical and prodromal stages of neurodegenerative diseases.
2. Establishing large, open-source, multicenter datasets with diverse demographics is critical for improving ML model generalizability.
3. Enhancing the interpretability of ML models is essential for gaining trust and adoption in clinical practice.
4. Retinal imaging could be further developed to monitor disease progression and therapeutic response.
5. Embedding ML systems in routine retinal imaging tools in clinics could revolutionize community-level screening for cognitive impairments.
6. Future research should explore the potential of technologies such as adaptive optics and hyperspectral imaging for early diagnosis.
7. Investigating retinal imaging for less common neurodegenerative diseases, such as Huntington's disease and amyotrophic lateral sclerosis, remains an untapped area.
8. Studies that integrate retinal imaging with systemic biomarkers and advanced imaging techniques to refine diagnostic accuracy are encouraged.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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