CrossMark

REVIEW

Ocular indicators of Alzheimer's: exploring disease in the retina

Nadav J. Hart[1] · Yosef Koronyo[1] · Keith L. Black[1] · Maya Koronyo-Hamaoui[1,2]

Abstract Although historically perceived as a disorder confined to the brain, our understanding of Alzheimer's disease (AD) has expanded to include extra-cerebral manifestation, with mounting evidence of abnormalities in the eye. Among ocular tissues, the retina, a developmental outgrowth of the brain, is marked by an array of pathologies in patients suffering from AD, including nerve fiber layer thinning, degeneration of retinal ganglion cells, and changes to vascular parameters. While the hallmark pathological signs of AD, amyloid β-protein (Aβ) plaques and neurofibrillary tangles (NFT) comprising hyperphosphorylated tau (pTau) protein, have long been described in the brain, identification of these characteristic biomarkers in the retina has only recently been reported. In particular, Aβ deposits were discovered in post-mortem retinas of advanced and early stage cases of AD, in stark contrast to non-AD controls. Subsequent studies have reported elevated $A\beta_{42/40}$ peptides, morphologically diverse Aβ plaques, and pTau in the retina. In line with the above findings, animal model studies have reported retinal Aβ deposits and tauopathy, often correlated with local inflammation, retinal ganglion cell degeneration, and functional deficits. This review highlights the converging evidence that AD manifests in the eye, especially in the retina, which can be imaged directly and non-invasively. Visual dysfunction in AD patients, traditionally attributed to well-documented cerebral pathology, can now be reexamined as a direct outcome of retinal abnormalities. As we continue to study the disease in the brain, the emerging field of ocular AD warrants further investigation of how the retina may faithfully reflect the neurological disease. Indeed, detection of retinal AD pathology, particularly the early presenting amyloid biomarkers, using advanced high-resolution imaging techniques may allow large-scale screening and monitoring of at-risk populations.

Keywords Alzheimer's disease · Amyloid-beta · Tauopathy · Retinal biomarkers · Ocular abnormalities · Neurodegenerative disease

Introduction

Since Alzheimer's disease (AD)-type senile dementia was first described in 1905 by Alois Alzheimer, great efforts have been made to better understand its manifestation in the brain [67, 76]. The disease is characterized by a spectrum of cognitive and neuropsychiatric symptoms, including severe memory loss, behavioral changes, disorientation, visual impairments, sleep disturbances, and, at late stages: difficulties walking, swallowing and, invariably, death [88, 153]. Classical AD neuropathology involves the accumulation of misfolded endogenous proteins, hallmarked as extracellular amyloid β-protein (Aβ) plaques, and intracellular neurofibrillary tangles (NFT), which result from the aggregation of hyperphosphorylated tau protein (pTau) [11, 66, 76, 153, 165, 166]. These insidious pathologies can arise decades before substantial neurodegeneration and brain atrophy. Unfortunately, by the time symptoms suggestive of clinical diagnosis appear, damage may be too extensive for effective intervention [88]. A century

✉ Maya Koronyo-Hamaoui
maya.koronyo@cshs.org

1 Department of Neurosurgery, Maxine Dunitz Neurosurgical Research Institute, Cedars-Sinai Medical Center, 127 S. San Vicente Blvd., Los Angeles 90048, CA, USA

2 Department of Biomedical Sciences, Cedars-Sinai Medical Center, 110 George Burns Rd., Los Angeles, CA 90048, USA

following its first report, AD and associated dementia are estimated to afflict 47 million people worldwide, a number projected to triple by 2050 [15]. This age-dependent epidemic is a major concern for the aging population, with an incidence that rises sharply after 65 years of age, affecting roughly 50 % of individuals aged 85 and older [51].

Clinical, genetic, physiologic, and biochemical evidence suggest that the primary and earliest pathological event leading to AD is the accumulation of Aβ in the brain, which appears as a net result of imbalance between production and clearance [76, 88, 127, 153, 166]. Amyloid β-protein precursor (AβPP), a large transmembrane protein, undergoes multiple cleavage events to generate Aβ peptides [76, 165]. According to the prevalent amyloid hypothesis of AD, the disease-associated amyloidogenic pathway involves cleavage by both β-secretase and γ-secretase to produce the longer, aggregation-prone $A\beta_{40}$ and $A\beta_{42}$ alloforms [76, 85, 165]. $A\beta_{42}$, which is more specifically associated with AD, may exert its neurotoxic and cognitively detrimental effects through an array of conformational structures, ranging from small, soluble oligomers to insoluble fibrils that often culminate in degenerating neurites, termed senile (neuritic) plaques [76, 156, 165, 166]. Our expanding knowledge of tauopathy in AD brains, including intracellular tangles and threads of aggregated pTau, has grown to encompass a diversity of extracellular soluble and insoluble assemblies, which may induce seed-like self-propagation into synaptically dense regions [11, 33, 66, 77, 84, 94, 182]. Currently, the detection of plaques and NFTs by histological brain examination at autopsy provides the most definitive diagnosis of AD [4, 55, 76, 81, 88, 95, 166]. Although plaque burden may plateau at a presymptomatic stage of the disease, obscuring its relationship with disease progression, it is postulated that the early assemblies of misfolded Aβ also elicit chronic, low-grade neuroinflammation that correlates with cognitive decline [27, 131, 153, 169, 186].

Modern brain-imaging techniques, such as magnetic resonance imaging, that detect cerebral atrophy or measure functional metabolic changes are instrumental in differentiating healthy aging from pathological conditions [29, 43, 54]. However, these tissue alterations are common to many neurodegenerative disorders, and thus cannot be used to unequivocally distinguish AD from other types of dementia [96, 153]. Advanced positron emission tomography (PET) brain imaging of hallmark amyloid and tau AD pathology using various radioactive tracers (e.g., ^{11}C-Pittsburgh compound B, PiB [125], ^{18}F-florbetapir [45], ^{18}F-flutemetamol [80], ^{18}F-florbetaben [173], ^{18}F-TKH5105, and ^{18}F-T807 [89]) provides disease specificity and facilitates ongoing research. However, it may be difficult to deploy this technology for population-wide screening of preclinical signs due to high cost, necessity of using radioactive isotopes, limited resolution, and the resulting unfeasibility of

longitudinal studies [144]. Should screening become possible, early stage intervention at the level of Aβ aggregation, pTau, synaptic dysfunction, and inflammation may allow clinicians to modulate disease progression. To better serve the population at risk for developing AD, new methods of definitive and non-invasive diagnosis are needed.

With various reports of retinal structural deficits, other ocular abnormalities, and even visual dysfunctions experienced by AD patients [19–22, 31, 35, 59, 60, 69, 81, 90, 97, 98, 107, 108, 113, 130, 163, 180], it is no surprise that the field has begun shifting its attention to the eye as a site of AD manifestation. The retina is a CNS tissue originating in the developing diencephalon, and it contains high-density neuronal cells and fibers that form a sensory extension of the brain [25]. It also shares many structural and functional features with the brain, including the presence of neurons, glial cells, a blood barrier, and similar cell-fate specification of embryonically related tissues as well as tight regulation of endothelial cell proliferation [25, 126, 176]. Furthermore, axons of the optic nerve connect the retina to the brain directly and facilitate the transportation of AβPP synthesized in RGCs in small transport vesicles [136].

The first evidence of nerve degeneration in the human AD eye was reported by Hinton et al., in 1986 [81]. Since then, the reports of retinal pathology in patients with AD have grown to include RGC loss, NFL atrophy, thinning of the macular ganglion cell complex, and widespread axonal degeneration in the optic nerve [17, 19, 21, 22, 38, 73, 81, 92, 97, 147, 174]. Other changes, such as blood flow rate [19, 50, 59, 183], signs of inflammation [20, 21], and varied cellular degeneration mirroring those observed in the AD brain may reflect cerebral pathology [21, 76, 128, 186], but do not indicate AD as strongly as disease hallmarks. However, the subsequent identification of retinal Aβ plaque pathology was specific to AD patients and early stage cases, and matched amyloid pathology in the brain [107]. This was further validated by other independent studies on AD patients [1, 113, 178] that parallel findings in animal models of the disease. The latter, predominantly involving transgenic (Tg) rodents, reported similar retinal patterns, where Aβ deposits often colocalize with sites of apoptosis, neuroinflammation, impairments of function and structure, and plaque formation that even precedes that seen in the brain [46, 107, 108, 139, 148, 149, 152].

As the only CNS tissue not shielded by bone, the retina offers unique access for direct and non-invasive imaging to study possible pathological changes in the brain. Moreover, since recent studies suggest that other diseases, such as multiple sclerosis, ischemic stroke, and Parkinson's disease, also exhibit retinal abnormalities similar to the cerebral pathologies observed, the retina represents an appealing target to detect neurodegenerative disease [7, 26, 143]. The evidence of Aβ accumulation in early stage cases and

amyloid-related neurodegeneration in the AD retina [107, 113] may support its status as a site of presymptomatic stage imaging, and even suggests that Alzheimer's is both a cerebral and an ocular disease. This review provides an updated report of ocular hallmark pathologies and other abnormalities observed in patients and animal models of AD, as well as methods used to detect these changes in vivo and to monitor them in response to therapeutic intervention.

Hallmark pathology in ocular tissues of AD patients

As established cerebral hallmarks of AD, Aβ and pTau protein aggregates most strongly indicate the occurrence of the disease [76, 77, 159, 165, 166]. Nearly a century following the first description of these signs in the brain, documentation of their manifestation in ocular tissues has begun to emerge [1, 69, 91, 100, 107, 113, 163, 178]. Table 1 presents key findings from research on hallmark AD pathology in the ocular tissues of human patients.

Before amyloid-related aggregation was shown in the AD-afflicted eye, Aβ immunoreactivity in the sub-retinal pigment epithelium (RPE) was reported in normal aged eyes by Loeffler et al. [119]. While the study did not examine eyes from AD patients, Goldstein et al. [69] reported the detection of Aβ nanoaggregates in the human AD lens, a non-CNS tissue. Notably though, it was not until 2010 that Koronyo-Hamaoui and colleagues (2011) were able to demonstrate the existence of extra-cerebral Aβ deposits in the human AD retina, a CNS tissue [107]. Sequence-specific monoclonal antibodies and amyloid conformation-detecting compounds (i.e., curcumin and thioflavin-S) were used to identify Aβ deposits in flat-mount retinas from definite AD patients and suspected early stage cases [107]. In this study, AD diagnosis was determined by pre-mortem cognitive assessment and a detailed neuropathological report assessing existence of cerebral neuritic plaques, neurofibrillary tangles, neuropil threads, and amyloid angiopathy; age- and gender-matched non-AD controls did not meet these criteria. Subsequent studies revealed that retinal plaques possibly associate with blood vessels in the superior quadrant and exhibit a morphological array similar to amyloid pathology observed in the brain [107, 113, 178]. In retinas from human patients, Aβ deposits with single or multiple compact globular cores appeared more frequently than classical plaques with central Aβ cores and radiating fibrils [107]. Examples of extracellular Aβ plaques, containing $A\beta_{40}$ and $A\beta_{42}$ alloforms, and intracellular $A\beta_{40}$ immunoreactivity detected by several labeling techniques in retinas of AD patients in contrast to age-matched controls are shown in Fig. 1; unpublished data and data reported in La Morgia and colleagues [113].

Shortly thereafter, a study by Alexandrov et al. [1] that used both biochemical methods and histological examination of post-mortem eyes provided evidence for increased Aβ peptide levels, particularly $A\beta_{42}$, in retinas from AD patients (Table 1). In addition, AβPP immunoreactivity was elevated in AD retinas, justifying the expected elevation of $A\beta_{40}$ and $A\beta_{42}$ peptides, as well as the resulting formation of amyloid plaques [1]. In 2014, Aβ plaque-like structures morphologically denser than those observed in a Tg rat brain in the same study were described in two retinas from AD patients [178]. Later that year, in vivo detection of amyloid deposits in AD retinas using a method of guided optical coherence tomography (OCT) was reported. Findings included mostly perimacular and perivascular spots in the outer plexiform layer (OPL), ganglion cell layer (GCL), and NFL [100].

More recently, La Morgia and colleagues (2016) further demonstrated the appearance of classical and morphologically diverse Aβ aggregates, which often appear in clusters in retinal flat-mounts from definite AD patients. Importantly, this study was the first to report the accumulation of Aβ deposits in and around degenerating melanopsin retinal ganglion cells (mRGC), further suggesting that Aβ is toxic to retinal cells. Colocalized Aβ immunoreactivity was also detected in degenerating neurites of mRGCs [113]. Figure 2 illustrates AD-related ocular findings in the human eye, with an emphasis on the retina. In addition to the above findings, the evidence of the neurotoxicity of Aβ to retinal cells has been shown in various investigations. Cell-line studies have demonstrated Aβ-induced RGC cell death and RPE senescence [28, 179]. Animal model studies have shown RGC apoptosis accompanied by and colocalizing with Aβ deposits in retinas from rodent models of AD or glaucoma, while the reduction of Aβ levels by immunization led to the structural preservation of the RPE and visual protection in a murine model of Age-related Macular Degeneration (AMD), suggesting that Aβ causes neurodegeneration in these models [44, 74, 139]. Furthermore, a study reported that retinal Aβ injection induced photoreceptor degeneration in a wild type (WT) mouse, and that exposing RPE cells to Aβ in vitro reduced mitochondrial redox potential and production of reactive oxygen species [24].

