Retinal correlates of neurological disorders

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Abstract: Considering the retina as an extension of the brain provides a platform from which to study diseases of the nervous system. Taking advantage of the clear optical media of the eye and ever-increasing resolution of modern imaging techniques, retinal morphology can now be visualized at a cellular level *in vivo*. This has provided a multitude of possible biomarkers and investigative surrogates that may be used to identify, monitor and study diseases until now limited to the brain. In many neurodegenerative conditions, early diagnosis is often very challenging due to the lack of tests with high sensitivity and specificity, but, once made, opens the door to patients accessing the correct treatment that can potentially improve functional outcomes. Using retinal biomarkers *in vivo* as an additional diagnostic tool may help overcome the need for invasive tests and histological specimens, and offers the opportunity to longitudinally monitor individuals over time. This review aims to summarise retinal biomarkers associated with a range of neurological conditions including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and prion diseases from a clinical perspective. By comparing their similarities and differences according to primary pathological processes, we hope to show how retinal correlates can aid clinical decisions, and accelerate the study of this rapidly developing area of research.

Keywords: Alzheimer's disease, amyotrophic lateral sclerosis, biomarker, multiple sclerosis, neurodegeneration, optical coherence tomography, parkinson's disease, prion disease, retina

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Introduction

The eye provides a unique opportunity for direct observation of an extension of the central nervous system (CNS) through the clear optical media of the eye, consisting of the cornea, aqueous humour, lens and vitreous body. This has earned its title of 'window to the brain'. The ability to study the retina *in vivo* with noninvasive techniques brings with it the possibility of finding novel biomarkers and surrogate endpoints with which to diagnose and monitor neurological conditions. There are clear benefits of this approach over pathological diagnosis, not requiring the risk of neurosurgery, the removal of potentially important neurones, or postmortem diagnoses. In comparison to brain imaging, retinal imaging holds two key advantages: the lack of ionising radiation and the direct visualization and cellular resolution that is achievable,[1] with or without the use of contrast agents. However, the biological plausibility between correlates and disease must also be explored if the retina is to have a use as a surrogate marker in diseases of the CNS.[2,3]

Discovering biomarkers or 'surrogate markers' that predict future clinical outcomes in neurodegenerative conditions may provide a window of opportunity in which to start treatment early prior to secondary degenerative processes taking hold in response to a variety of initial triggers.[4] Given the poor ability of the human CNS to regenerate, minimising cell loss is likely to equate to better long-term outcomes.[5]

What is common to many neurodegenerative CNS disorders is the difficulty in early detection and a delay in diagnosis.[6] As well as the lack of specificity of symptoms, cognitive function testing has inherent issues of repeatability,[7] with day-to-day fluctuation sometimes being a key disease characteristic.[8]

In comparison, objective retinal biomarkers offer good repeatability and reproducibility.[9,10] The ease of retinal imaging coupled with its ability to monitor specific cell populations through time in the same individual are attractive prospects.

This review provides an update on retinal findings, correlates, and staging of patients with neurodegenerative conditions. A variety of studies are covered, including those attempting to show an association with retinal biomarkers and disease severity, duration and functional loss. Validation of these biomarkers is crucial to enable their use as surrogates in research trials and clinical practice.

Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia (60–70%) in which there is a long 'preclinical' phase,[11] with pathological features thought to appear years prior to symptoms.[12] Diagnostic delay of AD has detrimental effects on efficacy of pharmacological treatments as well as wider ranging social and economic effects.[13–15] Often manifesting in mild, nonspecific cognitive and psychological disturbances, early disease is often challenging to differentiate from the 'normal' ageing process. Similarly, concomitant ocular and systemic neurodegenerative and cardiovascular conditions that may contribute to retinal nerve fibre layer (RNFL) thinning such as glaucoma and microvascular ischaemia become more prevalent as age increases. These confounders are challenging to identify and rarely controlled for.

Only 8% of patients with mild cognitive impairment (MCI) have been shown to progress to AD.[16,17] Biomarkers have been introduced into the clinical criteria for AD,[18] including detection of amyloid-beta and tau deposition using positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) sampling,[19–23] as well as detection of neuronal injury using fluorodeoxyglucose (FDG)-PET and single photon emission computed tomography (SPECT) imaging.[19] However, methods to image individual cells and distinct populations of cells are still lacking.

Pathological studies

AD is macroscopically characterised by loss of brain volume, with heterogenous patterns of atrophy seen in the medial temporal lobes, paralimbic, temporal and parietal cortices on structural mag-netic resonance imaging (MRI).[24,25] Microscopically, characteristic amyloid-beta plaques in the brain parenchyma, and hyperphosphorylation of tau proteins forming neurofibrillary tangles lead to neuronal and synaptic degeneration, most commonly attributed to abnormal processing of the amyloid precursor protein (APP).[6,26]

Visual abnormalities in AD are often detectable early in the disease, and therefore provide the rationale behind retinal biomarkers in early AD. Deficits can be found in visual acuity,[27] colour and motion perception,[28] contrast sensitivity and visual fields.[29–31] Pathological studies attempt to explain this, demonstrating diffuse axonal degeneration with retinal ganglion cell (RGC) and RNFL loss post mortem.[32–35] Disruption of circadian rhythm has been proposed to be due to the loss of melanopsin RGCs, with reduced numbers and abnormal morphology in AD.[36] Despite multiple transgenic models of AD demonstrating amyloid-beta plaques and tau accumulations,[37,38] human evidence for these in the retina remain controversial, with amyloid-beta plaques reported to be present and absent when compared with age-matched controls,[37–40] with explanations offered including different assays or methods of tissue preparation.[40] Although hyperphosphorylated tau protein has been detected in the retinas of patients with AD,[41] the characteristic aggregates have not.[32,40] Evidently, it is still unclear as to whether AD changes seen in the eye are as a primary or secondary consequence of amyloid-beta.

In an AD mouse model (APPSWE/PS1ΔE9) intravenous curcumin was used to demonstrate retinal amyloid-beta plaques, verified with immunohistochemistry, and their accumulation with disease progression.[38] Curcumin is a polyphenol found in turmeric (*Curcuma longa*) and is an attractive, inherently fluorescent, diagnostic agent as it is also a novel neuroprotective treatment under investigation.[42,43] Supporting amyloid-beta accumulation in the AD retina, proof-of-concept data has demonstrated retinal amyloid curcumin visualisation, with a 2.1-fold increase in AD patients *versus* age-matched controls ($p=0.0031$).[44] Hyperspectral imaging (HSI) microscopy is a novel imaging technique that has shown promise by analysing the 'spectral signature' reflected from the retina, reporting amyloid-beta deposition in postmortem retinal samples and *in vivo* animal studies.[45] This latter study also claimed to have detected amyloid-beta

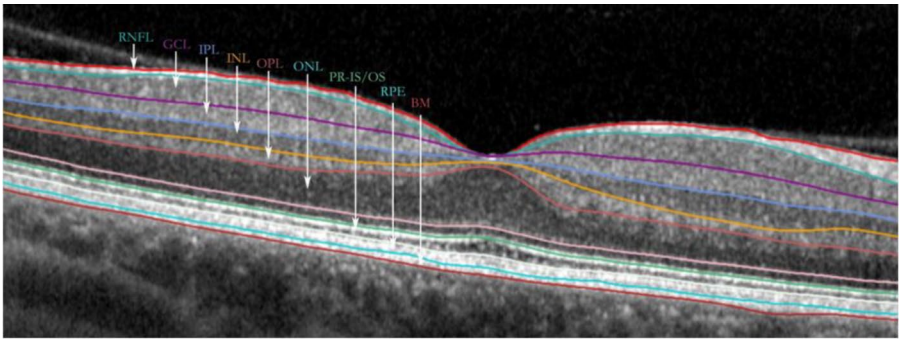

Figure 1. A spectral domain OCT cross-sectional macula scan of the retinal layers.
BM, Bruch's membrane; GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; OCT, optical coherence tomography; ONL, outer nuclear layer; OPL, outer plexiform layer; PR IS/OS, photoreceptor inner segment/outer segment; RNFL, retinal nerve fibre layer; RPE, retinal pigment epithelium.

plaques in mice retinas prior to plaque development in the brain, critical for early diagnosis.

