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The Retina as a Window or Mirror of the Brain Changes Detected in Alzheimer's Disease: Critical Aspects to Unravel

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Abstract

Alzheimer's disease is the most frequent cause of dementia worldwide, representing a global health challenge, with a massive impact on the quality of life of Alzheimer's disease patients and their relatives. The diagnosis of Alzheimer's disease constitutes a real challenge, because the symptoms manifest years after the first degenerative changes occurring in the brain and the diagnosis is based on invasive and/or expensive techniques. Therefore, there is an urgent need to identify new reliable biomarkers to detect Alzheimer's disease at an early stage. Taking into account the evidence for visual deficits in Alzheimer's disease patients, sometimes even before the appearance of the first disease symptoms, and that the retina is an extension of the brain, the concept of the retina as a window to look into the brain or a mirror of the brain has received increasing interest in recent years. However, only a few studies have assessed the changes occurring in the retina and the brain at the same time points. Unlike previous reviews on this subject, which are mainly focused on brain changes, we organized this review by comprehensively summarizing findings related with structural, functional, cellular, and molecular parameters in the retina reported in both Alzheimer's disease patients and animal models. Moreover, we separated the studies that assessed only the retina, and those that assessed both the retina and brain, which are few but allow establishing correlations between the retina and brain. This review also highlights some inconsistent results in the literature as well as relevant missing gaps in this field.

Keywords Alzheimer's disease · Retina · Brain · Biomarkers · Diagnosis

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that causes memory deficits and progressive deterioration of cognitive functions. In 2010, it was estimated that there were about 35.6 million people with dementia worldwide and this number is predicted to reach 81.1 million by 2040 [1]. AD is characterized by the presence of amyloid-β (Aβ) plaques, and neurofibrillary tangles (NFTs), as well as the selective loss of neurons and synaptic connections [2]. Aβ plaques consist of Aβ peptide aggregates that are organized mainly into oligomers, fibrils or plaques (reviewed in [3]), while NFTs are composed by aggregates of hyperphosphorylated tau (p-tau) protein [4].

The diagnosis of AD remains a challenge. Brain changes are already implemented for several years before diagnosis. Moreover, it is still difficult to establish a link between an early detection biomarker and the later appearance of symptoms in AD [5]. The analysis of cerebrospinal fluid (CSF), magnetic resonance imaging (MRI) or positron emission tomography (PET) for AD diagnosis constitutes invasive and/or expensive techniques. In fact, the definitive diagnosis of AD only occurs after the post-mortem identification of Aβ plaques and neurofibrillary tangles in the brain of AD patients [6]. With the aim of having earlier treatments for AD patients,

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it is also crucial to have a better and earlier diagnosis. For this, there is an urgent need to identify reliable biomarkers of AD onset [7].

The idea of the retina as a potential diagnostic tool in AD has emerged as a novel concept that has been increasingly explored. In fact, there is a close relationship between the eye and the brain. The outcomes of retina research can be relevant to understand the brain in health and disease, since the retina and brain present many similarities. They share the same embryological origin, extending both from the neural tube. The retina belongs to the central nervous system (CNS) exhibiting typical properties of the brain [8].

Visual alterations, including visual field defects, changes in contrast sensitivity and visual acuity, and impaired color vision discrimination, have been detected in AD patients [7, 9–15]. Indeed, even before the appearance of the first symptoms of AD, many patients present visual problems [16, 17], putting forward the possibility of using the retina as a tool for AD diagnosis.

Several studies already demonstrated the presence of Aβ aggregates [18–21] and p-tau [20, 22] in the retina of AD patients, suggesting that the retina is affected in AD. However, it must be emphasized that most studies that assessed the retina or visual function in the context of AD analyzed few parameters, and generally, those studies did not take into account the evaluation of potential alterations in the retina and the brain at the same time. Therefore, there are still many missing links regarding the alterations that occur in the retina and the brain of AD patients due to the lack of longitudinal and integrative studies investigating changes in both regions at similar time points. It is still not possible to integrate and consequently to clearly understand how changes found in the retina and the brain correlate in AD, remaining several open questions that have not been addressed yet. Currently, these gaps still preclude looking at the retina as a reliable window or mirror of what happens in the brain from the pathophysiological point of view in the context of AD. Herein, we reunite the findings regarding structural, functional, molecular, and cellular changes detected in the retina of AD patients and animal models, evidencing the missing gaps that need to be solved.