In addition to growing reports of retinal Aβ accumulation, one study has reported hallmark pTau in the retina, while another has reported indirect indication of pTau [91, 163]. A notable study by Schön et al. [163] provided the first evidence of pTau in retinal cross sections of AD patients, particularly in the innermost layers (Fig. 2), although the group was unable to detect fibrillar Tau and Aβ aggregates. Tau hyperphosphorylation was detected by anti-AT8 immunoreactivity, which binds phosphorylated groups at Ser202 and Thr205 [163]. A subsequent study showed significant evidence that changes in retinal

Table 1 Abnormalities observed in ocular tissues of AD patients

Tissue	Pathology	Findings	References
CNS			
Retina	Amyloid	Elevated AβPP expression	[1, 69]
		Increased $A\beta_{40}$ and $A\beta_{42}$ peptide levels	[1]
		Classical and diffuse extracellular Aβ plaques, plaque-like structures, and intracellular Aβ deposits, particularly in the superior quadrant and innermost layers	[100, 107, 113, 178]
		Aβ deposits inside and around degenerating melanopsin (m)RGCs[a]	[113]
	Tau	pTau positive in GCL, IPL, INL, ONL, and OPL	[91, 163]
	Neuronal degeneration	NFL thinning and macular volume loss in all quadrants; Mostly in superior and inferior quadrants; Diffuse dropout; NFL thickness correlated with MMSE[b] score, NFL abnormalities	[10, 14, 19, 20, 34, 50, 79, 87, 91, 104, 106, 110, 113, 114, 118, 121, 124, 135, 137, 142, 145–147, 160, 167, 177]
		GCL degeneration from mild to severe; RGC swelling; Loss of mRGCs and dendritic arborization	[20, 113, 160]
	Inflammation	Extensive cell processes suggesting gliosis from ILM[c] adjacent to GCL	[20]
	Vascular	Perivascular Aβ deposition	[113]
		Reduction of venous blood flow, column diameter, speed, arteriolar and venular fractal dimensions, branching complexity and geometric optimality; Changes to arteriolar and venular tortuosity; Increased width variation; Blood flow correlated with NFL thickness	[19, 32, 50, 59, 183]
		Elevated oxygen saturation	[49]
	Other	*In vivo* FLIO[d] imaging: Auto-fluorescence changes correlated with MMSE score and CSF pTau	[91]
Optic nerve	Structural	Large caliber fiber loss; Superior and nasal quadrant axonal loss, overall reduction; Cup-to-disc ratio increase; Intraocular pressure susceptibility increased; Optic disc paleness; Suggested link to glaucoma	[81, 113, 160], [14, 16, 40, 81, 121, 171, 177]
Non-CNS			
Lens	Amyloid	Elevated AβPP expression	[69]
	Other	Cytosolic electron-dense Aβ nanodeposits in supranuclear, cortical regions and in anterior epithelial subregion in DS[e] lens	[69, 101, 133]
		Supranuclear cataracts; Opacity[f]; PS1[g] expressed in DS lens	[18, 49, 57]
Cornea	Other	PS1 expressed in the DS cornea	[57]
Aq. humor	Amyloid	Increased $A\beta_{40}$ levels	[69]
Choroid	Structural	Thickness reduction	[63, 178]

[a] Retinal ganglion cell

[b] Mini-Mental State Examination

[c] Inner limiting membrane

[d] Fluorescence lifetime imaging ophthalmoscopy

[e] Down's syndrome

[f] Opacity difference not statistically significant

[g] Presenilin-1 protein
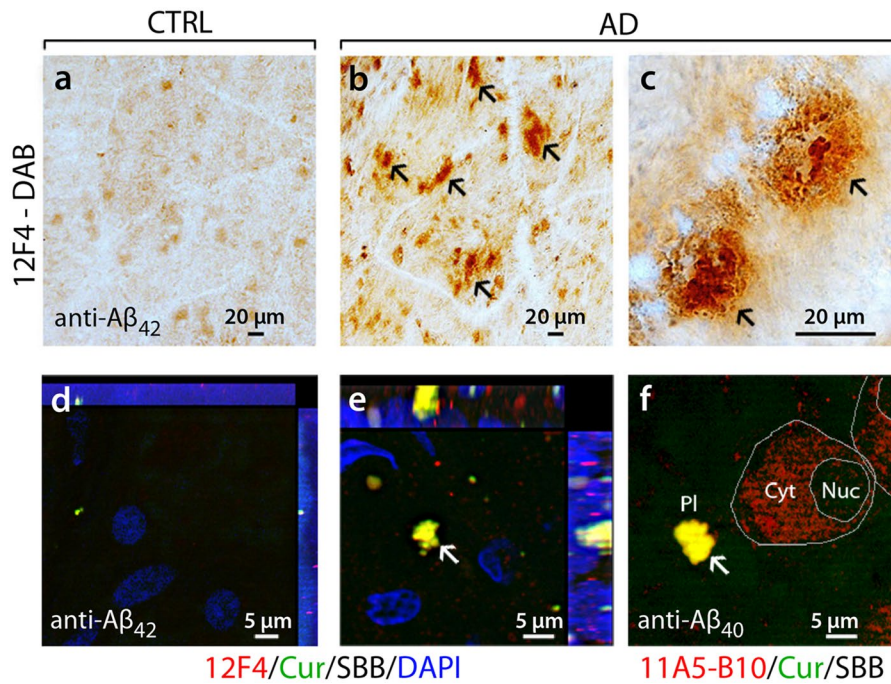
Fig. 1 Flat-mount retinas from AD patients exhibit the accumulation of Aβ deposits. **a–c** Representative microscopic images from a definite AD patient (74 years) and a matched control individual (CTRL; 71 years) stained with anti-Aβ$_{42}$ C-terminal-specific antibody (12F4) and visualized with peroxidase-based labeling (DAB). Blood vessel structures seen as lighter lanes. **c** Classical mature Aβ plaques observed along a retinal blood vessel. **d, e** Fluorescence labelling of Aβ$_{42}$-containing deposits detected in retina of AD patient (*yellow*), using curcumin (*green*), 12F4 antibody (*red*), and DAPI nuclear staining (*blue*). Sudan Black B (SBB) is used to quench non-specific autofluorescent signal. **f** Compact extracellular Aβ plaque and cytosolic Aβ$_{40}$ accumulations observed following curcumin and anti-Aβ$_{40}$ C-terminal-specific antibody (11A5-B10) staining in post-mortem retinas of AD patients. *Arrows* indicate various types of Aβ plaques. Images **a-c** adopted from La Morgia et al., Annals of Neurology, vol. 79, no. 1, pp. 90–109, 2015

Fig. 2 Manifestations of AD in the Human Retina. **a** Visual pathway. **b** Eye-sagittal plane. **c** Retinal flat-mount shows the geometric distribution of pathology by quadrant with more consistent findings of NFL thinning indicated by darker shading. **d** Cross section of retina and adjacent ocular tissues shows the distribution of pathology by tissue layer. *Aβ* amyloid beta-protein, *pTau* phosphorylated tau, *NFL* nerve fiber layer, *GCL* ganglion cell layer, *IPL* inner plexiform layer, *INL* inner nuclear layer, *OPL* outer plexiform layer, *ONL* outer nuclear layer, *ILM* inner limiting membrane, *OLM* outer limiting membrane, *IS/OS* inner and outer segments of photoreceptor layer, *RPE* retinal pigment epithelium, *P. Pole* posterior pole
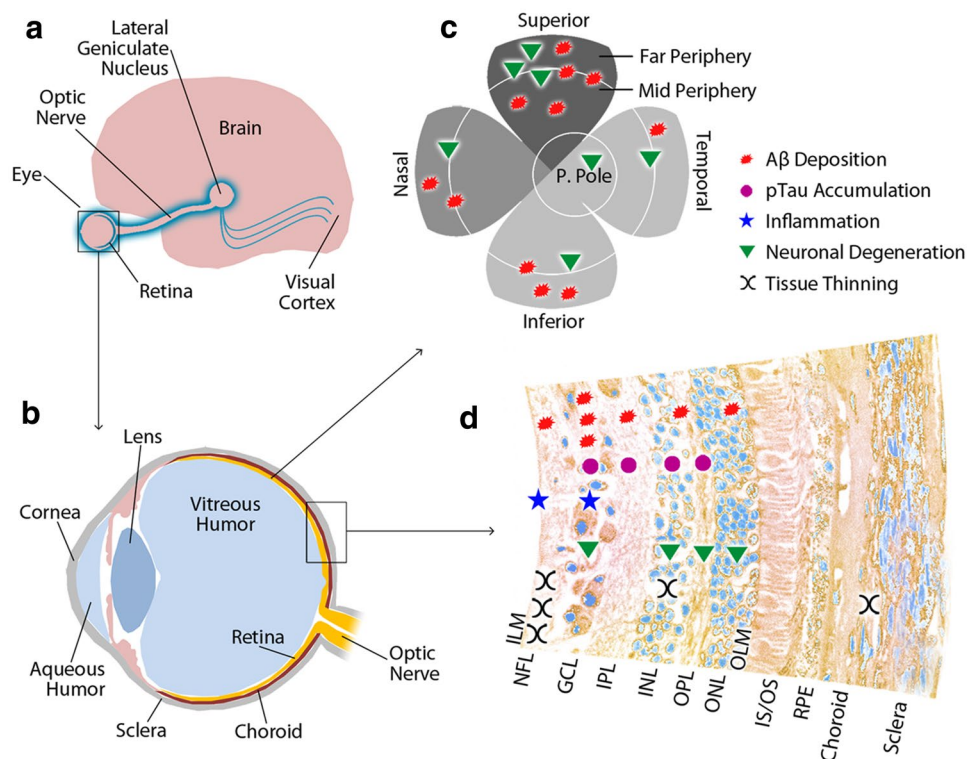
fluorescent lifetime imaging ophthalmoscopy correlate with total Tau and pTau-181 concentration in the cerebrospinal fluid (CSF) [91]. On the other hand, a study employing the standard staining protocols for brain tissues, was unable to detect aggregates of Aβ, pTau, or α-synuclein upon examination of retinal cross sections and other ocular tissues from AD and Parkinson's disease (PD) patients [82]. It is important to note, however, that studies from eight independent groups examining eyes from AD patients have consistently found retinal tauopathy and increased formation of Aβ deposits in retinas and lenses [1, 69, 101, 102, 107, 113, 133, 163, 178], and two recent studies examining retinas from patients with PD or Tg mice modeling PD and Dementia with Lewy Bodies reported the presence of misfolded α-synuclein within the inner retinal layers, along with impaired vision [23, 155].

Although outnumbered by evidence of changes in the neurosensory retina, a CNS tissue, some studies have reported the detection of Aβ peptides and nanoaggregrates in non-CNS ocular tissues. These include the description of amyloid-related changes to the human AD and Down's Syndrome (DS) lens, including AβPP immunoreactivity and Aβ nanoaggregation in supranuclear, cortical, and anterior epithelial subregions of the lens [69, 101, 133]. Individuals with DS, in which chromosome 21 trisomy results in triple copies of the AβPP gene, are at increased risk for early onset AD, and as such offer valuable data pertaining to the disease [185]. Interestingly, one of these studies reported that Aβ burden in the lens of a 2-year-old DS individual was comparable with those observed in a 57-year-old familial AD patient and an 85-year-old sporadic AD patient [133]. In a recent study, in vivo detection of Aβ was reported in the lens, with a technique later used to successfully predict clinical AD diagnoses [101, 102]. Another report of non-CNS Aβ accumulation describes detection in the aqueous humor [69]. In contrast to the above findings, one study specifically reported no Aβ immunoreactivity in lenses and corneas from post-mortem AD donors [132]. While the accessibility of the lens has inspired enthusiastic study and subsequent reports of characteristic AD pathology, one must consider the degree to which lenticular and other non-CNS protein aggregates can accurately reflect cerebral amyloid burden during disease progression and in response to therapy.

As discussed above, recent studies have shown that certain tissues of the eye, particularly specific regions of the retina, present an abundance of characteristic AD pathology. Among these, parameters of amyloid aggregation coupled with RGC degeneration in the superior quadrant of the innermost retinal layers (i.e., NFL and GCL) might distinguish ocular pathology specific to AD from that observed in other neurodegenerative diseases, such as AMD and glaucoma [92, 93, 116, 120]. The evidence of key AD

biomarkers Aβ and pTau in the neuroretina urges further exploration of Alzheimer's in this ocular tissue.

Non-specific ocular abnormalities in AD patients

In addition to hallmark biomarkers, the complex pathology of AD manifests as an array of ocular abnormalities, many of which have been repeatedly observed in AD patients. In this section, we explore cellular, structural, vascular, and other changes that may be associated with increased neurotoxic Aβ in the AD-affected eye (Table 1).

Pathological changes in the AD eye were first documented in 1986, when Hinton and colleagues reported optic nerve degeneration, a decrease in ganglion cell numbers, and thinning of the NFL [81]. Further reports of GCL pathology described the severe degeneration of RGCs, including a phenotype of vacuolated mitochondria and nerve fiber cell degeneration. The evidence of AD-related GCL degeneration has been accumulating since then, including a report of 25 % neuronal loss in the GCL, with the greatest losses noted in the superior and inferior retinal quadrants [20–22, 38]. Interestingly, two of these studies reported that while GCL loss is age-dependent in control retinas, it does not correlate with age in the AD eye [22, 38]. Sadun and colleagues [160] reported a loss of the largest caliber fibers in the optic nerve and degeneration of RGCs. Further studies of the AD eye have followed, reporting NFL and macular thinning, as well as optic nerve degeneration. Findings of NFL thinning have indicated a significant reduction of thickness among quadrants of this tissue layer [10, 13, 19, 34, 62, 87, 104, 106, 113, 114, 124, 135, 145–147, 167], although some findings did not reach statistical significance [1, 50, 79, 91, 110, 111, 167]. A small number of studies have provided evidence against NFL thinning. Two of these studies reported no change in NFL thickness compared with controls [91, 103]. In another study, age was found to be the greatest factor contributing to NFL thickness, while AD patients showed no significant thinning in comparison to controls [111]. Although reports of NFL thinning vary, there appears to be an overwhelming majority of evidence supporting a significant thinning of the superior quadrant of the NFL in the AD retina (Fig. 2) [19, 62, 79, 87, 104, 110, 113, 118, 121, 137, 142, 145–147, 160, 177].