OCT in AD

Optical coherence tomography (OCT) is a rapid, noninvasive, reliable and reproducible imaging tool using near-infrared light to form cross-sectional images of the retina and optic disc.[46,47] Axial resolutions of up to 5–7 microns enable individual retinal layers to be studied using the principles of interferometry (Figure 1).[48] AD findings of atrophy in the anterior visual pathways post mortem have been associated with OCT evidence of RNFL thinning around the optic nerve (peripapillary RNFL, pRNFL) (Figure 2).[32] This effect in AD has been noted around the optic disc globally,[49–72] but also to have a preponderance in superior and inferiorperipapillary sectors,[49,50,52–55,57–59,61–69,71–75] and, to a lesser extent, in the nasal and temporal sectors also (Table 1).[52,55,56,58,62,64–66,71,72,74,75] In contrast, a smaller proportion of studies deny finding this association.[76–79] Many of these studies have been included in meta-analyses supporting RNFL thinning in AD.[80,81] Rate of RNFL thinning also appears greater in AD compared with 'normal' ageing over a 12-month period, especially in the inferior quadrant, and in parallel with cognitive decline,[54] thus suggesting the rate of pRNFL thinning could function as a potential surrogate marker in itself, as has been proposed in glaucoma.[82] Furthermore, the inferior pRNFL sector has been proposed as the most sensitive for detecting cognitive decline in AD.[68,83] These patterns have also been functionally correlated to pattern electroretinogram (ERG) abnormalities[72,75,84] and visual function tests.[50] The challenge will be to separate pathological progression from RNFL thinning due to ageing alone.[85] RNFL thinning has been reported to correlate with scores of cognitive function[53–55,86]; however, this not supported by

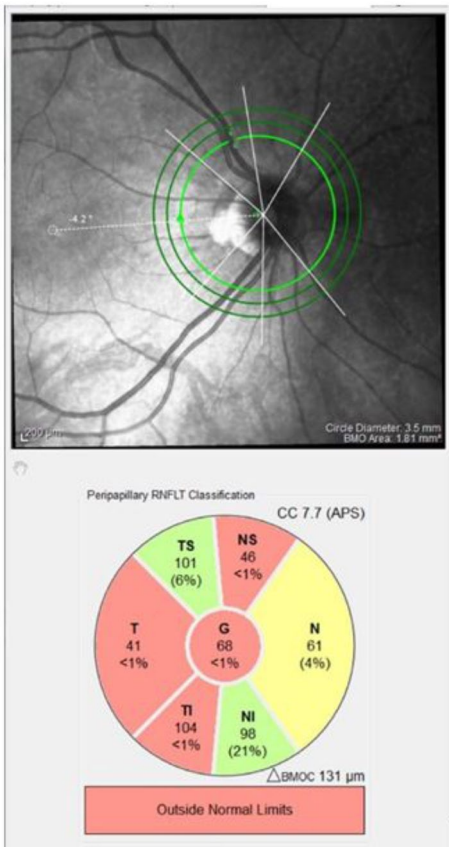

Figure 2. An SD-OCT pRNFL scan of the right eye of a patient who has had ON, demonstrating temporal pRNFL thinning. Red sectors indicate those outside normal limits.
pRNFL, peripapillary retinal nerve fibre layer; ON, optic neuritis; SD-OCT, spectral domain optical coherence tomography.

Table 1. A summary of studies reporting sector analysis of peripapillary RNFL changes in Alzheimer's disease, mild cognitive impairment (MCI) and Parkinson's disease. Effect size has been calculated as mean percentage difference in average RNFL thickness per sector in disease *verus* healthy controls.

Alzheimer's disease	OCT type	Global	Superior		Temporal	Inferior		Nasal
Study			**ST**	**SN**		**IT**	**IN**	
Ascaso[65,b]	TD	45.4%	49.8%		28.6%	44.3%		53.1%
Bambo[62]	SD	12.1%	70.1%		5.3%	10.4%		15.8%
Cheung[63]	SD	4.0%	7.1%		0.6%	5.5%		–0.6%
Choi[55]	SD	7.5%	11.2%		3.3%	5.3%		12.5%
Cunha[53]	SD	9.4%	9.6%		8.3%	14.6%		4.5%
Cunha[52]	SD	11.8%	18.0%	10.5%	10.6%	12.4%	10.1%	8.4%
Eraslan[61]	SD	8.3%	12.3%	8.4%	[a]	5.5%	5.9%	[a]
Gao[58]	SD	13.7%	14.1%		16.6%	16.0%		5.2%
Garcia-Martin[56]	SD	3.7%	3.2%	5.5%	6.1%	5.7%	1.6%	0.7%
Gharbiya[79]	SD	–0.9%	1.2%		–3.9%	–2.3%		–1.6%
Gunes[64]	SD	24.2%	19.5%		18.5%	29.2%		23.1%
Iseri[71]	TD	25.6%	19.6%		10.8%	31.4%		40.6%
Kesler[68]	TD	10.7%	10.5%		9.4%	14.3%		13.4%
Kirbas[67]	SD	14.3%	32.0%		4.0%	1.9%		1.3%
Kromer[74]	SD	[a]	[a]	[a]	[a]	[a]	[a]	[a]
Kwon[73]	SD	4.7%	7.7%		3.9%	–0.1%		2.9%
La Morgia[57]	SD	7.6%	11.5%		3.1%	4.9%		10.9%
Larrossa[66]	SD	3.0%	4.0%		5.1%	5.6%		2.6%
Liu[59]	SD	8.8%	9.0%		10.8%	10.4%		21.6%
Moschos[75,b]	TD	[a]	10.5%		12.9%	16.0%		11.4%[e]
Parisi[72]	TD	50.7%	36.8%		77.2%	39.5%		59.8%
Pillai[77]	SD	–4.1%	–1.1%		–4.5%	–5.1%		–8.0%
Polo[50]	SD	7.0%	8.0%		5.9%	8.8%		3.6%
Trebbastoni[54]	SD	0.9%	3.3%		–1.4%	–1.0%		2.9%
MCI - Study	**OCT type**	**Global**	**Superior**		**Temporal**	**Inferior**		**Nasal**
Ascaso 2014	TD	17.3%	23.8%		11.2%[d]	19.2%		12%
Cheung 2015	SD	1.3%	2.3%		0.6%	1.9%		–1.2%
Gao 2015	SD	6.5%	8.6%		11.4%	3.0%		1.7%

(Continued)

Table 1. (Continued)