Structural and Functional Changes in the Retina of Alzheimer's Disease Patients

The use of the eye as a tool to study CNS disorders has emerged as a promising research avenue to follow [8]. The structure and function of the retina can be more easily assessed than the brain by imaging and electrophysiology techniques. Understanding how the retina is affected in AD or how it mirrors the AD brain changes can give us clues to unravel whether we can identify and define novel retinal biomarkers for early AD detection.

Retinal Structural Changes

Growing evidence has shown that AD patients present visual abnormalities, including visual acuity alterations, color discrimination deficits, contrast sensitivity changes, and vision field loss [14, 23–31]. In addition, it has been detected optic nerve damage [32, 33], loss of ganglion cells [34, 35], and retinal thinning [14, 36–55] in AD patients. The reduction of retinal thickness has been reported mainly in its innermost part, namely the retinal nerve fiber layer (RNFL) [14, 36–42, 44–50, 52–55], ganglion cell layer (GCL), and inner plexiform layer (IPL) [41, 43, 44, 49, 52].

Most studies evaluating retinal structural changes classified the patients according to the stage of the disease into mild cognitive impairment (MCI) and mild, moderate, and severe AD, based on the Mini-Mental State Exam (MMSE) score. However, there are discrepancies among the reports in this classification, which hinder the correlations between MMSE scores with the extent of retinal changes in AD patients. While some studies established different groups of AD patients taking into account different disease stages (with different MMSE scores), other studies joined patients in different disease stages in the same group. Based on that, some studies reported that mild AD comprises the patients with MMSE between 20 and 25 and moderate AD between 11 and 19 scores [36], while others reported that mild to moderate AD patients have the MMSE between 15–26 [41] and 14–19 scores [46], respectively. The reduction of RNFL has been already reported in patients with MCI [36, 37, 42, 45, 47, 52], presenting a MMSE score above 25 [36, 37, 45, 47, 52], with the exception of one study that considered a mean MMSE score of 19.3 [42]. A reduction of RNFL thickness has been also found in patients with mild and moderate AD. However, it is important to highlight that some studies consider different MMSE scores for mild stage (21–26 [53], 20–25 [36], 18–25 [39], 23 [37, 52]) and moderate stage (10–20 [40], 11–19 [36], 19 [48], 17 [43, 49, 52]), while others consider in the same group, "mild to moderate", patients with MMSE scores between 19–26 [50], 15–26 [41], 14–19 [46, 54] and 15 [14]. Despite the variability of the disease classification based on the MMSE score, most studies demonstrate that patients with MCI or AD present a reduction of RNFL thickness that seems to worsen with the disease progression [36, 47, 50]. Additionally, there are studies demonstrating no correlation between the MMSE score and the retinal thinning [39, 45, 46, 53] and also studies reporting a correlation between the MMSE score and optical coherence tomography (OCT) parameters, namely, retinal thickness [40, 42, 43] and macular volume [55]. In fact, different meta-analyses evidence the reduction of RNFL thickness in AD patients, as well

as the degeneration of retinal ganglion cells (RGCs) as key neuropathological changes related with AD pathology [56, 57]. A recent clinical trial (NCT01555827) confirmed the reduction of the RNFL in AD patients [58]. However, there are also evidences reporting RNFL thinning in patients with other type of dementias, as frontotemporal dementia, dementia with Lewy bodies, and dementia associated with Parkinson's disease [38, 52]. Therefore, it is vital to unravel whether the RNFL thinning is a specific feature of AD. On the other hand, there are studies reporting no differences in RNFL or GCL–IPL thickness in AD patients [59–63]. These conflicting findings may possibly be related with the patients enrolled in the study, cohort size, stage of the disease, retinal zone assessed (peripapillar versus macular zone) as well as with the type of imaging technique used (stratus OCT, spectral domain OCT, confocal scanning laser ophthalmoscopy and/or scanning laser polarimetry) that differ in technical aspects and analysis/algorithms.