Interestingly, NFL thinning has been correlated with an abnormal pattern electroretinography (pERG) response [146]. More recently, two studies reported a correlation between degree of cognitive impairment and either NFL thinning or macular volume reduction [87, 142]. Other findings have indicated that AD patients and control subjects show no significant differences when comparing the latency of visual evoked potential (VEP) P100 component

[87], and no correlation between NFL thinning and Mini-Mental State Examination (MMSE) score [62]. Data showing NFL thinning and *macula lutea* reduction in AD seem to mirror results from studies on MCI [62, 104, 145]. While degeneration has been observed most notably in the NFL and GCL, it has also been observed in the inner nuclear layer (INL) [178]. It appears that the innermost layers of the retina show greater and more significant thinning than the outer retinal layers [17] (Fig. 2). A recent meta-analysis of NFL thinning in AD patients, including many of the above-described studies, reported that, after correction for varied methodology, the field shows consensus for a significant mean thinning of the NFL in AD [34]. While research strongly suggests that NFL measurement may be useful for the early diagnosis and evaluation of disease progression [87], further study is needed to optimize the utility of this method as a specific ocular biomarker of the disease. More recently, in a clinical study on AD patients exhibiting circadian abnormalities, La Morgia and colleagues (2016) described NFL thinning in the superior quadrant, measured by OCT [113]. More importantly, this study described degeneration specific to a photoreceptor subtype, mRGC, which makes up 1–2 % of all RGCs [112, 113]. Degenerating mRGCs were associated with Aβ deposits within and around mRGCs in post-mortem retinas from AD patients [113]. The mRGCs are known to modulate circadian photoentrainment by projecting to the hypothalamus suprachiasmatic nucleus (SCN), the circadian pacemaker of the brain [112]. This study may provide the first mechanistic explanation for the circadian dysfunction often reported in AD patients [113].

Since 2007, numerous findings of retinal angiopathy and other related vascular changes have also been documented in AD patients. These changes include narrowed veins, reduction of blood flow, vascular attenuation, increased width variation, reduction of branching complexity and optimality, smaller fractal dimensions, and changes in tortuosity [19, 32, 50, 59, 183]. A recent study by Einarsdottir et al. [49] reported that although vascular diameter was not changed, blood oxygen saturation was notably elevated in the AD retina with oximetry data closely matching that seen in AMD.

An interesting abnormality observed in the retina relates to the abnormal expression of members of the synuclein family of proteins (α-, β-, and γ-synuclein), with a retinal layer occurrence in AD patients distinct from that seen in healthy individuals [170].

One aspect of ocular pathology that has been repeatedly documented in AD patients is a significant elevation of cup-to-disc ratio, with one study reporting a threefold increase [16, 40, 121, 171, 177]. Interestingly, since cup-to-disc ratio is used to measure the progression of glaucoma [3], a number of investigations have explored the potential

connection between glaucoma and AD. Two of these studies examined AD patients and found a relationship with one reporting that 25.9 % of the sample was positive for glaucoma, a condition that is only prevalent in about 5 % of the general population [16, 171]. Conversely, two recent studies that examined the risk of glaucoma patients developing AD found no relationship [12, 105]. Recently, optic disc color pallor, indicative of axon loss, has been investigated as a potential biomarker, given that the optic discs of AD patients show a significant paleness compared with those of controls [13]. In light of overlap between AD and glaucoma, some researchers have even termed glaucoma "Ocular AD" [16, 129]. However, apparent differences between glaucoma and the ocular manifestations of AD challenge such a notion. While glaucoma shows optic disc cupping accompanied by a specific pattern of loss in the optic nerve and GCL [3, 41], the ocular findings in AD have overwhelmingly indicated damage to the NFL and GCL along with hallmark molecular signs in peripheral retinal regions [20–22, 81, 107, 113, 163]. Since evidence linking the two diseases remains controversial, further research would be warranted before claims of common etiology could be made about these diseases.

Although most research on ocular degeneration in AD has focused on CNS tissues like the retina, a number of studies have reported changes in lenses of the AD and DS eyes. Reports have indicated supranuclear and deep cortical cataracts, opacity due to increased light scattering, and other changes that may be associated with the findings of Aβ peptides in the lens [49, 69, 101, 102, 133]. On the other hand, a study that examined amyloidopathy in cortical cataracts was unable to detect Aβ in lenses of patients with and without AD [132]. Studies examining changes in the AD eye have also reported significant thinning of the choroid [17, 63, 178].

Visual dysfunction in AD patients and animal models

Among the earliest symptoms documented in some AD patients are visual impairments, especially loss of contrast and color sensitivity, limited visual field, compromised visual attention, reduced stereopsis, deficits in the perception of shape from motion, and impaired object and face recognition [9, 31, 90, 97, 138, 140, 161, 162, 174]. However, unlike well-established retinal structural deficits, various changes in visual function appear to manifest inconsistently across AD patients, and further study should expand upon the currently limited findings.

While many aspects of visual acuity, such as recognition, localization, and target detection, were not found to be significantly different in AD patients when compared

with controls [31, 90], loss of contrast sensitivity was markedly different [64, 90, 157]. Since the latter parameter may be detected clinically in a routine eye examination, it may serve as a biomarker for AD-related neurodegeneration [31]. However, loss of color sensitivity and the possibility of using this parameter to determine AD status remain highly controversial [9, 31]. Abnormal visual field has also been correlated with disease severity, with AD patients showing sensitivity loss greater than controls [31, 90, 175]. Deficits in motion perception have been associated with severity of dementia, and evidence suggests that AD patients may have impaired motion sensitivity due to selective damage to the magnocellular pathway [31, 65, 83, 99]. Although reduced depth perception and stereopsis have been linked with cognitive impairment, opinions regarding the effect of stereopsis in AD patients are mixed [31, 115, 158]. Finally, saccadic eye movement is among the most well-described deficits to ocular motor function in AD patients [36, 53]. Nevertheless, related visual dysfunction, such as pupil size and pupillary light reflexes are not exclusive to AD and may also be found in healthy older individuals and in other neurological conditions such as PD [71].

Thus far, other functional changes detected through electrophysiology techniques have been limited but offer unexpected clues to the roots of visual abnormalities arising from neuroretinal dysfunction. Delayed pace of processing, measured by responsiveness of pERG, has been documented in AD patients [146, 147]. A study examining pattern VEP in AD patients found no significant difference between the AD and non-AD groups and no correlation with MMSE score [87]. Additional reports of AD-related electrophysiology deficits have come from animal model studies, showing abnormal flash VEP measurements in APP$_{SWE}$/PS1$_{\Delta E9}$ mice [61]. Two studies reporting ERG measurements in 5xFAD and APP$_{SWE}$/PS1$_{\Delta E9}$ mice found that the response was not significantly different between Tg and WT groups, but was instead correlated with age [150, 152].

While data regarding visual dysfunction have not been definitive, recent findings show a promising connection between circadian rhythm and retinal neuronal degeneration. La Morgia and colleagues (2016) reported that a subgroup of AD patients suffers from significantly reduced sleep efficiency due to circadian rhythm disruption that may be caused by RGC loss and Aβ toxicity in the retina [113]. This study diverges from the historical attribution of visual and ocular-related dysfunctions in AD patients to brain abnormalities [112, 113].

Although most of these changes are modest in magnitude, taken together they may impact daily activity and cognitive performance significantly. These studies suggest that visual abnormalities in AD, historically attributed to brain pathology, may arise directly from pathology in the retina, such as Aβ- and tau-derived neurodegeneration, optic nerve atrophy, inflammation, and vascular attenuation. As we continue to explore potential treatment, growing evidence of the ocular aspects of AD suggests that therapeutic intervention should address visual as well as cognitive dysfunctions. Mitigation of deficits, such as contrast insensitivity, delayed pace of processing, and retinally regulated circadian functions, could meaningfully improve quality-of-life for those suffering from this debilitating disease.

Ocular findings shared by AD and AMD

Certain similarities between AD and AMD have drawn attention to a potential connection between these degenerative conditions. AMD is an ocular disease characterized by sub-RPE drusen deposits, thickening of Bruch's membrane, and degeneration of the RPE and photoreceptors within the *macula centralis* [2]. Like AD, the risk of developing AMD increases exponentially with age [58, 141]. As AMD progresses, patients show central visual field loss [2, 141], which differs from the inferior visual field loss described in some AD patients [175]. The primary degeneration noted in AMD typically takes place in the photoreceptors of the macula and in the underlying RPE, while AD retinas primarily show degeneration in the GCL and NFL [10, 13, 19, 21, 22, 34, 62, 81, 87, 104, 106, 113, 114, 124, 135, 145–147, 167]. Interestingly, Aβ has been detected in the eyes of both AMD and AD patients, within drusen deposits in AMD [42, 122] and as the primary constituent of extracellular fibrillar plaques in AD retinas [107, 113]. In the report by Dentchev et al. [42], Aβ was detected in drusen deposits in the retinas of 4 out of 9 AMD patients, but not in drusen deposits from normal eyes. Another study examining drusen deposits did not find amyloid fibrils within drusen, but identified amyloidogenic oligomers, suggesting that Aβ oligomers may be involved in the biogenesis of drusen deposits [122]. Interestingly, in an earlier study by Loeffler et al. [119], patchy Aβ immunoreactivity was detected in sub-RPE deposits in eyes from normal older persons but not in retinas from patients with AMD. These deposits corresponded to either soft drusen or basal linear deposits [119]. Other abnormalities common to AMD [156, 168] have also been observed in the eyes of AD patients, including abnormal retinal blood circulation [19], vascular changes [58, 141], reduced NFL thickness [145], foveal RGC degeneration [20], and choroidal thinning [63].

In the 5xFAD Tg mouse model, RPE degeneration, which is also characteristic of AMD, has been reported in two recent studies [148, 150], one of which even found drusen-like deposits and Bruch's membrane thickening [148].

Multiple genetic studies on these diseases have revealed a tight connection to the ApoE gene. However, while the associated risk of sporadic AD increases with the ApoE4 allele and decreases with the ApoE2 allele, the opposite has been observed in AMD (reviewed in [168]). Shared components of the complement system, a part of innate immunity, suggest that common inflammatory mechanisms are involved in AD and AMD. In addition, the oxidative stress experienced by photoreceptors of AMD patients is mirrored by the AD brain as increased reactive oxygen species, oxidative damage, and mitochondrial dysfunction [168]. Taken together, the findings of AD and AMD commonalities suggest a degree of overlap, yet, key differences in retinal layer and geometric distribution of hallmark pathologies warrant further investigation towards defining differential diagnosis.

AD-specific ocular pathology in animal models

Recent work on animal models of AD has shed light on the biological role of AβPP, soluble Aβ peptides, insoluble Aβ aggregates, and pTau species in the eye. Advances include the identification of the species and aggregates that may interfere with essential cellular mechanisms at early stages of the disease. This section summarizes the current findings of characteristic AD abnormalities in the eyes of rodent and fly models of the disease (Table 2).

AβPP immunoreactivity has been detected in the eye in a number of AD animal models. These include several Tg strains of drosophila, established Tg mouse models (Tg2576, hTgAPP$^{tg/tg}$, APP$_{SWE}$/PS1$_{\Delta E9}$, and APP$_{SWE}$/PS1$_{M146L/L286V}$), and *Octodon degus* (*O. degus*), a WT rodent native to Chile that exhibits symptoms of sporadic AD [8, 46, 47, 56, 117, 139, 188]. Specifically, animal model findings of cytoplasmic AβPP in the photoreceptor layer have been shown to increase in Tg rodents [47, 139], while in *O. degus*, AβPP expression was shown to decrease with age [46]. Strong AβPP and mRNA transcript signals have been reported in the cornea and lens [47, 56]. A drosophila model study has provided additional support for ocular AβPP in AD models, reporting the ubiquitous expression of AβPP in the compound eye [72].

The elevation of soluble and insoluble Aβ peptide levels has been observed in AD animal models, where the increase is age-dependent and corresponds to disease progression. These include the Tg2576, APP/PS1, 3xTg, 5xFAD mice, the TgF344-AD rat, and *O. degus* [1, 46–48, 107, 117, 134, 148, 150, 152, 154, 178, 184]. It has been reported that levels of Aβ$_{40}$ and particularly Aβ$_{42}$ are elevated in the retina, as well as in the lens, vitreous humor, and choroid of AD rodent models (Table 2) [1, 46, 47, 117, 148, 150, 154, 178, 184]. Interestingly, in a

study examining the effects of metal in the diet, retinal Aβ abundance was found to increase dramatically in an aluminum-fed 5xFAD mouse [154]. The potential involvement of metal in AD has been reported before [37, 172]. In two other studies using the 5xFAD mouse, retinal Aβ$_{40}$ and Aβ$_{42}$ elevation were reported, with notable detection in the RPE [148, 150]. In the Tg2576 and APP$_{SWE}$/PS1$_{\Delta E9}$ mice, possible cytoplasmic Aβ elevation has been documented in the INL, within vacuolar structures in the peripheral GCL, and in the cornea and lens [47]. Interestingly, in this study, enzyme-linked immunosorbent assay (ELISA), other biochemical assays, and immunohistochemistry (IHC) yielded very different results regarding the presence of Aβ peptide in the retina. The AD biomarker was not successfully detected by every method, but definitive evidence was ultimately provided by IHC and ELISA [47]. Two additional studies examining drosophila models of AD have also provided support for the elevation of ocular Aβ peptides [30, 52]. The diverse findings in the studies above emphasize how varied methodologies have driven controversy regarding the detection of AD hallmarks in the eye.