MCI - Study	OCT type	Global	Superior		Temporal	Inferior		Nasal
Kesler 2011	TD	9.4%	8.2%		5.5%	12.6%		14.8%
Liu 2015	TD	4.9%	3.4%		5.4%	4.4%		6.7%
Pillai 2016	SD	−5.3%	−3.1%		−7.0%	−7.4%		−4.2%
Parkinson's Disease	**OCT type**	**Global**	**Superior**		**Temporal**	**Inferior**		**Nasal**
Study			**ST**	**SN**		**IT**	**IN**	
Aaker[87]	SD	0.0%	3.0%	−3.8%	4.1%	0.0%	0.0%	−2.7%
Albrecht[88]	SD	1.8%	3.7%		1.1%	−0.4%		−2.1%
Altintaş[89]	TD	14.8%	10.1%		1.4%	12.2%		26.8%
Archibald[90,b]	TD	−4.6%	−9.4%		1.5%	1.6%		−13.4%
Aydin[91]	SD	6.9%	7.4%	8.4%	2.7%	2.7%	8.1%	5.6%
Bittersohl[92]	SD	0.4%	1.3%	−1.1%	1.5%	6.1%	−1.1%	−0.1%
Garcia-Martin[93]	SD	2.2%	2.2%		6.9%	1.5%		0.9%
Inzelberg[94]	TD	[a]	−3.8%		22.0%	26.0%		16.7%
Jiménez[95]	TD	17.4%	7.7%		6.4%	6.9%		10.7%
Kirbas[96]	SD	14.5%	2.3%		12.8%	1.8%		0.0%
La Morgia[97]	TD	5.2%	4.4%		10.6%	3.0%		5.3%
Matlach[98]	SD	5.4%	8.3%		2.5%	3.4%		2.8%
Moschos[99]	TD	7.5%	3.0%		12.2%	10.2%		5.5%
Moschos[100]	SD	8.8%	4.8%		14.6%	2.5%		5.2%
Pillai[77]	SD	−3.7%	−3.8%		−0.2%	−2.9%		−8.6%
Rohani[101]	SD	11.8%	14.6%		9.2%	13.9%		8.4%
Satue[102]	SD	7.1%	7.0%		5.9%	7.0%		0.3%
Sen[103]	SD	8.0%	3.2%		[a]	11.0%		[a]
Sengupta[104]	SD	19.5%	26.1%	5.9%	28.9%	32.4%	8.9%	11.2%
Tsironi[105]	TD	−0.1%	4.6%		−2.2%	−1.2%		−2.8%
Visser[106]	SD	1.1%	−0.9%		11.4%	7.6%		−1.5%

[a]Data not available.
[b]Mean of right and left eyes.
[c]Significance data missing
[d]OD significant only
[e]OS significant only
Grey shading indicates statistical significance as chosen by each study investigator.
IT, inferotemporal; IN, inferonasal; SD, spectral domain; TD, time domain; ST, superotemporal, SN, superonasal.

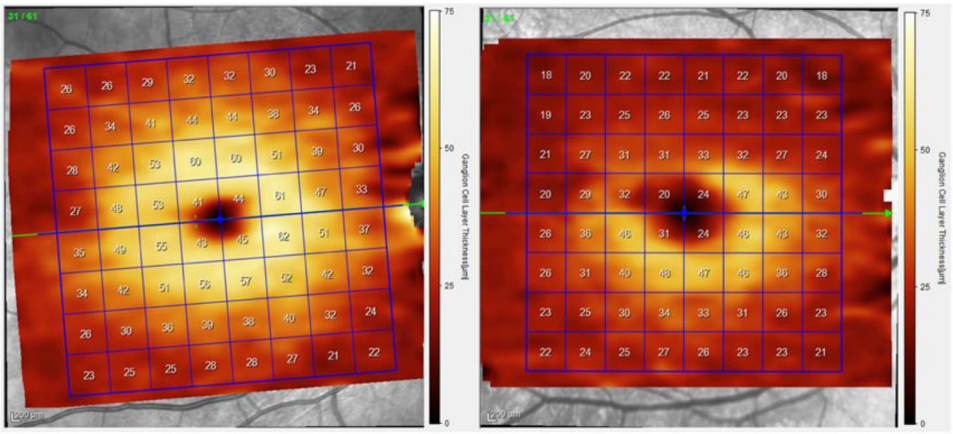

Figure 3. Ganglion cell layer thickness maps from a segmented SD-OCT scan of the macula from the right eye of a healthy (left) and ON (right) patient. The segmented GCL is selected in this example, demonstrating superior loss of ganglion cells and corresponding thinning.
GCL, ganglion cell layer; ON, optic neuritis; SD-OCT, spectral domain optical coherence tomography.

other studies,[64] possibly affected by mental fluctuation and disease heterogeneity. Retinal correlates and patient-related endpoints such as quality-of-life (QoL) scores are still to be assessed in a holistic manner.

OCT imaging of the macula and posterior pole also allows for further examination of retinal cell populations (Figure 3), of which the inner layers, including the RNFL, ganglion cell layer (GCL) and inner plexiform layer (IPL), are of most current interest in neurodegeneration. GCIPL (ganglion cells and inner plexiform layers combined) thinning has been observed by multiple studies in AD,[49,51,53,55,56,61,63,66,76,107] with some studies showing diagnostic superiority when compared with pRNFL changes.[63] Changes in both macular volume and GCIPL thickness have been found to correlate with mini mental state examination (MMSE) scores (average GCIPL $r=0.487$, $p=0.003$).[51,71] Extended-depth imaging (EDI) using OCT has been used to consistently report choroidal thinning to be associated with AD, further hypothesising that cerebrovascular disease and hypoperfusion may play a common role in CNS and chorioretinal atrophy.[79,108–110] Furthermore, these findings have also been also associated with MMSE scores.[109]

The risk of AD rises from 1 to 2% per year in the normal population to 10–15% in those classified with MCI.[111] Therefore, RNFL has been assessed as a correlate with long-term prognosis. Global differences in pRNFL in mCI *versus* healthy controls have been reported in several studies (Table 1),[49,51,59,60,65,68,70] and specifically inferior, superior, and even temporal sectors.[49,58,59,68] To differentiate stable MCI and those progressing to AD, several peripapillary and macular parameters correlate with risk of progression to AD including temporal RNFL thickness and global GCIPL thickness.[55] Rate of decay in RNFL thickness has also been reported to be greater in AD than MCI.[49] Evidence suggesting retinal correlates can predict future AD in 'healthy' individuals, similar to CSF amyloid-beta levels is limited,[112–114] with confirmatory studies required. Clearly, differentiating AD and non-AD cognitive decline using OCT parameters will present challenges given the correlations with cognitive decline in general.[115]

Other retinal imaging in AD

Retinal oximetry is a metabolic imaging technique that estimates the oxygen saturation of haemoglobin in retinal arterioles and venules. Most widely studied in ischaemic diabetic retinopathy and vascular occlusions, some studies have shown a potential role in AD. Higher arteriolar and venular oxygen saturations in moderate AD compared with healthy individuals[116] has been reported; however, the absence in early disease limits early diagnosis potential. Uptake of this technique into clinical practice has been limited thus far due to poor disease specificity and the unclear mechanism behind this correlate. Arteriolar and venous pulsations have also been

shown to correlate with amyloid-beta imaging in the brain, with increased arteriolar amplitudes and decreased venous amplitudes correlating with neocortical 18F-florbetaben (FBB)-positron emission tomographic amyloid imaging.[76] Optic disc colour has been proposed as a biomarker in AD, with pallor suggested as an indicator of axonal loss. Although significantly correlated with AD ($p < 0.003$), the diagnostic prowess and dynamic range of this technique are still to be fully revealed.[62] The likely poor disease specificity may limit its potential in diagnosis.

The role of OCT angiography in CNS conditions is still being explored,[117] with the foveal avascular zone (FAZ), retinal vascular density and inner foveal thickness shown to differ in AD,[118] while other parameters such as outer retinal and choroidal flow-rates have not.[119] This requires further studies to corroborate these results.