Regarding the optic nerve (ON) assessment, while some studies reported no changes in topographic parameters in the optic nerve head (ONH) of AD patients [61, 64], another study reported changes in some ONH features, such as rim volume and rim area, among other features [32]. Additionally, alterations in fiber integrity were also detected in ONs of AD patients [33]. The findings regarding retinal structural changes in AD patients are summarized in Table 1.

Most studies reported only retinal structural changes, but not brain structural changes, making impossible to establish correlations between these two regions. In fact, those studies assessed retinal structural changes in MCI or AD patients, classified into mild, moderate, and severe AD, based in their neurological exams, but did not explore the brain structural alterations. To our knowledge, there are two studies that assessed both the retina and brain. In patients with increased neocortical Aβ score [68] and increased amount of total- and p-tau in CSF fluid [69], a reduction in the RNFL thickness was found (Table 2).

In general, many studies that evaluated changes in retinal thickness in AD patients found a thinning in RNFL, even at the early stages of AD disease or in MCI patients. However, in other pathologies affecting the brain, such as Parkinson's disease, a reduction in retinal thickness was also observed, indicating that these retinal changes are not exclusive of AD. As mentioned above, most studies assessed only the retina, and therefore, further studies need to be performed to explore simultaneously retinal and brain structural changes in AD patients to disentangle possible correlations between these two regions. These correlations are likely to be more useful for a better and earlier diagnosis of AD than assessing only the retinal thickness.

Retinal Functional Changes

Several reports have demonstrated the existence of functional changes in the retina of AD patients. Those studies, mainly based in pattern electroretinogram (PERG) recordings, reported a decrease in the amplitude [54, 70–73] and a delay in the latency [54, 72] of the RGCs response, without changes in the visual acuity [70–73]. These studies enrolled patients with AD dementia type [70], as well as patients with mild [71–73] and moderate AD [54], suggesting that the abnormal RGCs response might start in the early course of the disease. However, in a few studies, PERG [65, 66, 74] and ERG [67, 70] recordings in AD patients were normal (Table 1). As for the retinal thickness, these conflicting results might be due, at least in part, to the sample size of the cohort studied and/or the sample selection criteria. More studies, with a higher number of patients, are needed to give a better insight and help clarifying the changes occurring in the retina of AD patients.

Interestingly, there are a few studies assessing simultaneously the retina and brain function, trying to establish possible correlations. These studies reported a decrease of the PERG amplitude in AD patients that is consistent with a delay in the latency of visual evoked potentials (VEPs) [70, 72, 73].

Table 1 Retinal structural and functional changes detected in AD patients—studies assessing only the retina

Retinal structural and functional changes in AD patients		
Retinal structure		References
↓ RFNL thickness		[14, 36–42, 44–50, 52–55]
↓ GCL/GCL-IPL thickness		[41, 43, 44, 49, 52]
No changes in RFNL and GCL-IPL thickness		[59–63]
Retinal function		References
PERG	ERG	
↓ Amplitude ↑ Latency	–	[54]
No changes	–	[65, 66]
–	No changes	[67]

RFNL retinal fiber nerve layer, *GCL* ganglion cell layer, *IPL* inner plexiform layer, – not assessed

Table 2 Retinal structural and functional changes detected in AD patients—studies assessing the retina and brain simultaneously