Deposits of insoluble Aβ species and subsequent plaque formation have been documented in the retinas of Tg2576, APP$_{SWE}$/PS1$_{\Delta E9}$, APP$_{SWE}$/PS1$_{M146L/L286V}$, 3xTg, and 5xFAD mice, as well as *O. degus* [1, 46–48, 107, 108, 117, 134, 139, 152, 184, 187, 188]. In the Tg2576 mouse, plaques have been identified most consistently in retinal layers ranging from the GCL to the ONL, and rarely in the photoreceptors and optic nerve [117, 184]. In both the APP$_{SWE}$/PS1$_{\Delta E9}$ mouse and Tg344F-AD rat models, which share the same double transgenes, plaques and extracellular deposits have been identified in retinal layers ranging from the NFL to the INL, and even in the sclera and choroid [107, 139, 152, 178]. Importantly, Aβ plaques were detected in the retina of APP$_{SWE}$/PS1$_{\Delta E9}$ mice as early as 2.5 months of age, 2–3 months prior to their cerebral counterparts [107]. Another study compared plaque load between male and female mice, and found that in old mice, between 12 and 16 months of age, a significantly greater number of female APP$_{SWE}$/PS1$_{\Delta E9}$ mice exhibited retinal plaque formation compared with age-matched males [152]. In *O. degus*, a natural model of sporadic AD, Aβ deposits have been observed in the NFL, GCL, and photoreceptors of young animals, while aged animals show intense Aβ staining throughout all retinal layers [46, 86]. The study also reported that the staining of deposits and oligomeric Aβ occurred most intensely in the central retina. In addition, the group noted that while Aβ deposits were confirmed by other means, Congo red did not provide an accurate detection of Aβ [46]. Additional evidence for ocular Aβ deposits and senile plaques has been documented in studies using AD drosophila models [30, 72]. Aβ specifically deposited

in and around ocular vasculature, sometimes in association with damaged capillaries, has been detected in the retinas and choroids of APP$_{SWE}$/PS1$_{\Delta E9}$ mice and Tg344F-AD rats [47, 117, 139, 178]. Despite a majority agreement on Aβ elevation in the eyes of AD animal models, one study using animal models positive for cerebral plaques was unable to detect Aβ plaques in the eye [47].

Evidence of pTau has been observed from the GCL to the ONL in the Tg2576 mouse and in the soma of RGCs in the APP$_{SWE}$/PS1$_{\Delta E9}$ mouse (Table 2) [117, 187]. In *O. degus*, pTau expression has been reported primarily in the NFL and GCL [46]. In the UAS-Gal4 drosophila model of AD, Tau species at various degrees of phosphorylation have been detected in the retina [70]. In addition to pTau species, NFTs have also been detected in the retinas of APP$_{SWE}$/PS1$_{M146L/L286V}$ mice [78, 188].

Non-specific ocular abnormalities in animal models of AD

Additional ocular changes have been reported in AD animal models, including retinal degeneration, inflammation, structural alterations, and other changes that may be associated with Aβ elevation and deposit formation. Many of these findings mirror those recorded in AD patients (Table 3) [5, 6, 30, 39, 48, 52, 56, 72, 117, 123, 139, 148, 152, 154, 178, 184].

A number of studies have reported that retinal tissues in rodent models presenting the elevation of the neurotoxic Aβ peptide also show significant degeneration compared with those of control animals [56, 148, 178, 187]. An array of degenerative markers has been documented in different animal models. Cellular swelling, nuclear disorganization, shape irregularity, and organelle loss in cortical fiber cells have been observed in the lens of an hTgAPP$^{tg/tg}$ mouse [56]. The RPE has shown hypopigmentation, large vacuoles, and Bruch's membrane thickening with drusen-like deposits in a 5xFAD mouse [148], as well as hypertrophy in the TgF344-AD rat [178]. RGC distribution in the retina of APP$_{SWE}$/PS1$_{\Delta E9}$ mice is sparse and overall numbers show a significant decrease when compared with matched WT controls [61, 75]. Amacrine cell apoptosis has also been noted in the retina of the APP$_{SWE}$/PS1$_{\Delta E9}$ mouse [61]. Evidence from drosophila studies supportive of ocular degeneration in AD models has indicated severe photoreceptor abnormality, lens fission, and axonal degeneration in the optic nerve [30, 39, 52, 72].

Inflammatory processes are well documented in the brains of AD patients [68, 128, 186]. In 2008, Ning and colleagues were the first to show that the accumulation of Aβ in the retina of Tg mice was associated with neurodegeneration and inflammation [139]. Since then, several reports of

ocular inflammation in rodent models of AD have indicated increases in microgliosis, GFAP$^+$ astrogliosis, retinal infiltration of lymphocytes and monocytes, and upregulation of MCP-1, among other markers in many layers of the retina and choroid [6, 48, 61, 117, 139, 152, 154, 178, 187].

Structural changes in the retinas of AD animal models have included tight junction attenuation, variations in vascular branching and budding, and decreases in complexity, field area, and length of RGC dendrites (Table 3) [5, 6, 123, 148, 184]. While synaptic density in the Tg2576 mouse has shown no change in either pre- or post-synaptic markers [184], synaptic loss and impairment, typically related to cognitive deficits when observed in the brain, have been reported in the ApoE4 mouse retina [5, 6]. Changes observed outside of ocular CNS tissues in rodent and fly eyes have included thinning of the choroid [178], as well as cellular swelling, organelle disorganization, and opacity in the lens [39, 56]. Furthermore, altered expression levels of various proteins and mRNA transcripts essential to normal cell function have been detected, including a report of increased ATP release in the retina of an APP/PS1 mouse model [151].

Intracellular malformations have also been documented in retinal cells, including increases in double nuclei and hypertrophy in the RPE, as well as cellular swelling, crista fragmentation, and complexity reduction in mitochondria of Tg rodent models [152, 178, 184]. In addition, two studies investigating ocular changes in the ApoE4 mouse reported increased neovascularization following laser-driven injury and decreased VEGF levels in the choroid [6, 123]. Overall, the above studies, predominantly those pertaining to genetic murine models of AD, indicate that the effects of Alzheimer's known to afflict the brain, especially synaptic loss and neuronal degeneration, also manifest in the retina.

In vivo imaging of AD in the eyes of patients and animal models

Visualization of the retina and its AD-related abnormalities may be achieved with non-invasive optical imaging technologies and advanced electroretinogram techniques. Advanced OCT has been widely used in recent years to accurately image cross sections of the retina. This technique has provided evidence for significant thinning of the peripapillary NFL, macular volume loss, and nerve fiber density decrease in patients with mild to severe AD, suggesting that thinning might occur early in disease progression [10, 14, 50, 62, 87, 91, 92, 100, 104, 113, 114, 121, 135, 142, 145]. Used in conjunction with Fundus Auto-Fluorescence (FAF), a method for detection of highly fluorescent structures, areas of interest for OCT examination have

Table 2 AD-specific ocular biomarkers in animal models

AD pathology	Species	Model	Findings	References
Amyloid-related				
AβPP expression	Drosophila	AβPP^a/dBACE^b/ dPsn^c	Expression in fly eye; Over-expression in all murine retinal layers, optic nerve, cornea, lens	[46, 47, 56, 72, 117, 139, 188]
	Mouse	Tg2576^d, APP/ PS1^e		
	O. degus^f	Sporadic AD (aged)		
Aβ peptides	Drosophila	pGMR-Aβ^g, dBACE-AβPPL^h	Increased levels in retinal extracts from fly; NFL, GCL, IPL, INL, OPL, OS^i; RPE (extra- and intracellular), choroid, cornea, lens, vitreous humor, including oligomeric Aβ species and Aβ engulfed by astrocytes; In O. degus, more peptides and oligomers detected in central retina	[1, 30, 39, 46, 48, 52, 72, 75, 107, 117, 134, 139, 148, 150, 154, 184]
	Mouse	Tg2576, APP/ PS1, 3xTg^j, 5xFAD^k		
	O. degus	Sporadic AD (aged)		
Aβ deposits	Drosophila	AβPP, dBACE-AβPPL, pGMR-Aβ_{42}	Retinal extracts from fly; Deposits and/or plaques in most retinal layers (strongest in GCL and central retinal region), optic nerve, sclera; Endogenous dAβ^l deposits	[1, 30, 46–48, 72, 75, 107, 117, 139, 152, 178, 187]
	Mouse	Tg2576, APP/ PS1, 3xTg, 5xFAD		
	O. degus	Sporadic AD (aged)		
	Rat	TgF344-AD^m		
Vascular Aβ	Mouse	Tg2576, APP/ PS1	Vascular-associated deposition in GCL, IPL, INL, OPL, and choroid in rodents	[47, 107, 117, 139]
	Rat	TgF344-AD		

Table 2 continued

AD pathology	Species	Model	Findings	References
Tau-related				
pTau	Drosophila	hTau[n]	Differential cell type-specific pTau variants in fly eye; Increased in most retinal layers, strongest in GCL, none in NFL, RPE; NFL, GCL, and AT8[o] reactivity in *O. degus*	[46, 70, 117, 188]
	Mouse	Tg2576, APP/PS1		
	O. degus	Sporadic AD (aged)		
NFT[p]	Mouse	APP/PS1	Immunoreactivity in murine retina, particularly in GCL and RPE	[78, 187, 188]

[a] Drosophila expressing amyloid β-protein precursor

[b] Drosophila expressing β-secretase 1

[c] Model expressing drosophila presenilin-1 protein

[d] Mouse overexpressing APP isoform 695 bearing Swedish double mutations K670M/N671L

[e] Mouse overexpressing APP$_{SWE}$/PS1$_{\Delta E9}$ or APP$_{SWE}$/PS1$_{M146L}$

[f] *Octodon degus*, WT rodent native to Chile showing symptoms of sporadic AD

[g] Glass multiple reporter drosophila model expressing Aβ$_{42}$

[h] Drosophila expressing AβPP-like protein

[i] Outer segment of photoreceptors

[j] Mouse overexpressing APP$_{SWE}$/PS1/TAU$_{P301L}$

[k] Mouse overexpressing APP$_{SWE/FL/LON}$/PS1$_{M146L/L286V}$

[l] Drosophila amyloid β-protein

[m] APP$_{SWE}$/PS1$_{\Delta E9}$ rat model

[n] Drosophila expressing human Tau protein

[o] Antibody binding pTau phosphorylated at Ser202 and Thr205

[p] Neurofibrillary tangle

been suggested, thereby leading to a possible visualization of perimacular and perivascular Aβ deposits primarily in the OPL, GCL, and NFL of AD patients [100]. A modified HRA OCT system has been further employed to detect pTau in the GCL, OPL, IPL, and INL of a P301S mouse model [163].

Thus far, a consensus has not been met regarding the correlation between NFL thinning and degree of cognitive impairment. One study that measured impairment by MMSE and Montreal Cognitive Assessment (MOCA) found a positive correlation [142], while two others specifically reported no correlation between NFL thinning and either MMSE score or AD status [62, 111]. Notably, a study investigating NFL thinning as a diagnostic tool reported successful prediction of AD status from NFL thickness data [114].

While ex vivo staining has suggested that amyloid plaques can be detected in the eye, the first in vivo detection of Aβ deposits in a Tg model of AD came in 2010, when Koronyo-Hamaoui et al. reported high-resolution detection of curcumin-labeled Aβ plaques in the APP$_{SWE}$/PS1$_{\Delta E9}$ retina using an adapted optical imaging microscope [107, 108]. Other improvements and modifications to established OCT techniques, including Fourier Domain OCT, Spectral Domain OCT, Functional OCT, and Doppler OCT, have allowed researchers to document degeneration in specific ocular tissues and cell types, as well as changes in blood flow and blood oxygen saturation in the retina [17, 106, 110, 114, 124, 181].

Various imaging techniques have been used to study other aspects of degeneration in the AD eye. For example, lens opacity measured by light scattering was not found to correlate significantly with AD disease progression [18]. Digital photography has been used to examine changes to retinal vasculature, including vascular narrowing and attenuation, changes in tortuosity, increased width variation, and reduction of branching complexity [32, 59]. Fluorescent Ligand Eye Scanning (FLES) is another approach to detect Aβ peptides in AD lenses in vivo, which was used in another study to predict clinical diagnoses in probable AD patients [101, 102]. An additional study examining changes in retinal blood oxygen saturation used spectrophotometric non-invasive retinal oximetry to report the elevation of blood oxygen saturation, yielding data similar to that of AMD in AD patient retinas [49]. Furthermore, scanning with laser ophthalmoscopy (SLO) has revealed a reduction in the number of fibers in the AD optic nerve [40]. Confocal SLO has also been used for in vivo monitoring of apoptotic RGC death in a 3xTg AD mouse model, which could be applied to future research on neurodegeneration in AD patients [35]. Dysfunction in RGCs and changes in the optic nerve were also detected by pERG in patients with AD [109, 146, 147].

Although many of these changes are common to other neurodegenerative diseases [120], the ability to monitor increasingly detailed changes in the AD eye can illuminate those processes specific to the disease, such as deposition of Aβ. More importantly, these studies suggest that retinal imaging technologies with high resolution and sensitivity could be adapted to detect AD-specific pathology, which could facilitate the early diagnosis and monitoring of disease progression.

Therapeutic response in the retina of murine AD models

Advances in imaging of retinal Aβ in vivo facilitate the possibility of monitoring changes in amyloid burden in response to therapeutic intervention. Immunotherapies targeting Aβ deposits and accumulation have been studied in a handful of rodent models.

The first examination of the effects of immunization therapy on AD-related pathology in the rodent eye came from Liu et al. [117]. In this study, experimental groups of Tg2576 mice were immunized subcutaneously with a number of Aβ-related molecules [i.e., islet amyloid polypeptide (IAPP), Aβ oligomer, or Aβ fibril], and various parameters were measured. Instances of retinal plaque formation and resulting plaque density observed by immunohistochemistry were shown to decrease, though these results reached statistical significance solely in the Aβ oligomer- and IAPP-immunized groups. Amyloid angiopathy score increased significantly in all groups. Interestingly, retinal thinning was attenuated, but microglial infiltration and astrogliosis increased in the immunized groups compared with controls [117].