An emerging imaging biomarker for clinical trials is DARC (detection of apoptosing retinal cells).[120] Using confocal scanning light microscopy, this technique utilizes intravenous fluorescent annexin-A5 binding to phosphatidylserine on the cell membrane in early apoptosis. The Phase I trial primarily confirmed safety and tolerability, and also observed differences between glaucomatous and healthy eyes.[121] Given the similar loss of retinal ganglion cells in AD, there is potential for the technique in early diagnosis of AD. A phase II trial has been completed with the results yet to be published, including a cohort of people with Down syndrome, known to display similar amyloid-beta deposition to that in AD.[122] The lack of consistent findings of human retinal plaque deposition leaves open the hypotheses of secondary neurodegeneration in AD. Many other genetic risk factors identified in AD may also be contributing, distinct from amyloid precursor protein and apolipoprotein E.[123]

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative condition causing rigidity, tremor and bradykinesia.[124] In addition, cognitive, autonomic and visual functioning can be affected.[125] Its pathological hallmark is intraneuronal aggregation of α-synuclein, which in the substantia nigra leads to loss of dopaminergic neurones and the extra pyramidal symptoms.[126] Postmortem evidence has similar features in the retinas of PD patients, including reduced dopamine content and α-synuclein accumulation,[127] specifically the inner nuclear layer (INL), inner plexiform layer and the ganglion cell layer.[128] Combining biomarkers is the current approach to diagnosing PD, integrating brain imaging (SPECT), PET and MRI with genetic and biochemical biomarkers.[129] Retinal imaging could emerge as a possible biomarker that has the potential to add another dimension to this matrix. In its investigation, careful consideration is yet to be given to controlling confounding ocular and systemic conditions more commonly found in older people, that may also affect RNFL thickness.

OCT tomography in PD

RNFL thinning in PD has been studied comprehensively by many researchers (Table 1), with many reporting pRNFL thinning. The frequency of this finding is noticeably less common than in AD (see Table 1), with a different peripapillary distribution. Significant thinning in global, superior, inferior, nasal and temporal pRNFL have been observed. [89,91,93–97,99–104,106,119] In contrast, several studies have reported no significant differences.[77,87,88,90,92,105] A total of 13 case-control studies were included in a meta-analysis, supporting pRNFL thinning in all four quadrants (WMD = 25.76, 95% CI: 28.99–22.53, $p = 0.0005$).[130] Reports concerning laterality have been conflicting, with one study observing a *post hoc* association between superior quadrant pRNFL thinning in eyes ipsilateral to the side most affected by bradykinesia.[98] However previous work has shown the contrary[97]. Foveal contour has also been studied, characterising the breadth and depth of the foveal pit. Superior/inferior sloping was found to be the most shallowed in PD, with an error rate of around 34% at detecting PD from healthy controls.[131] Interocular asymmetry of foveal contour has also been proposed as a feature of PD.[132]

As with pRNFL findings, results of macular OCT segmentation have been inconsistent at demonstrating differences between PD patients and healthy age-matched controls, concluding both significant and nonsignificant differences between groups.[87,89,98,133–137] To our knowledge, all studies examining both pRNFL and mRNFL thickness in PD have had a similar conclusion with both parameters, be this either no difference or a significant difference.[87,89,134–137] This may indicate

similar sensitivity of pRNFL and mRNFL OCT scanning as a biomarker in PD, or indicate a correlation of these two parameters with disease severity. Conflicting results are likely due to variability in disease severity between study populations, and the challenges in its quantification. Given that studies examining RNFL thinning in different stages of disease indicate progression towards global thinning across all sectors, any disease specificity may be found only in the order or rate at which they are affected (Table 1).

Establishing the role of OCT in assessing the rate of progression associated with functional decline is important. This may provide prognostic information for patients and surrogacy for therapies in clinical trials. A 5-year prospective longitudinal trial has been completed using OCT imaging and functional testing in order to investigate several aspects of this paradigm.[134] OCT demonstrated increased rates of RNFL thinning over superotemporal and temporal peripapillary sectors, and in seven of the nine macular zones in PD. Furthermore, moderate correlations were found between low contrast visual acuity, superotemporal and inferotemporal pRNFL sector thinning and symptom severity.[138] Mild association between superotemporal pRNFL thinning and progression of Parkinsonian symptoms was seen in the PD group ($r=-0.389$, $p=0.028$), suggesting OCT progression could play a role in predicting functional and visual outcomes, and possibly even benefits gained from treatment in a clinical trial setting. However logistic regression revealed no parameters of visual function that were able to predict symptomatic decline. Confounding these studies are the difficulties encountered with testing visual function in patients with advanced dementia.

RNFL thinning on OCT imaging has also been correlated with retinal function and dopaminergic activity in the substantia nigra using, microperimetry and PET/MRI imaging.[139] RNFL thinning in the temporal and inferior foveal zones was observed in PD when compared with healthy age-matched controls. Retinal thinning in certain sectors was also found to correlate with macular sensitivity and dopaminergic loss in the substantia nigra. The hypothesis that a pathologic connection exists between retinal and nigral dopaminergic cells could raise useful biomarkers in trials of neuroprotective treatment strategies. Similarly, there is a partial treatment effect with l-DOPA on recovering contrast sensitivity in PD patients.[140] A further study has suggested dopaminergic treatment effect is visible in retinal changes; however, this is only in the absence of a significant difference between untreated, and treated patients who have more severe disease.[103]

Disease-specific OCT biomarkers still remain to be found, with some studies failing to show any differences between RNFL characteristics in different dementia types.[77] The predilection for temporal RGC loss in PD correlates with the papillomacular bundle and parvocellular pathway, which is distinct from that reported in AD, where the RGCs in the magnocellular pathways are commonly seen to be preferentially affected.[141] Selective thinning of the photoreceptor layer *in vivo* has also been reported in PD as has generalised retinal thinning,[133,136,142] to accompany similar postmortem evidence in humans and animal models.[127,143] Considering the dopaminergic input to photoreceptors in the retina, trans-synaptic degeneration may explain this observation, preferentially noted to affect blue cones.[144,145] Less dramatic RNFL thinning in PD may be explained by the reduced number of RGCs with dopaminergic inputs.[146] The more varied OCT findings in PD compared with AD reflect the wider variety of phenotypes contained in the PD spectrum, in which various diseases display Parkinsonian-like traits.[147] The observation that mutations in genes such as LRRK2 and those encoding α-synuclein and tau can cause varying clinical syndromes does not support a purely pathogenetic disease process or primary retinal pathology, but implicates environmental factors as supported by associations seen with heavy metal exposure and other environmental toxins.[148,149]

Combining structural and functional biomarkers is likely to increase diagnostic yield in PD using the retina. For example, parafoveal thickness and contrast sensitivity provided an area under the receiver-operator characteristic (AUROC) curve of 0.784, improving to 0.844 with the addition of visual evoked potentials.[150] The reliance on non-imaging parameters may also become necessary in advanced disease due to tremor precluding the acquisition of high-quality images.

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune demyelinating disorder of the CNS.[151] Approximately 2 million people are affected worldwide, making it

one of the most common causes of nontraumatic neurological disability affecting young adults.[152] Demyelination leads to neuro-axonal loss causing progressive neurological disability and functional decline.[153]

Multiple clinical features affecting motor, sensory, visual or autonomic pathways exist, commonly presenting in the third or fourth decades with a female predominance. MS may be categorised according to the timing and pattern of disease.[154] The commonest type is relapsing-remitting (RRMS, 85%), in which 18% evolve to secondary-progressive disease (SPMS); 15% exhibit progressive disease at onset, with or without relapses.[155,156]

Ophthalmic involvement is a frequent cause of disability encompassing optic neuritis (ON), uveitis, internuclear ophthalmoplegia (INO) and nystagmus. Half of patients will experience ON over the disease course.[157,158] It is the presenting feature in 30% of cases, manifested as retrobulbar pain on eye movement, proceeding to visual loss and dyschromatopsia. Recovery is often incomplete due to demyelination and axonal loss.[159,160] Timely recognition of atypical causes of ON can prevent irreversible visual loss or side effects by inappropriate usage of drug therapy.[161] OCT has proven useful for diagnosis and monitoring of ON longitudinally.[162] Functional connectivity by adaptive reorganisation in the visual system occurs following ON.[163]