Retinal structural and functional changes in AD patients			
Retinal structure		Brain parameters (not brain structure)	References
↓ RFNL thickness		↑ Neocortical Aβ score	[68]
↓ RFNL thickness		↑ Total- and p-tau in CSF	[69]
Retinal function		Brain function	References
PERG	ERG	VEPs	
↓ Amplitude No changes in latency	No changes	↑ Latency	[70]
↓ Amplitude	–	No changes	[71]
↓ Amplitude ↑ Latency	–	↑ Latency	[72]
↓ Amplitude	–	↓ Amplitude ↑ Latency	[73]
No changes	–	↑ Latency	[74]

RFNL retinal fiber nerve layer, *Aβ* amyloid beta, *p-tau* phosphorylated tau, *CSF* cerebrospinal fluid, – not assessed

Only one study has described reduced PERG amplitude without changes in VEPs [71], while another reported no changes in PERG recordings and an increase of the latency in VEPs [74] (Table 2).

Psychophysical methods have been used as a tool to assess the visual deficits occurring in patients with AD. However, there are unique challenges in designing and interpreting psychophysical experiments for AD patients. These tests imply a good understanding and memorization of the tests rules and instructions, which may be a challenge for AD patients. Based on that, it is important to understand whether the visual abnormalities detected result from visual problems or from the poor execution of the task. The psychophysical exams frequently performed in AD patients include visual acuity, contrast sensitivity, color perception, and visual field examination. There are studies only focusing on these ophthalmologic exams, while others assess psychophysical exams in parallel with OCT and/or PERG or ERG. In fact, in studies where both retinal structure and function are assessed, different scenarios are found: there are studies where the information about the psychophysical evaluation is scarce or even absent [36, 43–45]; in other studies, AD patients were excluded because they were diagnosed with diseases affecting the eye or optic nerve [37, 52]; and there are studies that did not exclude AD patients with visual problems, reporting the precise changes detected in the psychophysical exams. Therefore, there is some controversy in literature since some studies reported no changes in the ophthalmic exams, namely, visual acuity, visual fields, and color vision tests [38–42, 70, 72, 73], while others reported changes, namely reduced visual acuity [14, 46–48, 50, 53]. Interestingly, there is one study that found a correlation between changes in contrast sensitivity and color vision, with macular structural changes in AD patients [14].

In the context of AD, there are several studies using psychophysical tests in AD patients, but most of them are not focused in the assessment of retinal thickness and retinal function by ERG and/or PERG. Despite it has been reported a reduction of visual acuity in AD/dementia patients [13, 75, 76], many studies describe normal visual acuity in AD/dementia patients [10, 11, 77–81]. Regarding contrast sensitivity, there are also inconsistent findings. Although some studies reported no changes in the contrast sensitivity of AD patients [78–80], there are more studies demonstrating a decrease in contrast sensitivity in AD patients [10–15, 82], highlighting this parameter as a potential predictive biomarker for this disease [29]. Additionally, despite a study demonstrating absence of color perception changes in AD patients [13], most studies report color perception deficiency or decreased color discrimination [10, 12, 14, 15, 23, 81, 83–85], specifically in the blue-violet region of the spectrum [10, 23]. There is also evidence of visual fields constriction in AD patients [12, 86]; however, this is a topic that deserves further investigation and clarification.

In summary, psychophysical methods have been used to assess visual alterations in AD patients. However, there are some challenges difficult to overcome, because the performance of the patients, unrelated with vision, can affect the outcome of the tests. Despite of that, alterations in visual acuity, contrast sensitivity, and color perception have been reported, although other studies reported no changes in these parameters. Based on the amount of evidence gathered, it is likely that those visual alterations do occur in AD patients. However, it would be important to complement the information obtained from psychophysical tests with OCT and electrophysiological parameters, and many studies do not perform all those tests. To get more reliable results, additional studies, with very well-characterized and large cohorts, also including brain assessments, would help clarifying these issues, since better correlations could be performed between different retinal and vision parameters, as well as with retinal, vision, and brain

parameters, thus facilitating the identification of more reliable predictive biomarkers and biomarkers of disease progression.