Among the considerations involved in developing new therapies for neurodegeneration is the possibility of repurposing existing or even FDA-approved drugs to combat different pathologies. In 2012, Koronyo et al. published findings from a study using the sub-cutaneous immunization of glatiramer acetate (GA), a drug approved for the treatment of relapsing-remitting multiple sclerosis [108, 164]. Their previous study also involved a modified myelin oligodendrocyte glycoprotein-derived peptide (MOG45D) loaded on dendritic cells (DC-45D) in the retinas of APP$_{SWE}$/PS1$_{\Delta E9}$ mice [107]. In the latter study, the authors measured and described the ex vivo quantitative reduction of amyloid plaque burden in the brain matching that observed in the retina [107]. In the subsequent study, in vivo imaging of mouse retinas following GA immunization displayed a reduction in Aβ plaque number after 1 month, and further reduction, as well as a dynamic pattern of plaque formation and clearance, after 2 months [108]. Next, Yang et al. investigated the effects of bone marrow transplantation (BMT) on APP$_{SWE}$/PS1$_{\Delta E9}$ mice, and reported a significant reduction in

Table 3 Non-specific ocular abnormalities in animal models of AD

Abnormality	Species	Model	Findings	References
Retinal degeneration	Drosophila	AβPP[a]/dBACE[b]/dPsn[c], pGMR-Aβ[d]/dBACE/AβPPL[e], hAβ$_{42}$tg[f]	Photoreceptor, optic nerve axonal degeneration, and overall abnormality in the fly eye; Thinning, amacrine cell apoptosis and other signs of degeneration in all layers, particularly NFL, GCL, IPL, and RPE	[30, 39, 52, 56, 61, 72, 75, 139, 148, 184, 187]
	Mouse	Tg2576[g], APP/PS1[h], 5xFAD[i], hAβPPtg/tg[j]		
Inflammation	Mouse	Tg2576, APP/PS1, 3xTg[k], 5xFAD, ApoE4[l]	Increased microgliosis, MCP-1[m] upregulation, infiltration by lymphocytes and monocytes, and abnormally shaped GFAP-astrocytes[n] engulfing Aβ, other signs of inflammation in most retinal layers, particularly in and near GCL, choroid	[6, 48, 61, 117, 139, 152, 154, 178, 187]
	Rat	Tg344-AD[o]		
Structural	Mouse	Tg2576, APP/PS1, 5xFAD, ApoE4	Retina. Synaptic impairment and density decrease of axons and synapses; tight junction attenuation; increased vascular branching and budding; RPE-adjacent Drusen-like deposits along Bruch's membrane; RGC dendritic complexity, field area, length decreases; cell loss and sparse distribution, GCL displaced cholinergic amacrine cell degeneration, ILM thickening	[5, 6, 62, 123, 148, 184]
	O. degus[p]	Sporadic AD (aged)	Retina. Post-synaptic dysfunction	[8]
	Rat	TgF344-AD	Choroid. Thickness reduction and vascular changes	[178]
	Drosophila	hAβ$_{42}$tg	Lens. Fission resulting in glazed-eye phenotype and reduced compound eye; swelling, organelle disorganization, opacity	[39, 56]
	Mouse	Tg2576, hAβPPtg/tg		
Other	Mouse	Tg2576, APP/PS1, ApoE4	Retina. Double nuclei and hypertrophy in RPE; increased ATP[q] release; Mitochondrial swelling, crista fragmentation and reduced complexity	[75, 151, 152, 178, 184]
	Rat	TgF344-AD		
	Mouse	ApoE4	Choroid. Increased neovascularization post-LDI[r], decreased VEGF[s], damage to neonatal vascular branching	[6, 123]

[a] Drosophila expressing amyloid β-protein precursor

[b] Drosophila expressing β-secretase 1

[c] Model expressing drosophila presenilin-1 protein

[d] Glass multiple reporter drosophila model expressing Aβ$_{42}$

[e] Drosophila expressing AβPP-like protein

[f] Drosophila model expressing human Aβ$_{42}$

[g] Mouse overexpressing APP isoform 695 bearing Swedish double mutations K670 M/N671L

[h] Mouse overexpressing APP$_{SWE}$/PS1$_{ΔE9}$ or APP$_{SWE}$/PS1$_{M146L}$

[i] Mouse overexpressing APP$_{SWE/FL/LON}$/PS1$_{M146L/L286V}$

[j] Drosophila model expressing human AβPP

[k] Mouse overexpressing APP$_{SWE}$/PS1/TAU$_{P301L}$

[l] Apoliprotein E mouse model

[m] Monocyte chemoattractant protein-1

[n] Astrocytes positive for glial fibrillary acidic protein

[o] APP$_{SWE}$/PS1$_{ΔE9}$ rat model

[p] *Octodon degus*, WT rodent native to Chile showing symptoms of sporadic AD

[q] Adenosine triphosphate, in APP$_{SWE}$/PS1$_{ΔE9}$ model overexpressing ATP

[r] Laser-driven injury

[s] Vascular endothelial growth factor

numbers of both retinal and cerebral Aβ deposits in BMT-treated Tg mice. The study also reported that the total number of retinal microglia, possibly involved in phagocytosis of Aβ plaques, was normalized to non-disease levels comparable to those seen in WT mouse retinas. GCL neuronal loss, inner retinal thinning, and other signs of age-related degeneration were mitigated in BMT-treated mice [187].

More recent investigations have yielded other promising results. He et al. [78] reported that treatment with Ginsenoside Rg1 significantly decreased NFT formation in the RPE cells of $APP_{SWE}/PS1_{M146L}$ mice compared with untreated Tg controls. Parthasarathy et al. [150] investigated the effects of intra-vitreally delivered sNEP (a recombinant form of the neprylisin catalytic domain) in the eyes of 5xFAD mice. The study reported a decrease in Aβ levels in sNEP-treated eyes compared with untreated Tg controls [150]. Retinal $Aβ_{40}$ appeared to have been more strongly affected, as a significant reduction of $Aβ_{40}$ was observed 2 h following treatment, while the reduction of $Aβ_{42}$ reached statistical significance only after 3 days. Although ERG response improved with sNEP treatment, this finding was not statistically significant [150]. Recently, Gao et al. [61] reported that memantine (MEM), an uncompetitive antagonist of the N-methyl-D-aspartate receptor, markedly increased RGC count (by NeuN-IR staining) and significantly decreased the number of apoptotic RGCs in retinas of MEM-treated Tg mice when compared with untreated Tg controls. Müller cell adapted response appeared to be inhibited in MEM-treated mice, and inner limiting membrane (ILM) thickening was mitigated compared to that of the untreated Tg controls. In addition, visual function showed improvement in MEM-treated mice, as the pERG P50 component showed a significant increase in amplitude and the pERG P2 component delay was significantly attenuated compared with deficits observed in untreated Tg controls [61].

Although these animal model studies involve diverse methodology, they collectively suggest that the retina is a tissue that may faithfully mirror brain pathology. Furthermore, the availability of the retina as a site for clinical monitoring of disease progression in response to therapeutic intervention also alludes to the possibility of potential therapeutic intervention via the retina. In the current absence of effective therapy for AD, the retina may yet prove useful as a site of retrograde drug administration, by exploiting the molecular delivery systems of the optic nerve.

Conclusions

Over the past decade, our understanding of AD has grown far beyond its established definitive signs, cerebral Aβ

plaques and NFTs. In this highly dynamic field, novel disease biomarkers are continually revealed. Amyloid-related findings include phosphorylated or conformationally diverse forms of Aβ, prone to extra- and intracellular aggregation. Other key molecular findings include assemblies of pTau, which are typically intracellular, but can also be observed in extracellular space, and may exhibit self-propagating properties. Many of these hallmarks, along with neuroinflammation and related abnormalities, have been observed in the retinas of AD patients and animal models.

Owing to the embryological ties of the neuroretina and brain structures affected by AD, it is no surprise that research has yielded increasing indications of degeneration in the AD retina as well. Recent evidence of early Aβ aggregation and amyloid-related neuronal degeneration in retinal tissues has mirrored that reported in human AD and Tg animal model brains. This not only supports the status of the retina as a target of presymptomatic AD imaging, but also suggests that Alzheimer's simultaneously affects both the brain and the retina.

Advances in retinal imaging and evidence of a positive response to therapy in the eyes of AD animal models hold promise for widespread population screening, early diagnosis and monitoring, and ultimately developing disease-modifying intervention. Although we learn much from observing AD in the brain, a key goal is to screen for the earliest signs and progression of the disease, and to intervene before it manifests as irreversible clinical symptoms. Therefore, one can no longer ignore the possibility that the retina—a CNS tissue uniquely accessible for direct, high resolution, non-invasive imaging—provides invaluable access to study and monitor Alzheimer's disease.

Compliance with ethical standards

Conflict of interest YK, MKH, KLB, founding members of NeuroVision Imaging (NVI).

References

1. Alexandrov PN, Pogue A, Bhattacharjee S, Lukiw WJ (2011) Retinal amyloid peptides and complement factor H in transgenic models of Alzheimer's disease. NeuroReport 22:623–627

2. Algvere PV, Kvanta A, Seregard S (2016) Drusen maculopathy: a risk factor for visual deterioration. Acta Ophthalmol 94:427–433. doi:10.1111/aos.13011

3. Almazroa A, Burman R, Raahemifar K, Lakshminarayanan V (2015) Optic disc and optic cup segmentation methodologies for glaucoma image detection: a survey. J Ophthalmol 2015:180972. doi:10.1155/2015/180972

4. Aloisi A, Barca A, Romano A, Guerrieri S, Storelli C, Rinaldi R, Verri T (2013) Anti-aggregating effect of the naturally occurring dipeptide carnosine on abeta1-42 fibril formation. PLoS One 8:e68159. doi:10.1371/journal.pone.0068159

5. Antes R, Ezra-Elia R, Weinberger D, Solomon A, Ofri R, Michaelson DM (2013) ApoE4 induces synaptic and ERG impairments in the retina of young targeted replacement apoE4 mice. PLoS One 8:e64949

6. Antes R, Salomon-Zimri S, Beck SC, Garcia Garrido M, Livnat T, Maharshak I, Kadar T, Seeliger M, Weinberger D, Michaelson DM (2015) VEGF mediates ApoE4-induced neovascularization and synaptic pathology in the choroid and retina. Curr Alzheimer Res 12:323–334

7. Archibald NK, Clarke MP, Mosimann UP, Burn DJ (2009) The retina in Parkinson's disease. Brain J Neurol 132:1128–1145. doi:10.1093/brain/awp068

8. Ardiles AO, Tapia-Rojas CC, Mandal M, Alexandre F, Kirkwood A, Inestrosa NC, Palacios AG (2012) Postsynaptic dysfunction is associated with spatial and object recognition memory loss in a natural model of Alzheimer's disease. Proc Natl Acad Sci USA 109:13835–13840. doi:10.1073/pnas.1201209109

9. Armstrong R, Kergoat H (2015) Oculo-visual changes and clinical considerations affecting older patients with dementia. Ophthalmic Physiol Opt 35:352–376. doi:10.1111/opo.12220

10. Ascaso FJ, Cruz N, Modrego PJ, Lopez-Anton R, Santabarbara J, Pascual LF, Lobo A, Cristobal JA (2014) Retinal alterations in mild cognitive impairment and Alzheimer's disease: an optical coherence tomography study. J Neurol 261:1522–1530. doi:10.1007/s00415-014-7374-z

11. Avila J, Pallas N, Bolos M, Sayas CL, Hernandez F (2016) Intracellular and extracellular microtubule associated protein tau as a therapeutic target in Alzheimer disease and other tauopathies. Expert Opin Ther Targets 20:653–661. doi:10.1517/14728222.2016.1131269

12. Bach-Holm D, Kessing SV, Mogensen U, Forman JL, Andersen PK, Kessing LV (2002) Normal tension glaucoma and Alzheimer disease: comorbidity? Acta Ophthalmol 90:683–685

13. Bambo MP, Garcia-Martin E, Gutierrez-Ruiz F, Pinilla J, Perez-Olivan S, Larrosa JM, Polo V, Pablo L (2015) Analysis of optic disk color changes in Alzheimer's disease: a potential new biomarker. Clin Neurol Neurosurg 132:68–73. doi:10.1016/j.clineuro.2015.02.016

14. Bambo MP, Garcia-Martin E, Otin S, Pinilla J, Larrosa JM, Polo V, Pablo LE (2015) Visual function and retinal nerve fibre layer degeneration in patients with Alzheimer disease: correlations with severity of dementia. Acta Ophthalmol 93:e507–e508. doi:10.1111/aos.12635

15. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H (2015) Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimer's Dement J Alzheimer's Assoc 11:718–726. doi:10.1016/j.jalz.2015.05.016

16. Bayer AU, Ferrari F, Erb C (2002) High occurrence rate of glaucoma among patients with Alzheimer's disease. Eur Neurol 47:165–168

17. Bayhan HA, Aslan Bayhan S, Celikbilek A, Tanik N, Gurdal C (2015) Evaluation of the chorioretinal thickness changes in Alzheimer's disease using spectral-domain optical coherence tomography. Clin Exp Ophthalmol 43:145–151. doi:10.1111/ceo.12386

18. Bei L, Shui YB, Bai F, Nelson SK, Van Stavern GP, Beebe DC (2015) A test of lens opacity as an indicator of preclinical Alzheimer Disease. Exp Eye Res 140:117–123

19. Berisha F, Feke GT, Trempe CL, McMeel JW, Schepens CL (2007) Retinal abnormalities in early Alzheimer's disease. Invest Ophthalmol Vis Sci 48:2285–2289

20. Blanks JC, Hinton DR, Sadun AA, Miller CA (1989) Retinal ganglion cell degeneration in Alzheimer's disease. Brain Res 501:364–372

21. Blanks JC, Schmidt SY, Torigoe Y, Porrello KV, Hinton DR, Blanks RH (1996) Retinal pathology in Alzheimer's disease. II. Regional neuron loss and glial changes in GCL. Neurobiol Aging 17:385–395