In combination with clinical evaluation, several clinical and paraclinical biomarkers inform the MS diagnostic process. Oligoclonal bands in the CSF are an indicator of CNS immune activity, and MRI detects inflammation and atrophy within the brain and spinal cord.[160] The revised McDonald diagnostic criteria have a high degree of sensitivity and specificity in early disease.[164–167]

OCT in multiple sclerosis

Numerous studies have shown that MS sufferers display neurodegenerative and inflammatory signs in the retina, mirroring those of the CNS seen on MRI.[164] OCT quantification of RNFL thickness in MS was first described in 1999.[168] Subsequent reports have been made of RNFL thickness and other OCT biomarkers with and without ON *versus* healthy controls.[168–171] Unmyelinated RGC axons within the RNFL provide an objective indicator of axonal loss in the retina, and potentially the CNS globally. The presence of blood vessels contributes to 13% of RNFL thickness, altering the reliability of measurements, especially in severe thinning.[172]

RNFL thickness is reduced in ON and MS patients compared with healthy controls (Figure 2). This is seen using OCT in eyes with prior ON,[171,173–187] particularly temporally and inferiorly.[176,177,188] The majority of studies also identified reduced pRNFL thickness in MS patients without prior history of ON (MS-NON), although to a lesser extent.[189] Temporal preponderance may be explained by the presence of the large papillo-macula bundle containing a high density of parvocellular axons appearing to be most susceptible to oxidative stress.[190] Increased RNFL thinning in ON is associated with incomplete visual recovery.[191] Few studies, however, report RNFL thinning after ON to be similar in affected and unaffected eyes.[192] RNFL thickness is also a biomarker for MRI-estimated whole brain atrophy in MS patients.[193,194]

RNFL thinning in the absence of ON suggests underlying CNS disease activity. RNFL thickness was inversely related to optic radiation lesion volume in patients with MS, and CIS patients including those without previous ON.[195] RNFL thinning may therefore be related to ON-related retrograde degeneration due to damage propagating backwards from the site of injury.[196] It may be either trans-synaptic *via* the lateral geniculate nucleus for posterior visual pathway lesions, or direct retrograde degeneration, beginning at the ganglion cell axons (RNFL), progressing to GCL cell bodies and finally IPL dendrites.[186] Wallerian or anterograde degeneration has also been proposed, due to pathology in the retinal layers leading to RNFL thinning.[197] Animal studies have suggested this may not play a major role in MS pathogenesis however.[198]

The GCIPL thickness is often measured together due to low contrast differences of OCT images. GCIPL comprises RGC cell bodies and retinal astrocytes. As the highest density of RGCs is at the macula, GCIPL is regularly measured as perifoveal volume in cubic millimetres.[199] Thinning of the IPL and GCL has been reported in isolated episodes of ON in clinically isolated syndrome[183] (Figure 3).

Macula volume measures the size of axons and their associated ganglion cell bodies, with studies demonstrating reduction compared with age-matched controls in both MS-NON and MS-ON eyes.[182,199,200] However, other studies have reported conflicting results,[201] suggesting inconsistencies in disease duration and severity amongst study cohorts.

Whilst pRNFL and macula volume are the most common OCT markers used in MS, there has been increasing interest in the INL and, less so, in outer retinal layers. The INL contains the cell bodies of the horizontal, bipolar and amacrine cells. Thinning of the INL has been reported in PPMS.[202] INL thickening is associated with a range of disorders including inflammatory disease activity in MS.[203–205] It may also be characterised by microcystic macular oedema (MME),[205–207] the presence of INL cysts occurring with RNFL thinning.[207,208] MME was previously thought to reflect blood–retinal barrier breakdown with or without microglial inflammation; however, the absence of leakage on angiography refutes this.[209] Impaired water or potassium homeostasis have also been proposed as contributing factors.[207] The most likely cause is of retrograde degeneration of the inner retinal layers causing impaired macula fluid resorption.[210] INL thickness may prove useful for monitoring response to immunotherapy in inflammatory states.[211]

Thickening of the outer nuclear layer (ONL) (containing photoreceptor cell bodies) and photoreceptor layer followed by thinning has been reported in ON. Outer retinal dysfunction measured by ERG has also been reported despite normal sublayer thickness measurements.[212–214] Transient ONL thickening has also been reported during the active phase of ON, alongside reduced RNFL and total macula volume.[213] ONL thickening was observed 4 months following ON, and correlates well with GCIPL thinning.[212] From 4 to 12 months ONL thickness returned to baseline. Reports have also identified no ONL differences between MS patients and healthy controls, supporting presence of thickening in active inflammation only.[186,202]

Retinal vascular changes in MS

OCT angiography (OCTA) detects the motion of red blood cells, providing noninvasive angiography and flow rates of the deep and superficial retinal plexuses, with potential in the management of MS and other neurological disorders.[215] There is parafoveal vessel reduction in superficial and deep vascular plexuses in MS independent of ON history.[216,217] This correlates with pRNFL and GCIPL layer thinning and also with general disability level, as assessed by the Extended Disability Status Scale (EDSS).[216] A longitudinal study, however, showed an increase in parafoveal vessel density over a median follow-up period of 1 year, particularly in patients who demonstrated disease stability.[218] There is evidence of reduced flow velocity in parafoveal and optic nerve head vessels in eyes with prior ON, compared with MS-NON eyes and healthy controls.[219,220] This may reflect the reduced metabolic demand of the retina due to the retinal thinning, decreased perfusion due to inflammation-induced endotheliopathy and a retinal increase of hypoxia-inducing factors during neurodegeneration.[156] However, image artefacts in OCTA have been reported to occur frequently.[221] Further studies are needed to improve acquisition and analysis of OCTA images and to assess the course of MS longitudinally to identify useful disease correlates.

OCT to predict visual prognosis and MS subtypes

The use of OCT retinal correlates to measure the severity or duration of MS could prove inexpensive and rapid compared with repeated MRI studies, and more precise than clinical evaluation. Active MS, as identified clinically or radiologically, is associated with accelerated RGC and IPL thinning, fastest in those with clinical relapse, gadolinium-enhancing lesions, and new T2 lesions simultaneously.[222] The most severe subtypes of MS showed more marked decreases in RNFL and macula volume than RRMS cases.[170,223] Longitudinal studies show progressive RNFL and macula volume reductions in MS patients within 1 year, in particular affecting the mean RNFL thickness even in the absence of ON.[224–226] Herrero's study, which followed patients up over 3 years, identified increased RNFL loss in the superior and inferior regions.[226] After 2 years, macular GCIPL layer thinning was also identified. These changes were most apparent in the early phase of the disease, perhaps indicating a later plateau.[227] Contradictory results using time-domain OCT to monitor RNFL thickness have also been reported; however, this was

using inferior resolution technology.[228] In patients with clinically isolated syndrome, OCT assessment of GCIPL and pRNFL thinning are valuable predictors of future MS diagnosis.[229] This subset of patients appear to behave similarly to patients with radiologically isolated syndrome (RIS), in which there is an incidental finding of demyelination on MRI. These patients have reduced RNFL and increased INL and ONL volumes, correlating with prospective disease activity and progression in MS.[230]

Studies have suggested that OCT may predict levels of disability associated with MS and QoL outcomes.[231,232] RNFL thickness correlates with visual acuity and EDSS,[200,233] with GCIPL thinning also associated with low-contrast visual acuity.[212,213] Other studies have demonstrated thinner GCIPL and RNFL layers in MS patients are associated with worse visual functional and QoL assessments.[186,234]

Visual evoked potentials (VEP) and pattern electroretinograms (PERG) are altered in MS[200,235–237] showing prolonged P(100) latencies and normal amplitudes. However, studies are contradictory as to whether VEP findings correlate with RNFL thickness, perhaps suggesting that RFNL loss detected by OCT in some cases is insufficient to cause functional deterioration.

A study evaluating VEPs, in particular P(100) latency, amplitude and waveform morphology, demonstrated a correlation with MS as assessed by the Kurtzke EDSS and whole brain atrophy (BPF).[236] A moderate correlation between RFNL thickness, EDSS score and QoL (based on the 54-item Multiple Sclerosis Quality of Life Scale score) was identified.[177] The use of functional tools such as VEPs and PERG may be important for identifying subclinical axonal damage in the early stages of MS.

OCT in paediatric patients has been shown to be sensitive to retinal changes in clinical ON, whereas VEPs are useful to detect disseminated lesions in the visual pathway. One study demonstrated RNFL thinning in those with prior ON and also prolonged VEP latency (>109 ms) regardless of ON history.[238]

A growing body of evidence supports the value of OCT in monitoring MS disease progression, in particular, the use of RNFL thinning to predict QoL. Due to the lack of disease specificity, OCT must be used in combination with MRI and clinical assessment. Combining these with VEPs and PERG may prove useful to link structural and functional change as biomarkers for axonal degeneration.

Neuromyelitis optica spectrum disorders

OCT has been valuable in differentiating ON and MS from differential diagnoses, including neuromyelitis optica spectrum disorders (NMOSD), MOG-IgG seropositive autoimmune inflammatory disorders, and Susac syndrome. NMOSD are rare, chronic autoimmune inflammatory CNS diseases.[239] Autoantibodies against the aquaporin-4 (AQP4) water channel located on astrocyte foot processes lead to recurrent attacks of ON, myelitis and brainstem syndromes.[240–242] IgG and complement deposition, reduced AQP4 expression, astrocytopathy, neutrophil accumulation and demyelination with axonal loss are the underlying pathogenic processes.[243] NMOSD-ON is commonly more severe, bilateral and recurrent than MS-ON. Despite treatment, recovery is often incomplete and remission rarely occurs. Relapsing NMOSD accounts for approximately 85% of cases, wherein neurologic defects frequently accumulate.

Whilst it is most commonly initially misdiagnosed as MS, clinical, immunological and imaging studies establish NMOSD as firmly separate from MS, with treatment strategies for MS ineffective and even harmful in NMOSD.[244,245] Treatment strategies for acute relapses include high dose intravenous or oral steroid therapy and apheresis therapies, including plasma exchange and immunoabsorption.[246] For long-term treatment, immunosuppressive drugs are used in a stepwise approach.[247]

In NMOSD, ON often occurs bilaterally, followed by severe structural retinal damage without segmental predominance, and profound visual impairment,[205,248,249] with diffuse RNFL thinning seen by OCT in NMOSD patients, when compared with idiopathic disease.[250] This is in comparison to MS ON, where temporal RNFL is preferentially thinned.[205,251] Nasal thinning of the pRNFL persists in NMOSD in eyes, both with and without prior ON. Temporal thinning of the mRNFL also persisted in NMOSD-ON compared with MS-ON.[251]

A recent study demonstrated severe bidirectional degeneration in the visual pathway following NMOSD-ON, in particular the lateral geniculate nucleus volume, primary visual cortex volume and decreased integrity of optic radiations, compared with NMOSD without ON.[252] Furthermore, there is increased functional connectivity in the primary and secondary visual networks in NMOSD, which correlates with increased visual impairment and reduced structural retinal damage on OCT.[253]

There is no consensus yet as to whether retinal changes occur in NMOSD without ON. Studies have demonstrated alterations of the optic radiation, GCIPL loss, and altered foveal shape, suggesting astrocytopathy in NMOSD patients.[254–256] There is evidence of reduced temporal and superotemporal pRNFL loss in NMOSD-NON (NMOSD eyes without prior ON history) eyes compared with MS-NON.[257] It has also been reported that GCIPL, pRNFL, foveal thickness and macula volume are all reduced in NMOSD regardless of ON status.[258] In NMOSD, GCIPL thinning occurs longitudinally, independent of ON attacks.[258] This finding was, however, contradicted by a small longitudinal observational study showing no change compared with in MNOSD-ON eyes.[259]

Clinical and histopathological studies indicate attack-independent lesions in the brain and spinal cord in NMOSD.[260] Unlike in MS, a clear pattern of VEPs has not yet been defined in NMOSD patients due to conflicting results.[261] These may be attributed to difficulties ascertaining a prior history of ON, differences in OCT devices, or segmentation techniques. Further results are required to use OCT as a valuable diagnostic tool in NMOSD eyes without prior ON history.

Macula microcysts also occur more frequently in NMOSD (20–26% of patients) than in MS (5% of patients) and appear to occur exclusively in eyes with previous history of ON.[250,262,263] MME is associated with RNFL and INL thinning, and reduced visual acuity.[264]

OCTA studies showed peripapillary and parafoveal vessel density significantly decreased in NMOSD eyes independent of previous ON status.[265] There is reduced microvascular density in superficial and deep plexuses surrounding the macula with increasing prior episodes of ON.[266] This density correlated with both RNFL and GCIPL thickness, and also with visual acuity. Reduced microvascular density could occur prior to ON and RNFL atrophy, and it correlated well with visual function studies, suggesting its potential use as a predictor of visual outcomes. Further studies might consider differences between seropositive and seronegative NMOSD.[267]

Anti-MOG disease

In the 20–40% of patients with clinical signs of NMOSD but no AQP-4 antibodies,[245] a subset will have antibodies against myelin-oligodendrocyte-glycoprotein (MOG). MOG is a glycoprotein located on myelin sheath on the cell bodies and processes of oligodendrocytes. These syndromes are referred to as MOG-encephalomyelitis and is a different clinical entity to NMOSD. Here, single ON episodes appear to cause less severe damage, although the high frequency of ON may result in greater structural damage and visual impairment.[268] Similar to MS, there may be a temporal preponderance of pRNFL thinning in MOG-IgG seropositive patients.[269] Additionally, in paediatric patients, significant RNFL reductions were seen in most retinal segments compared with MOG-negative eyes, and despite this, visual acuities were well preserved.[270]

Susac syndrome

Susac syndrome (SuS) is a rare condition of presumed autoimmune etiology that features a triad of encephalopathy, hearing loss and visual defects due to microangiopathic occlusions. The combination of visual deficits with neurological disease in predominantly young female patients can make it a masquerade for MS. Fluorescein angiography typically reveals peripheral branch retinal arterial occlusions.[271] In SuS, there is hypoxic retinal destruction of the pRNFL, GCIPL, INL and outer plexiform layer, particularly in the temporal quadrant, compared with corresponding segments in RRMS retinae.[272] The ONL and photoreceptor layer are unaffected. Susac patients appear to show distinct sectoral patterns of retinal destruction, rather than the diffuse signs seen in RRMS.[273,274]

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of upper and lower motor neurons in the cerebral cortex, brainstem and spinal cord, predictably leading to fatal paralysis through respiratory failure usually within 3–5 years of diagnosis.[275,276] 90% of cases are sporadic and 10% are familial, of which approximately 60% of associated genes have been identified.[276] The exact pathogenesis is unclear, but an interplay of genetic and environmental factors is suspected, inducing oxidative stress, mitochondrial damage, neurofilament defects and defects in RNA processing.[277] Clinical presentation is typically limited to motor dysfunction leading to limb weakness and difficulties with speech, swallowing and breathing.