22. Blanks JC, Torigoe Y, Hinton DR, Blanks RH (1996) Retinal pathology in Alzheimer's disease. I. Ganglion cell loss in foveal/parafoveal retina. Neurobiol Aging 17:377–384

23. Bodis-Wollner I, Kozlowski PB, Glazman S, Miri S (2014) alpha-synuclein in the inner retina in parkinson disease. Ann Neurol 75:964–966. doi:10.1002/ana.24182

24. Bruban J, Glotin AL, Dinet V, Chalour N, Sennlaub F, Jonet L, An N, Faussat AM, Mascarelli F (2009) Amyloid-beta(1-42) alters structure and function of retinal pigmented epithelial cells. Aging Cell 8:162–177. doi:10.1111/j.1474-9726.2009.00456.x

25. Byerly MS, Blackshaw S (2009) Vertebrate retina and hypothalamus development. Wiley Interdiscip Rev Syst Biol Med 1:380–389. doi:10.1002/wsbm.22

26. Calabresi PA, Balcer LJ, Frohman EM (2010) Retinal pathology in multiple sclerosis: insight into the mechanisms of neuronal pathology. Brain J Neurol 133:1575–1577. doi:10.1093/brain/awq133

27. Calsolaro V, Edison P (2016) Neuroinflammation in Alzheimer's disease: current evidence and future directions. Alzheimer's Dement J Alzheimer's Assoc. doi:10.1016/j.jalz.2016.02.010

28. Cao L, Wang H, Wang F, Xu D, Liu F, Liu C (2013) Abeta-induced senescent retinal pigment epithelial cells create a proinflammatory microenvironment in AMD. Invest Ophthalmol Vis Sci 54:3738–3750. doi:10.1167/iovs.13-11612

29. Carlson NE, Moore MM, Dame A, Howieson D, Silbert LC, Quinn JF, Kaye JA (2008) Trajectories of brain loss in aging and the development of cognitive impairment. Neurology 70:828–833. doi:10.1212/01.wnl.0000280577.43413.d9

30. Carmine-Simmen K, Proctor T, Tschape J, Poeck B, Triphan T, Strauss R, Kretzschmar D (2009) Neurotoxic effects induced by the Drosophila amyloid-beta peptide suggest a conserved toxic function. Neurobiol Dis 33:274–281. doi:10.1016/j.nbd.2008.10.014

31. Chang LY, Lowe J, Ardiles A, Lim J, Grey AC, Robertson K, Danesh-Meyer H, Palacios AG, Acosta ML (2014) Alzheimer's disease in the human eye. Clinical tests that identify ocular and visual information processing deficit as biomarkers. Alzheimer's Dement J Alzheimer's Assoc 10:251–261. doi:10.1016/j.jalz.2013.06.004

32. Cheung CY, Ong YT, Ikram MK, Ong SY, Li X, Hilal S, Catindig JA, Venketasubramanian N, Yap P, Seow D et al (2014) Microvascular network alterations in the retina of patients with Alzheimer's disease. Alzheimer's Dement J Alzheimer's Assoc 10:135–142

33. Clavaguera F, Grueninger F, Tolnay M (2014) Intercellular transfer of tau aggregates and spreading of tau pathology: implications for therapeutic strategies. Neuropharmacology 76 Pt A:9–15. doi:10.1016/j.neuropharm.2013.08.037

34. Coppola G, Di Renzo A, Ziccardi L, Martelli F, Fadda A, Manni G, Barboni P, Pierelli F, Sadun AA, Parisi V (2015) Optical coherence tomography in Alzheimer's disease: a meta-analysis. PLoS One 10:e0134750. doi:10.1371/journal.pone.0134750

35. Cordeiro MF, Guo L, Coxon KM, Duggan J, Nizari S, Normando EM, Sensi SL, Sillito AM, Fitzke FW, Salt TE et al (2010) Imaging multiple phases of neurodegeneration: a novel approach to assessing cell death in vivo. Cell Death Dis 1:e3. doi:10.1038/cddis.2009.3

36. Crawford TJ, Devereaux A, Higham S, Kelly C (2015) The disengagement of visual attention in Alzheimer's disease: a longitudinal eye-tracking study. Front Aging Neurosci 7:118. doi:10.3389/fnagi.2015.00118

37. Cristovao JS, Santos R (2016) Metals and neuronal metal binding proteins implicated in Alzheimer's disease. Oxid Med Cell Longev 2016:9812178. doi:10.1155/2016/9812178

38. Curcio CA, Drucker DN (1993) Retinal ganglion cells in Alzheimer's disease and aging. Ann Neurol 33:248–257

39. Cutler T, Sarkar A, Moran M, Steffensmeier A, Puli OR, Mancini G, Tare M, Gogia N, Singh A (2015) Drosophila eye model to study neuroprotective role of CREB binding protein (CBP) in Alzheimer's disease. PLoS One 10:e0137691

40. Danesh-Meyer HV, Birch H, Ku JY, Carroll S, Gamble G (2006) Reduction of optic nerve fibers in patients with Alzheimer disease identified by laser imaging. Neurology 67:1852–1854

41. Davis BM, Crawley L, Pahlitzsch M, Javaid F, Cordeiro MF (2016) Glaucoma: the retina and beyond. Acta Neuropathol. doi:10.1007/s00401-016-1609-2

42. Dentchev T, Milam AH, Lee VM, Trojanowski JQ, Dunaief JL (2003) Amyloid-beta is found in drusen from some age-related macular degeneration retinas, but not in drusen from normal retinas. Mol Vis 9:184–190

43. Devanand DP, Pradhaban G, Liu X, Khandji A, De Santi S, Segal S, Rusinek H, Pelton GH, Honig LS, Mayeux R et al (2007) Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. Neurology 68:828–836. doi:10.1212/01.wnl.0000256697.20968.d7

44. Ding JD, Johnson LV, Herrmann R, Farsiu S, Smith SG, Groelle M, Mace BE, Sullivan P, Jamison JA, Kelly U et al (2011) Anti-amyloid therapy protects against retinal pigmented epithelium damage and vision loss in a model of age-related macular degeneration. Proc Natl Acad Sci USA 108:E279–E287. doi:10.1073/pnas.1100901108

45. Doraiswamy PM, Sperling RA, Johnson K, Reiman EM, Wong TZ, Sabbagh MN, Sadowsky CH, Fleisher AS, Carpenter A, Joshi AD et al (2014) Florbetapir F 18 amyloid PET and 36-month cognitive decline: a prospective multicenter study. Molecular Psychiatry 19:1044–1051. doi:10.1038/mp.2014.9

46. Du LY, Chang LY, Ardiles AO, Tapia-Rojas C, Araya J, Inestrosa NC, Palacios AG, Acosta ML (2015) Alzheimer's disease-related protein expression in the retina of octodon degus. PLoS One 10:e0135499. doi:10.1371/journal.pone.0135499

47. Dutescu RM, Li QX, Crowston J, Masters CL, Baird PN, Culvenor JG (2009) Amyloid precursor protein processing and retinal pathology in mouse models of Alzheimer's disease. Graefes Arch Clin Exp Ophthalmol 247:1213–1221

48. Edwards MM, Rodriguez JJ, Gutierrez-Lanza R, Yates J, Verkhratsky A, Lutty GA (2014) Retinal macroglia changes in a triple transgenic mouse model of Alzheimer's disease. Exp Eye Res 127:252–260

49. Einarsdottir AB, Hardarson SH, Kristjansdottir JV, Bragason DT, Snaedal J, Stefansson E (2015) Retinal oximetry imaging in alzheimer's disease. J Alzheimer's Dis JAD 49:79–83

50. Feke G, Hyman B, Stern R, Pasquale L (2015) Retinal blood flow in mild cognitive impairment and Alzheimer's disease. Alzheimer's Dementia 1:144–151

51. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y et al (2005) Global prevalence of dementia: a Delphi consensus study. Lancet (London, England) 366:2112–2117. doi:10.1016/s0140-6736(05)67889-0

52. Finelli A, Kelkar A, Song HJ, Yang H, Konsolaki M (2004) A model for studying Alzheimer's Abeta42-induced toxicity in Drosophila melanogaster. Mol Cell Neurosci 26:365–375

53. Fletcher WA, Sharpe JA (1986) Saccadic eye movement dysfunction in Alzheimer's disease. Ann Neurol 20:464–471. doi:10.1002/ana.410200405

54. Fox NC, Warrington EK, Rossor MN (1999) Serial magnetic resonance imaging of cerebral atrophy in preclinical Alzheimer's disease. Lancet (London, England) 353:2125. doi:10.1016/s0140-6736(99)00496-1

55. Fraller DB (2013) State of the science: use of biomarkers and imaging in diagnosis and management of Alzheimer disease. J Neurosci Nurs J Am Assoc Neurosci Nurs 45:63–70. doi:10.1097/JNN.0b013e3182829024

56. Frederikse PH, Ren XO (2002) Lens defects and age-related fiber cell degeneration in a mouse model of increased AbetaPP gene dosage in Down syndrome. Am J Pathol 161:1985–1990

57. Frederikse PH, Zigler JS Jr (1998) Presenilin expression in the ocular lens. Curr Eye Res 17:947–952

58. Frost S, Guymer R, Aung KZ, Macaulay SL, Sohrabi HR, Bourgeat P, Salvado O, Rowe CC, Ames D, Masters CL et al (2016) Alzheimer`s disease and the early signs of age-related macular degeneration. Curr Alzheimer Res (**Epub ahead of print**)

59. Frost S, Kanagasingam Y, Sohrabi H, Vignarajan J, Bourgeat P, Salvado O, Villemagne V, Rowe CC, Macaulay SL, Szoeke C et al (2013) Retinal vascular biomarkers for early detection and monitoring of Alzheimer's disease. Transl Psychiatry 3:e233

60. Frost S, Martins RN, Kanagasingam Y (2010) Ocular biomarkers for early detection of Alzheimer's disease. J Alzheimer's Dis JAD 22:1–16. doi:10.3233/jad-2010-100819

61. Gao L, Chen X, Tang Y, Zhao J, Li Q, Fan X, Xu H, Yin ZQ (2015) Neuroprotective effect of memantine on the retinal ganglion cells of APPswe/PS1DeltaE9 mice and its immunomodulatory mechanisms. Exp Eye Res 135:47–58. doi:10.1016/j.exer.2015.04.013

62. Gao L, Liu Y, Li X, Bai Q, Liu P (2015) Abnormal retinal nerve fiber layer thickness and macula lutea in patients with mild cognitive impairment and Alzheimer's disease. Arch Gerontol Geriatr 60:162–167. doi:10.1016/j.archger.2014.10.011

63. Gharbiya M, Trebbastoni A, Parisi F, Manganiello S, Cruciani F, D'Antonio F, De Vico U, Imbriano L, Campanelli A, De Lena C (2014) Choroidal thinning as a new finding in Alzheimer's disease: evidence from enhanced depth imaging spectral domain optical coherence tomography. J Alzheimer's Dis JAD 40:907–917

64. Gilmore GC, Groth KE, Thomas CW (2005) Stimulus contrast and word reading speed in Alzheimer's disease. Exp Aging Res 31:15–33. doi:10.1080/03610730590882828

65. Gilmore GC, Wenk HE, Naylor LA, Koss E (1994) Motion perception and Alzheimer's disease. J Gerontol 49:P52–P57

66. Goedert M (2015) NEURODEGENERATION. Alzheimer's and Parkinson's diseases: the prion concept in relation to assembled Abeta, tau, and alpha-synuclein. Science (New York, NY) 349:1255555. doi:10.1126/science.1255555

67. Goedert M, Spillantini MG (2006) A century of Alzheimer's disease. Science (New York, NY) 314:777–781. doi:10.1126/science.1132814

68. Goldeck D, Witkowski JM, Fulop T, Pawelec G (2016) Peripheral Immune Signatures in Alzheimer Disease. Curr Alzheimer Res 13:739–749

69. Goldstein LE, Muffat JA, Cherny RA, Moir RD, Ericsson MH, Huang X, Mavros C, Coccia JA, Faget KY, Fitch KA et al (2003) Cytosolic beta-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease. Lancet (London, England) 361:1258–1265

70. Grammenoudi S, Kosmidis S, Skoulakis EM (2006) Cell type-specific processing of human Tau proteins in Drosophila. FEBS Lett 580:4602–4606

71. Granholm E, Morris S, Galasko D, Shults C, Rogers E, Vukov B (2003) Tropicamide effects on pupil size and pupillary light reflexes in Alzheimer's and Parkinson's disease. Int J Psychophysiol 47:95–115

72. Greeve I, Kretzschmar D, Tschape JA, Beyn A, Brellinger C, Schweizer M, Nitsch RM, Reifegerste R (2004) Age-dependent neurodegeneration and Alzheimer-amyloid plaque formation in transgenic Drosophila. J Neurosci 24:3899–3906

73. Guo L, Duggan J, Cordeiro MF (2010) Alzheimer's disease and retinal neurodegeneration. Curr Alzheimer Res 7:3–14

74. Guo L, Salt TE, Luong V, Wood N, Cheung W, Maass A, Ferrari G, Russo-Marie F, Sillito AM, Cheetham ME et al (2007) Targeting amyloid-beta in glaucoma treatment. Proc Natl Acad Sci USA 104:13444–13449. doi:10.1073/pnas.0703707104

75. Gupta VK, Chitranshi N, Gupta VB, Golzan M, Dheer Y, Wall RV, Georgevsky D, King AE, Vickers JC, Chung R et al (2016) Amyloid beta accumulation and inner retinal degenerative changes in Alzheimer's disease transgenic mouse. Neurosci Lett 623:52–56. doi:10.1016/j.neulet.2016.04.059

76. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science (New York, NY) 297:353–356. doi:10.1126/science.1072994

77. Hasegawa M (2016) Molecular mechanisms in the pathogenesis of Alzheimer's disease and tauopathies-prion-like seeded aggregation and phosphorylation. Biomolecules. doi:10.3390/biom6020024