Early diagnosis is critical in ALS due to rapid disease progression. Timely introduction of treatment can extend the length and QoL of patients. However, diagnosis is challenging due to disease mimics and variability in initial presentation. The Awaji electrodiagnostic criteria have enabled earlier diagnosis in comparison to the previous gold standard revised El Escorial diagnostic criteria by evaluating the evidence of progressive lower and upper motor neuron dysfunction in the absence of other potential explanatory disease processes and placing equal importance on clinical and electrophysiological findings.[278,279]

Sensory abnormalities in ALS include aberrations in thermal perception, presence of numbness, neuropathic pain and tingling.[275,280] Although visual dysfunction is not predominant in ALS, extramotor features include reduced visual acuity and contrast sensitivity.[281,282] Furthermore, structural and functional alterations in the visual system have been identified through VEPs and MRI in ALS patients.[283,284] Specifically, reduced grey matter volume in the extramotor cortex, including the occipital cortex, has been identified.[280]

OCT in ALS

Given the genetic associations between primary open angle glaucoma and familial ALS,[285–291] the eye has been investigated as a course of biomarkers. However, OCT has been limited and have produced contradictory results (Table 2). A cross-sectional study of sporadic ALS patients identified reduced total macula thickness compared with controls.[292] Further manual segmentation also revealed thinning of the RNFL and INL but the corresponding GCIPL was unaffected.

A further study also demonstrated thinning of the RNFL and INL in ALS patients compared with healthy controls.[296] Significant correlation was further demonstrated between retinal thickness and fractional anisotropy, a measure of axonal density in the corticospinal tract. More recent studies have confirmed these findings of reduced RNFL thickness.[293,296,297] Reduced ONL thickness in ALS is reported in a single study.[298] However, earlier research contradicts the retinal changes seen in ALS. A study of 76 ALS patients failed to identify any significant difference in OCT measurements of retinal sublayers compared with healthy controls, nor any association with disease severity.[295] This negative finding may be explained by the selection of ALS sufferers, with only 19.7% having 'clinically definite' ALS, compared with 83.3% in Ringelstein's study.[295] A study examining symmetry in ALS eyes demonstrated significant interocular differences in retinal thickness.[296] This finding suggests that characteristic asymmetrical CNS involvement is not limited to the motor system. This may weaken the promise of retinal thinning as a robust biomarker for disease.

Macula thinning has also been a recognized feature in ALS, with total macular volume reduced in ALS patients compared with controls.[297] Another study however, showed total macula volume and other sublayers were unaffected, but did demonstrate selective RNFL thinning in ALS patients compared with healthy controls.[299] The contradictory results may be explained by cohort heterogeneity, including differences in diagnostic criteria used, and the subtype (familial *versus* sporadic) and duration of ALS. Further work should aim to allow comparison and consistency between studies.

The observed finding of RNFL thinning in ALS is likely to reflect extramotor axonal degeneration. INL thinning, however, may be explained by inhibitory pathophysiological mechanisms of neurodegeneration in ALS.[300] Bipolar, horizontal and amacrine cell bodies in the INL mainly mediate inhibitory circuits and

Table 2. A summary of studies reporting sector analysis of peripapillary RNFL changes in previous optic neuritis (MSON), multiple sclerosis without optic neuritis (MSNON), and amyotrophic lateral sclerosis (ALS). Effect size has been calculated as mean percentage reduction in disease *versus* healthy controls.

MSON - study	OCT type	Global	Superior		Temporal	Inferior		Nasal
Feng[176]	SD	34.8%	33.1%		37.5%	43.6%		37.4%
Garcia-Martin[177]	SD	10.1%	14.2%		20.4%	11.3%		19.7%
Khalil[181]	SD	33.4%	25.3%		25.4%	21.6%		29.6%
Lange[182]	SD	27.7%	22.2%		36.2%	27.0%		53.0%
Park[184]	SD	35.3%	32.4%		18.0%	36.3%		65.0%
Schneider[205]	SD	16.0%	13.2%[b]		31.6%[b]	12.7%[b]		21.3%[b]
MSNON - study	**OCT type**	**Global**	**Superior**		**Temporal**	**Inferior**		**Nasal**
Feng[176]	SD	10.4%	5.6%		10.2%	14.7%		10.7%
Lange[182]	SD	7.3%	4.6%		11.0%	8.4%		5.8%
Garcia-Martin[177]	SD	7.0%	11.7%		15.7%	10.1%		9.2%
ALS	**OCT type**	**Global**	**Superior**		**Temporal**	**Inferior**		**Nasal**
Study			**ST**	**SN**		**IT**	**IN**	
Mukherjee[293,a]	SD	7.51 μm	11.27 μm	10.68 μm	8.17 μm	−1.45 μm	2.13 μm	6.34 μm
Rohani[294]	SD	5.0%	9.0%		−1.0%	−1.0%		11.0%
Roth[295]	SD	−2.0%	−3.0%		1.0%	−4.0%		0.0%

[a]Mean of right and left eyes
[b]Significance data missing
Grey shading indicates statistical significance as chosen by each study investigator.
IN, inferonasal; IT inferotemporal; SD, spectral domain; ST, superotemporal; SN, superonasal; TD, time domain.

therefore may explain the thinning and degeneration of this layer.[296]

Retinal vessel pathology

Changes in skin, muscle and CNS microvasculature have been reported in patients with ALS.[301] The superior or inferior temporal branch of the retinal artery was assessed in ALS patients with increased outer wall thickness found compared with healthy controls,[298] with no differences in inner wall thickness or lumen diameter.

Intraretinal inclusions

Inclusions are the pathological hallmark of ALS, present in the spinal cord as well as certain regions of the brain including the frontal and temporal cortices, hippocampus and cerebellum.[302] In ALS, these are predominantly ubiquinated randomly orientated filaments, covered with fine granules.[302] Histopathological studies have identified the presence of intraretinal inclusions in one patient and within the inner plexiform layers of an ALS/dementia transgenic UBQLN2(P497H) mouse.[297] Further histopathological studies in two, related ALS patients with the C9orf72 mutation identified p62-positive, pTDP43-negative perinuclear inclusions in the inner nuclear layer of the retina and CNS.[303] These inclusions are of the type commonly found in the hippocampus and cerebellum in this form of ALS. Further colocalization suggested that the majority of retinal p62-positive inclusions were found within cone bipolar cells as well as some amacrine and horizontal cells. One of the patients had been noted to have contrast

sensitivity impairment, which may be explained by cone bipolar cell involvement.

Association with disease severity and duration

There have been contrasting results supporting the presence and absence of correlation between retinal thickness (pRNFL) and disease severity as assessed with the ALS functional rating scale (ALSFRS).[294–296,298] Pulmonary function tests are used to monitor neuromuscular involvement in ALS, and correlate well with survival time.[304,305] Simonett's study showed macula RNFL thickness correlated with forced vital capacity (% predicted) and forced expiratory volume in 1 s (% predicted).[299] Retinal thinning did not correlate with disease duration or function; however, many other factors are likely to affect this relationship. Disease duration has also been shown to correlate inversely with total macular thickness[297]; patients with disease duration longer than 40 months had significantly decreased total macular and pRNFL thicknesses compared with those with shorter disease durations. Further work may help address the lack of a widely established method to grade disease progression in ALS. In the future, OCT could be incorporated alongside other clinical, imaging and electrodiagnostic tools to form a prognostic scoring system.

The underlying pathophysiology of possible retinal changes in ALS remains elusive, as does the timeline of their onset. A primary retinal degenerative process involving neuronal and subsequent axonal degeneration causing retinal sublayer thinning is plausible. Given the relatively small OCT differences identified, larger scale studies are required to further confirm RNFL and macula thinning, as well as examining ALS subgroups such as familial, sporadic, juvenile or adult-onset subtypes to identify the specific pattern of visual dysfunction and retinal correlates in these patients.