78. He Y, Zhao H, Su G (2014) Ginsenoside Rg1 decreases neurofibrillary tangles accumulation in retina by regulating activities of neprilysin and PKA in retinal cells of AD mice model. J Mol Neurosci 52:101–106. doi:10.1007/s12031-013-0173-7

79. Hedges TR 3rd, Perez Galves R, Speigelman D, Barbas NR, Peli E, Yardley CJ (1996) Retinal nerve fiber layer abnormalities in Alzheimer's disease. Acta Ophthalmol Scand 74:271–275

80. Heurling K, Leuzy A, Zimmer ER, Lubberink M, Nordberg A (2016) Imaging beta-amyloid using [(18)F]flutemetamol positron emission tomography: from dosimetry to clinical diagnosis. Eur J Nucl Med Mol Imaging 43:362–373. doi:10.1007/s00259-015-3208-1

81. Hinton DR, Sadun AA, Blanks JC, Miller CA (1986) Optic-nerve degeneration in Alzheimer's disease. N Engl J Med 315:485–487. doi:10.1056/nejm198608213150804

82. Ho CY, Troncoso JC, Knox D, Stark W, Eberhart CG (2014) Beta-amyloid, phospho-tau and alpha-synuclein deposits similar to those in the brain are not identified in the eyes of Alzheimer's and Parkinson's disease patients. Brain Pathol 24:25–32

83. Hof PR, Morrison JH (1990) Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer's disease: II. Primary and secondary visual cortex. J Comp Neurol 301:55–64. doi:10.1002/cne.903010106

84. Holmes BB, Diamond MI (2014) Prion-like properties of Tau protein: the importance of extracellular Tau as a therapeutic target. J Biol Chem 289:19855–19861. doi:10.1074/jbc.R114.549295

85. Hook V, Schechter I, Demuth HU, Hook G (2008) Alternative pathways for production of beta-amyloid peptides of Alzheimer's disease. Biol Chem 389:993–1006. doi:10.1515/bc.2008.124

86. Inestrosa NC, Reyes AE, Chacon MA, Cerpa W, Villalon A, Montiel J, Merabachvili G, Aldunate R, Bozinovic F, Aboitiz F (2005) Human-like rodent amyloid-beta-peptide determines Alzheimer pathology in aged wild-type Octodon degu. Neurobiol Aging 26:1023–1028. doi:10.1016/j.neurobiolaging.2004.09.016

87. Iseri PK, Altinas O, Tokay T, Yuksel N (2006) Relationship between cognitive impairment and retinal morphological and visual functional abnormalities in Alzheimer disease. J Neuroophthalmol 26:18–24

88. Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B, Phelps CH (2011) Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement J Alzheimer's Assoc 7:257–262. doi:10.1016/j.jalz.2011.03.004

89. James OG, Doraiswamy PM, Borges-Neto S (2015) PET Imaging of tau pathology in Alzheimer's disease and tauopathies. Front Neurol 6:38. doi:10.3389/fneur.2015.00038

90. Javaid FZ, Brenton J, Guo L, Cordeiro MF (2016) Visual and ocular manifestations of alzheimer's disease and their use as biomarkers for diagnosis and progression. Front Neurol 7:55. doi:10.3389/fneur.2016.00055

91. Jentsch S, Schweitzer D, Schmidtke KU, Peters S, Dawczynski J, Bar KJ, Hammer M (2015) Retinal fluorescence lifetime imaging ophthalmoscopy measures depend on the severity of Alzheimer's disease. Acta Ophthalmol 93:e241–e247. doi:10.1111/aos.12609

92. Jindahra P, Hedges TR, Mendoza-Santiesteban CE, Plant GT (2010) Optical coherence tomography of the retina: applications in neurology. Curr Opin Neurol 23:16–23. doi:10.1097/WCO.0b013e328334e99b

93. Jones BW, Pfeiffer RL, Ferrell WD, Watt CB, Tucker J, Marc RE (2016) Retinal remodeling and metabolic alterations in human AMD. Front Cell Neurosci 10:103. doi:10.3389/fncel.2016.00103

94. Jucker M, Walker LC (2013) Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature 501:45–51. doi:10.1038/nature12481

95. Jung JS, Yan JJ, Li HM, Sultan MT, Yu J, Lee HS, Shin KJ, Song DK (2016) Protective effects of a dimeric derivative of ferulic acid in animal models of Alzheimer's disease. Eur J Pharmacol 782:30–34. doi:10.1016/j.ejphar.2016.04.047

96. Kalia LV, Lang AE (2015) Parkinson's disease. Lancet (London, England) 386:896–912. doi:10.1016/s0140-6736(14)61393-3

97. Katz B, Rimmer S (1989) Ophthalmologic manifestations of Alzheimer's disease. Surv Ophthalmol 34:31–43

98. Katz B, Rimmer S, Iragui V, Katzman R (1989) Abnormal pattern electroretinogram in Alzheimer's disease: evidence for retinal ganglion cell degeneration? Ann Neurol 26:221–225. doi:10.1002/ana.410260207

99. Kavcic V, Vaughn W, Duffy CJ (2011) Distinct visual motion processing impairments in aging and Alzheimer's disease. Vision Res 51:386–395. doi:10.1016/j.visres.2010.12.004

100. Kayabasi U, Sergott R, Rispoli M (2014) Retinal examination for the diagnosis of Alzheimer's disease. Int J Ophthalmic Pathol 3:4. doi:10.4172/2324-8599.1000145

101. Kerbage C, Sadowsky CH, Jennings D, Cagle GD, Hartung PD (2013) Alzheimer's disease diagnosis by detecting exogenous

fluorescent signal of ligand bound to Beta amyloid in the lens of human eye: an exploratory study. Front Neurol 4:62

102. Kerbage C, Sadowsky CH, Tariot PN, Agronin M, Alva G, Turner FD, Nilan D, Cameron A, Cagle GD, Hartung PD (2015) Detection of amyloid beta signature in the lens and its correlation in the brain to aid in the diagnosis of Alzheimer's disease. Am J Alzheimers Dis Other Demen 30:738–745. doi:10.1177/1533317513520214

103. Kergoat H, Kergoat MJ, Justino L, Chertkow H, Robillard A, Bergman H (2001) An evaluation of the retinal nerve fiber layer thickness by scanning laser polarimetry in individuals with dementia of the Alzheimer type. Acta Ophthalmol Scand 79:187–191

104. Kesler A, Vakhapova V, Korczyn AD, Naftaliev E, Neudorfer M (2011) Retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Clin Neurol Neurosurg 113:523–526. doi:10.1016/j.clineuro.2011.02.014

105. Kessing LV, Lopez AG, Andersen PK, Kessing SV (2007) No increased risk of developing Alzheimer disease in patients with glaucoma. J Glaucoma 16:47–51

106. Kirbas S, Turkyilmaz K, Anlar O, Tufekci A, Durmus M (2013) Retinal nerve fiber layer thickness in patients with Alzheimer disease. J Neuroophthalmol 33:58–61. doi:10.1097/WNO.0b013e318267fd5f

107. Koronyo-Hamaoui M, Koronyo Y, Ljubimov AV, Miller CA, Ko MK, Black KL, Schwartz M, Farkas DL (2011) Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. Neuroimage 54(Suppl 1):S204–S217

108. Koronyo Y, Salumbides BC, Black KL, Koronyo-Hamaoui M (2012) Alzheimer's disease in the retina: imaging retinal abeta plaques for early diagnosis and therapy assessment. Neurodegener Dis 10:285–293. doi:10.1159/000335154

109. Krasodomska K, Lubinski W, Potemkowski A, Honczarenko K (2010) Pattern electroretinogram (PERG) and pattern visual evoked potential (PVEP) in the early stages of Alzheimer's disease. Doc Ophthalmol 121:111–121. doi:10.1007/s10633-010-9238-x

110. Kromer R, Serbecic N, Hausner L, Froelich L, Aboul-Enein F, Beutelspacher SC (2014) Detection of retinal nerve fiber layer defects in Alzheimer's disease using SD-OCT. Front Psychiatry 5:22

111. Kurna SA, Akar G, Altun A, Agirman Y, Gozke E, Sengor T (2014) Confocal scanning laser tomography of the optic nerve head on the patients with Alzheimer's disease compared to glaucoma and control. Int Ophthalmol 34:1203–1211. doi:10.1007/s10792-014-0004-z

112. La Morgia C, Ross-Cisneros FN, Hannibal J, Montagna P, Sadun AA, Carelli V (2011) Melanopsin-expressing retinal ganglion cells: implications for human diseases. Vision Res 51:296–302. doi:10.1016/j.visres.2010.07.023

113. La Morgia C, Ross-Cisneros FN, Koronyo Y, Hannibal J, Gallassi R, Cantalupo G, Sambati L, Pan BX, Tozer KR, Barboni P et al (2016) Melanopsin retinal ganglion cell loss in Alzheimer disease. Ann Neurol. doi:10.1002/ana.24548

114. Larrosa JM, Garcia-Martin E, Bambo MP, Pinilla J, Polo V, Otin S, Satue M, Herrero R, Pablo LE (2014) Potential new diagnostic tool for Alzheimer's disease using a linear discriminant function for Fourier domain optical coherence tomography. Invest Ophthalmol Vis Sci 55:3043–3051. doi:10.1167/iovs.13-13629

115. Lee CN, Ko D, Suh YW, Park KW (2015) Cognitive functions and stereopsis in patients with Parkinson's disease and Alzheimer's disease using 3-dimensional television: a case controlled trial. PLoS One 10:e0123229. doi:10.1371/journal.pone.0123229

116. Lee SH, Lee EJ, Kim TW (2015) Structural characteristics of the acquired optic disc pit and the rate of progressive retinal nerve fiber layer thinning in primary open-angle glaucoma. JAMA Ophthalmol 133:1151–1158. doi:10.1001/jamaophthalmol.2015.2453

117. Liu B, Rasool S, Yang Z, Glabe CG, Schreiber SS, Ge J, Tan Z (2009) Amyloid-peptide vaccinations reduce {beta}-amyloid plaques but exacerbate vascular deposition and inflammation in the retina of Alzheimer's transgenic mice. Am J Pathol 175:2099–2110

118. Liu D, Zhang L, Li Z, Zhang X, Wu Y, Yang H, Min B, Zhang X, Ma D, Lu Y (2015) Thinner changes of the retinal nerve fiber layer in patients with mild cognitive impairment and Alzheimer's disease. BMC Neurol 15:14. doi:10.1186/s12883-015-0268-6

119. Loffler KU, Edward DP, Tso MO (1995) Immunoreactivity against tau, amyloid precursor protein, and beta-amyloid in the human retina. Invest Ophthalmol Vis Sci 36:24–31

120. London A, Benhar I, Schwartz M (2013) The retina as a window to the brain-from eye research to CNS disorders. Nat Rev Neurol 9:44–53. doi:10.1038/nrneurol.2012.227

121. Lu Y, Li Z, Zhang X, Ming B, Jia J, Wang R, Ma D (2010) Retinal nerve fiber layer structure abnormalities in early Alzheimer's disease: evidence in optical coherence tomography. Neurosci Lett 480:69–72. doi:10.1016/j.neulet.2010.06.006

122. Luibl V, Isas JM, Kayed R, Glabe CG, Langen R, Chen J (2006) Drusen deposits associated with aging and age-related macular degeneration contain nonfibrillar amyloid oligomers. J Clin Investig 116:378–385. doi:10.1172/jci25843

123. Maharshak I, Salomon-Zimri S, Antes R, Liraz O, Nisgav Y, Livnat T, Weinberger D, Colton CA, Solomon AS, Michaelson DM (2015) The effects of the apoE4 genotype on the developing mouse retina. Exp Eye Res 145:17–25. doi:10.1016/j.exer.2015.11.001

124. Marziani E, Pomati S, Ramolfo P, Cigada M, Giani A, Mariani C, Staurenghi G (2013) Evaluation of retinal nerve fiber layer and ganglion cell layer thickness in Alzheimer's disease using spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci 54:5953–5958. doi:10.1167/iovs.13-12046

125. Mathis CA, Mason NS, Lopresti BJ, Klunk WE (2012) Development of positron emission tomography beta-amyloid plaque imaging agents. Semin Nucl Med 42:423–432. doi:10.1053/j.semnuclmed.2012.07.001

126. Maude RJ, Dondorp AM, Abu Sayeed A, Day NP, White NJ, Beare NA (2009) The eye in cerebral malaria: what can it teach us? Trans R Soc Trop Med Hyg 103:661–664. doi:10.1016/j.trstmh.2008.11.003

127. Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE, Bateman RJ (2010) Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science (New York, NY) 330:1774. doi:10.1126/science.1197623

128. McGeer PL, McGeer EG (2002) Local neuroinflammation and the progression of Alzheimer's disease. J Neurovirol 8:529–538. doi:10.1080/13550280290100969

129. McKinnon SJ (2003) Glaucoma: ocular Alzheimer's disease? Front Biosci J Virtual Libr 8:s1140–s1156

130. Mendez MF, Mendez MA, Martin R, Smyth KA, Whitehouse PJ (1990) Complex visual disturbances in Alzheimer's disease. Neurology 40:439–443

131. Meraz-Rios MA, Toral-Rios D, Franco-Bocanegra D, Villeda-Hernandez J, Campos-Pena V (2013) Inflammatory process in Alzheimer's disease. Front Integr Neurosci 7:59. doi:10.3389/fnint.2013.00059

132. Michael R, Rosandic J, Montenegro GA, Lobato E, Tresserra F, Barraquer RI, Vrensen GF (2013) Absence of beta-amyloid in cortical cataracts of donors with and without Alzheimer's disease. Exp Eye Res 106:5–13

133. Moncaster JA, Pineda R, Moir RD, Lu S, Burton MA, Ghosh JG, Ericsson M, Soscia SJ, Mocofanescu A, Folkerth RD et al

(2010) Alzheimer's disease amyloid-beta links lens and brain pathology in Down syndrome. PLoS One 5:e10659

134. More SS, Vince R (2015) Hyperspectral imaging signatures detect amyloidopathy in Alzheimer's mouse retina well before onset of cognitive decline. ACS Chem Neurosci 6:306–315

135. Moreno-Ramos T, Benito-Leon J, Villarejo A, Bermejo-Pareja F (2013) Retinal nerve fiber layer thinning in dementia associated with Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease. J Alzheimer's Dis JAD 34:659–664. doi:10.3233/jad-121975

136. Morin PJ, Abraham CR, Amaratunga A, Johnson RJ, Huber G, Sandell JH, Fine RE (1993) Amyloid precursor protein is synthesized by retinal ganglion cells, rapidly transported to the optic nerve plasma membrane and nerve terminals, and metabolized. J Neurochem 61:464–473

137. Moschos MM, Markopoulos I, Chatziralli I, Rouvas A, Papageorgiou SG, Ladas I, Vassilopoulos D (2012) Structural and functional impairment of the retina and optic nerve in Alzheimer's disease. Curr Alzheimer Res 9:782–788

138. Ng S, Villemagne VL, Berlangieri S, Lee ST, Cherk M, Gong SJ, Ackermann U, Saunder T, Tochon-Danguy H, Jones G et al (2007) Visual assessment versus quantitative assessment of 11C-PIB PET and 18F-FDG PET for detection of Alzheimer's disease. J Nucl Med Off Publ Soc Nucl Med 48:547–552

139. Ning A, Cui J, To E, Ashe KH, Matsubara J (2008) Amyloid-beta deposits lead to retinal degeneration in a mouse model of Alzheimer disease. Invest Ophthalmol Vis Sci 49:5136–5143

140. Nolan JM, Loskutova E, Howard AN, Moran R, Mulcahy R, Stack J, Bolger M, Dennison J, Akuffo KO, Owens N et al (2014) Macular pigment, visual function, and macular disease among subjects with Alzheimer's disease: an exploratory study. J Alzheimer's Dis JAD 42:1191–1202. doi:10.3233/jad-140507

141. Ohno-Matsui K (2011) Parallel findings in age-related macular degeneration and Alzheimer's disease. Progress Retinal Eye Res 30:217–238. doi:10.1016/j.preteyeres.2011.02.004

142. Oktem EO, Derle E, Kibaroglu S, Oktem C, Akkoyun I, Can U (2015) The relationship between the degree of cognitive impairment and retinal nerve fiber layer thickness. Neurol Sci 36:1141–1146

143. Ong YT, De Silva DA, Cheung CY, Chang HM, Chen CP, Wong MC, Wong TY, Ikram MK (2013) Microvascular structure and network in the retina of patients with ischemic stroke. Stroke J Cereb Circ 44:2121–2127. doi:10.1161/strokeaha.113.001741

144. Ono M, Saji H (2011) SPECT imaging agents for detecting cerebral beta-amyloid plaques. Int J Mol Imaging 2011:543267. doi:10.1155/2011/543267

145. Paquet C, Boissonnot M, Roger F, Dighiero P, Gil R, Hugon J (2007) Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Neurosci Lett 420:97–99

146. Parisi V (2003) Correlation between morphological and functional retinal impairment in patients affected by ocular hypertension, glaucoma, demyelinating optic neuritis and Alzheimer's disease. Semin Ophthalmol 18:50–57

147. Parisi V, Restuccia R, Fattapposta F, Mina C, Bucci MG, Pierelli F (2001) Morphological and functional retinal impairment in Alzheimer's disease patients. Clin Neurophysiol 112:1860–1867

148. Park SW, Kim JH, Mook-Jung I, Kim KW, Park WJ, Park KH (2014) Intracellular amyloid beta alters the tight junction of retinal pigment epithelium in 5XFAD mice. Neurobiol Aging 35:2013–2020

149. Parnell M, Guo L, Abdi M, Cordeiro MF (2012) Ocular manifestations of Alzheimer's disease in animal models. Int J Alzheimers Dis 2012:786494. doi:10.1155/2012/786494

150. Parthasarathy R, Chow KM, Derafshi Z, Fautsch MP, Hetling JR, Rodgers DW, Hersh LB, Pepperberg DR (2015) Reduction of amyloid-beta levels in mouse eye tissues by intra-vitreally delivered neprilysin. Exp Eye Res 138:134–144. doi:10.1016/j.exer.2015.06.027

151. Perez de Lara MJ, Pintor J (2015) Presence and release of ATP from the retina in an Alzheimer's disease model. J Alzheimer's Dis JAD 43:177–181. doi:10.3233/jad-141005

152. Perez SE, Lumayag S, Kovacs B, Mufson EJ, Xu S (2009) Beta-amyloid deposition and functional impairment in the retina of the APPswe/PS1DeltaE9 transgenic mouse model of Alzheimer's disease. Invest Ophthalmol Vis Sci 50:793–800

153. Perrin RJ, Fagan AM, Holtzman DM (2009) Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. Nature 461:916–922. doi:10.1038/nature08538

154. Pogue AI, Dua P, Hill JM, Lukiw WJ (2015) Progressive inflammatory pathology in the retina of aluminum-fed 5xFAD transgenic mice. J Inorg Biochem. 152:206–209. doi:10.1016/j.jinorgbio.2015.07.009

155. Price DL, Rockenstein E, Mante M, Adame A, Overk C, Spencer B, Duong-Polk KX, Bonhaus D, Lindsey J, Masliah E (2016) Longitudinal live imaging of retinal alpha-synuclein:GFP deposits in a transgenic mouse model of Parkinson's Disease/Dementia with Lewy Bodies. Sci Rep 6:29523. doi:10.1038/srep29523

156. Ratnayaka JA, Serpell LC, Lotery AJ (2015) Dementia of the eye: the role of amyloid beta in retinal degeneration. Eye (London, England) 29:1013–1026. doi:10.1038/eye.2015.100

157. Risacher SL, Wudunn D, Pepin SM, MaGee TR, McDonald BC, Flashman LA, Wishart HA, Pixley HS, Rabin LA, Pare N et al (2013) Visual contrast sensitivity in Alzheimer's disease, mild cognitive impairment, and older adults with cognitive complaints. Neurobiol Aging 34:1133–1144. doi:10.1016/j.neurobiolaging.2012.08.007

158. Rizzo M, Anderson SW, Dawson J, Nawrot M (2000) Vision and cognition in Alzheimer's disease. Neuropsychologia 38:1157–1169

159. Ross CA, Poirier MA (2004) Protein aggregation and neurodegenerative disease. Nat Med 10(Suppl):S10–S17. doi:10.1038/nm1066

160. Sadun AA, Bassi CJ (1990) Optic nerve damage in Alzheimer's disease. Ophthalmology 97:9–17

161. Sadun AA, Borchert M, DeVita E, Hinton DR, Bassi CJ (1987) Assessment of visual impairment in patients with Alzheimer's disease. Am J Ophthalmol 104:113–120

162. Salobrar-Garcia E, de Hoz R, Rojas B, Ramirez AI, Salazar JJ, Yubero R, Gil P, Trivino A, Ramirez JM (2015) Ophthalmologic psychophysical tests support OCT findings in mild Alzheimer's disease. J Ophthalmol 2015:736949. doi:10.1155/2015/736949

163. Schon C, Hoffmann NA, Ochs SM, Burgold S, Filser S, Steinbach S, Seeliger MW, Arzberger T, Goedert M, Kretzschmar HA et al (2012) Long-term in vivo imaging of fibrillar tau in the retina of P301S transgenic mice. PLoS One 7:e53547

164. Schwartz M, Bukshpan S, Kunis G (2008) Application of glatiramer acetate to neurodegenerative diseases beyond multiple sclerosis: the need for disease-specific approaches. BioDrugs 22:293–299

165. Selkoe DJ (2004) Cell biology of protein misfolding: the examples of Alzheimer's and Parkinson's diseases. Nat Cell Biol 6:1054–1061. doi:10.1038/ncb1104-1054

166. Selkoe DJ (2008) Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. Behav Brain Res 192:106–113. doi:10.1016/j.bbr.2008.02.016

167. Shi Z, Wu Y, Wang M, Cao J, Feng W, Cheng Y, Li C, Shen Y (2014) Greater attenuation of retinal nerve fiber layer thickness in Alzheimer's disease patients. J Alzheimer's Dis JAD 40:277–283. doi:10.3233/jad-131898

168. Sivak JM (2013) The aging eye: common degenerative mechanisms between the Alzheimer's brain and retinal disease. Invest Ophthalmol Vis Sci 54:871–880. doi:10.1167/iovs.12-10827

169. Steardo L Jr, Bronzuoli MR, Iacomino A, Esposito G, Steardo L, Scuderi C (2015) Does neuroinflammation turn on the flame in Alzheimer's disease? Focus on astrocytes. Front Neurosci 9:259. doi:10.3389/fnins.2015.00259

170. Surguchov A, McMahan B, Masliah E, Surgucheva I (2001) Synucleins in ocular tissues. J Neurosci Res 65:68–77

171. Tamura H, Kawakami H, Kanamoto T, Kato T, Yokoyama T, Sasaki K, Izumi Y, Matsumoto M, Mishima HK (2006) High frequency of open-angle glaucoma in Japanese patients with Alzheimer's disease. J Neurol Sci 246:79–83

172. Thomas SC, Alhasawi A, Appanna VP, Auger C, Appanna VD (2015) Brain metabolism and Alzheimer's disease: the prospect of a metabolite-based therapy. J Nutr Health Aging 19:58–63. doi:10.1007/s12603-014-0511-7

173. Tiepolt S, Hesse S, Patt M, Luthardt J, Schroeter ML, Hoffmann KT, Weise D, Gertz HJ, Sabri O, Barthel H (2016) Early [F]florbetaben and [C]PiB PET images are a surrogate biomarker of neuronal injury in Alzheimer's disease. Eur J Nucl Med Mol Imaging. doi:10.1007/s00259-016-3353-1

174. Trick GL, Barris MC, Bickler-Bluth M (1989) Abnormal pattern electroretinograms in patients with senile dementia of the Alzheimer type. Ann Neurol 26:226–231. doi:10.1002/ana.410260208

175. Trick GL, Trick LR, Morris P, Wolf M (1995) Visual field loss in senile dementia of the Alzheimer's type. Neurology 45:68–74

176. Trost A, Lange S, Schroedl F, Bruckner D, Motloch KA, Bogner B, Kaser-Eichberger A, Strohmaier C, Runge C, Aigner L et al (2016) Brain and retinal pericytes: origin, function and role. Front Cell Neurosci 10:20. doi:10.3389/fncel.2016.00020

177. Tsai CS, Ritch R, Schwartz B, Lee SS, Miller NR, Chi T, Hsieh FY (1991) Optic nerve head and nerve fiber layer in Alzheimer's disease. Arch Ophthalmol 109:199–204

178. Tsai Y, Lu B, Ljubimov AV, Girman S, Ross-Cisneros FN, Sadun AA, Svendsen CN, Cohen RM, Wang S (2014) Ocular changes in TgF344-AD rat model of Alzheimer's disease. Invest Ophthalmol Vis Sci 55:523–534

179. Tsuruma K, Tanaka Y, Shimazawa M, Hara H (2010) Induction of amyloid precursor protein by the neurotoxic peptide, amyloid-beta 25-35, causes retinal ganglion cell death. J Neurochem 113:1545–1554. doi:10.1111/j.1471-4159.2010.06724.x

180. Tzekov R, Mullan M (2014) Vision function abnormalities in Alzheimer disease. Surv Ophthalmol 59:414–433. doi:10.1016/j.survophthal.2013.10.002

181. van Velthoven ME, Faber DJ, Verbraak FD, van Leeuwen TG, de Smet MD (2007) Recent developments in optical coherence tomography for imaging the retina. Prog Retinal Eye Res 26:57–77. doi:10.1016/j.preteyeres.2006.10.002

182. Wegmann S, Maury EA, Kirk MJ, Saqran L, Roe A, DeVos SL, Nicholls S, Fan Z, Takeda S, Cagsal-Getkin O et al (2015) Removing endogenous tau does not prevent tau propagation yet reduces its neurotoxicity. EMBO J 34:3028–3041. doi:10.15252/embj.201592748

183. Williams MA, McGowan AJ, Cardwell CR, Cheung CY, Craig D, Passmore P, Silvestri G, Maxwell AP, McKay GJ (2015) Retinal microvascular network attenuation in Alzheimer's disease. Alzheimers Dement (Amst) 1:229–235. doi:10.1016/j.dadm.2015.04.001

184. Williams PA, Thirgood RA, Oliphant H, Frizzati A, Littlewood E, Votruba M, Good MA, Williams J, Morgan JE (2013) Retinal ganglion cell dendritic degeneration in a mouse model of Alzheimer's disease. Neurobiol Aging 34:1799–1806. doi:10.1016/j.neurobiolaging.2013.01.006

185. Wiseman FK, Al-Janabi T, Hardy J, Karmiloff-Smith A, Nizetic D, Tybulewicz VL, Fisher EM, Strydom A (2015) A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. Nat Rev Neurosci 16:564–574. doi:10.1038/nrn3983

186. Wyss-Coray T (2006) Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat Med 12:1005–1015. doi:10.1038/nm1484

187. Yang Y, Shiao C, Hemingway JF, Jorstad NL, Shalloway BR, Chang R, Keene CD (2013) Suppressed retinal degeneration in aged wild type and APPswe/PS1DeltaE9 mice by bone marrow transplantation. PLoS One 8:e64246. doi:10.1371/journal.pone.0064246

188. Zhao H, Chang R, Che H, Wang J, Yang L, Fang W, Xia Y, Li N, Ma Q, Wang X (2013) Hyperphosphorylation of tau protein by calpain regulation in retina of Alzheimer's disease transgenic mouse. Neurosci Lett 551:12–16