Creutzfeld-Jakob disease and prion diseases

Prion diseases are rare, fatal neurodegenerative diseases marked by long incubation periods and fast progression.[306] Caused by PrPSc (proteinase-resistant prion proteins), a misfolded, infectious and abnormal form of a cell-surface protein, prion diseases are marked by accumulation in the CNS. The term 'prion disease' will be used to describe diseases caused by PrPSc.[307] The disease is characterised by neuronal loss with rapid increase in glial cells, lack of inflammatory response and formation of small vacuoles in the neuropil creating a 'spongiform' appearance throughout the CNS. Patients can present with rapid (weeks to months) cognitive decline including personality changes, visual impairment, memory loss and neurological deficits correlating to affected areas in the CNS.[308] Five types of human prion disease have been identified: Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), kuru, and Creutzfeldt-Jakob disease (CJD).

CJD is the most common of the human prion diseases, accounting for over 90% of cases worldwide,[306] including sporadic (sCJD), genetic/familial (gCJD), iatrogenic (iCJD) and variant CJD (vCJD) subtypes. Although the exact cause is unclear, it is thought that normal brain protein spontaneously misfolds, developing into prions,[309] with only 5–15% of cases due to gCJD caused by an inherited mutation (prion protein gene).[310] Less than 1% are acquired from iCJD or vCJD.[311,312] iCJD is spread through infected medical or surgical equipment, and was historically associated with growth hormone treatment; however, the advent of synthetic human growth hormones and heightened awareness have made iCJD very rare, reported as 1.44 cases per 1 million people worldwide.[313] vCJD results from infection through infected meat from cattle causing bovine spongiform encephalopathy (BSE).[314]

Clinical diagnosis tends to rely on evaluation of rapidly progressing dementia, myoclonus and ataxia. Changes on electroencephalogram, MRI, a positive 14-3-3 protein in the CSF, and tonsil and brain biopsies can make a 'probable' diagnosis, yet the latter procedures come with severe risks including brain damage, seizures and bleeding (CDC criteria). Several diagnostic criteria have been developed with the hope of allowing for earlier diagnosis,[311,315,316] but exclude atypical features such as unaffected cognitive profiles.[317] Visual disturbances are seen in up to 30–50% of sCJD cases at some point during the illness.[318,319] Cortical blindness, an early feature first described by Heidenhain in 1928, can occur in up to 25–50% of vCJD, reflecting the extent of pathology in the visual cortex.[319] Blurred or dimmed vision is the most commonly reported visual symptom in sCJD (9%).[320–328] Several case reports have described presentations of insidious and solitary visual

impairments removed from any other cognitive or neurophysiological impairment.[329,330]

Histopathology

Histological studies in CJD have described spongiform abnormalities in the RNFL coupled with loss of bipolar and ganglion cells, and photoreceptor changes.[331–334] Occasionally, optic nerve abnormalities have been reported,[331,332,335] as have normal optic nerves.[336] Prions themselves have been discovered in the retina,[307,337] specifically the central retina sequestered to the plexiform layers in sCJD at low levels.[337] More recently researchers observed prion seeding in the retina of sCJD eyes. Using immunohistochemistry, Orrù and colleagues detected prions in the majority of OPL and some IPL eyes of 11 patients, which coincided with accumulation of synaptic prions. Real-time quaking-induced conversion (RT-QuIC) assay detected prion seeds in the optic nerve, choroid, lens, vitreous, extraocular muscle, sclera, all corneas and a general trend towards increased prion seeds the closer tissue was to the brain.[307]

Ophthalmic exam and ERG

Optic disc pallor[335,338–341] and atrophy[331,332,335] are the most common findings, although are not always visible until after death.[332] RGC degeneration has also been described and may contribute to optic atrophy.[333] Electroretinogram (ERG) examination has found b-waves to be significantly decreased in late stages, correlated significantly to abnormalities in the outer plexiform layer of the retina post mortem.[334,342] However, Ishikawa and colleagues reported one patient with visual disturbances and normal ERG even after CJD progressed, suggesting visual problems may occur without retinal involvement.[343] In an animal study of BSE, cows inoculated with classical BSE showed no notable change in b-wave amplitude. Those inoculated with atypical high-type BSE (BSE-H) showed a decrease in b-wave amplitude but this was not statistically significant. However, significant changes in b-wave implicit times were noted during the incubation period, and significantly prolonged in clinically ill animals compared with baseline.[344]

OCT in prion disease

OCT studies of prion diseases are limited to case reports due to their low incidence and high mortality. In a 63-year-old female with Heidenhain vCJD, Chin and colleagues observed paracentral retinal thinning in both eyes 2.5 months after cognitive decline and neurophysiological symptoms began. This finding is consistent with thinning in the RNFL, ganglion cell and bipolar cell loss and demyelination of the optic nerve previously reported in histologic findings.[330–332,345,346] A study by Greenlee and colleagues of BSE and BSE-H inoculated cattle described antemortem changes in the dorsocentral retina visible up to 11 months before appearance of any other signs or symptoms of disease. Retinal thickness of inoculated cows were markedly decreased at 12 and 15 months post inoculation compared with baseline and prior to signs of disease,[344] a replication of findings from a prior study by the same group.[347]

Given the infectious nature of the disease, lack of treatment and rapid declines in cognition, early diagnosis could prevent unnecessary interventions, and prevent transmission especially in atypical clinical presentations.[330] The retina holds potential for studying the pathology of prion disease. Furthermore, because the retina is isolated, the accumulation of PRPSc may be easier to quantify more accurately compared with the rest of the CNS where dissection affects quantification of accumulation regionally.[344] It remains to be seen as to whether the use of retinal correlates can add value to the care of these patients, especially hampered by the difficulty in acquiring historic data prior to the clinical onset of such a rare group of diseases.

Conclusion

Retinal correlates have been observed in a range of some of the most common neurological disorders, some of which are not commonly associated with visual symptoms. Further to those conditions discussed, retinal correlates have been found in other neurological diseases such as idiopathic intracranial hypertension (IIH),[348] chronic migraines,[349–351] and a range of psychiatric conditions.[352,353] The majority of evidence exists in the form of cross-sectional studies comparing disease groups and healthy controls; however, further work must be done to take advantage of the unique opportunity the eye provides to serially image subjects through time. This will enable a better understanding of the natural history of retinal changes in neurological disorders and improve our knowledge of how to apply these to clinical scenarios.

Table 3. Summary of the magnitude of peripapillary RNFL thinning reported in a range of neurodegenerative diseases, as calculated by mean effect size.

Summary	Global	Superior	Temporal	Inferior	Nasal
Study					
Alzheimer's disease	++	++	+	++	++
Mild cognitive impairment	+	+	+	+	+
Parkinson's disease	+	+	+	+	+
Optic Neuritis	+++	+++	+++	+++	++++
Multiple sclerosis	+	+	++	+	+
Amyotrophic lateral sclerosis	+	+	-	-	+

+1–10%, ++ 11–20%, +++ 21–30%, ++++ 31–40%.
ALS, amyotrophic lateral sclerosis.

Although this review is not intended to be a meta-analysis, from observing the results of meta-analyses and studies relevant to this work (Tables 1–3), the literature does suggest particular characteristics of RNFL loss in a disease-specific manner. AD appears to preferentially cause peripapillary loss of the superior and inferior fibres, in contrast to PD, which appears to more commonly affect temporal RNFL than in AD. Inconsistent findings in the studies examined are likely due to the variation in concomitant medical and ophthalmic conditions within and between study cohorts. Additionally, confounds are likely to include age, duration of disease and treatment effect. Whilst the results from published studies demonstrate predilections for certain peripapillary zones and layers of the macula, these differences are unlikely to provide the specificity required in order to significantly contribute to specific diagnoses. However, with the multiple correlations seen between disease severity, treatment response and functional prognosis, there is sufficient evidence to suggest these correlates are useful in the setting of disease monitoring, and potentially as auxiliary surrogate markers in clinical trials.

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