Molecular and Cellular Changes in the Retina of AD Patients

As mentioned previously, several studies have reported visual changes in AD patients [12, 87], putting forward the importance of investigating signs of this neurodegenerative disease in the retina. The molecular and cellular AD-related changes that have been detected in the retina are associated with the presence of Aβ deposits and p-tau, glial reactivity, degeneration, and loss of neurons and reduction of the retinal nerve fibers and vascular changes.

Aβ and Tau

AD is characterized by Aβ deposition in the brain and by the presence of intracellular p-tau protein aggregates [88], which are associated with synaptic dysfunction and cognitive decline in AD patients [89, 90]. Measures of pathological alterations occurring in the retina have been proposed as potential biomarkers to improve an early diagnosis of this disease. Nevertheless, there are conflicting results in the literature regarding the presence of pathological hallmarks in the retina.

Three decades ago, no retinal neurofibrillary degeneration, neuritic plaques, or amyloid angiopathy, commonly seen in the brains of AD patients, were observed in post-mortem retinas of those subjects [91]. Accordingly, no Aβ deposits or abnormal tau aggregates were detected in the retina of AD patients, although they were present in their brains, indicating that Aβ and p-tau do not deposit in the retina similarly as in the brain [92] (Table 4). In another study, p-tau was detected in post-mortem retinas of AD patients, but no fibrillar tau or Aβ aggregates were observed, suggesting that Aβ or tau in the retina have no diagnostic value in AD [22]. However, in opposition to those findings, plaque-like structures were found in human post-mortem whole-mounted retinas [19]. Moreover, Aβ deposition was detected inside and around melanopsin subtype of retinal ganglion cells (mRGCs), indicating that these cells can be particularly affected in AD [93]. Consistent with brain pathology, retinal Aβ plaques were also found in post-mortem eyes from AD patients through plaque-labeling curcumin fluorochrome [18]. Interestingly, retinal curcumin-labeled plaques were detected earlier than in the brain and accumulated along with the progression of AD. Recently, retinal Aβ deposits were found in AD patients using in vivo imaging of curcumin. The retinas presented increased curcumin fluorescence comparing to healthy controls, demonstrating increased amyloid burden [21]. In the same study, neuritic-like Aβ deposits and increased retinal Aβ42 plaques were detected in whole-mounts and cross sections of post-mortem retinas from AD patients. Retinal Aβ was assembled into protofibrils and fibrils and plaques, which mirrored brain pathology. Thus, the possibility to noninvasively detect retinal amyloid deposits in vivo in AD patients may open new avenues for AD diagnosis [21].

Taking into account the conflicting results regarding the detection of Aβ and p-tau in the retina, this can hamper the establishment of a reliable retinal biomarker based on these proteins. However, most studies have reported the existence of Aβ pathology in the retina and the recent in vivo study using curcumin, if corroborated by other studies, with larger cohorts, might become a new approach to facilitate and improve the diagnosis of AD.

Glial Reactivity

Brain synaptic and cell loss that underlie cognitive decline in AD patients is accompanied by a neuroinflammatory response [94, 95]. Alterations in brain glial cells, microglia and astrocytes, have been associated with AD [96, 97]. The expression of common microglial markers that do not distinguish resting and activated microglia, such as Iba-1 and CD11b, is heterogeneous and does not demonstrate a consistent increase [98]. However, recently, it was reported that MHC class II and CD68, two markers of activated microglia activation, are consistently increased in the brain of AD patients, suggesting [98] that increases in microglia activation-associated markers are a feature of AD.

In retina whole-mounts from AD patients, MHC class II expression levels were significantly increased in endothelial cells, but the levels of MHC class II in microglia and perivascular macrophages were unchanged, although these cells presented a hypertrophied morphology [99]. Also in retina whole-mounts from AD patients, namely in the GCL in the peripheral retina, increased immunoreactivity for glial fibrillary acidic protein (GFAP) was detected in astrocytes, Müller cell end-feet and radial processes, compared to retinas from healthy controls [35], suggesting a reactive state of these cells in the retina in AD. An increase of 82% in the astrocyte/neuron ratio in the retina was observed concomitant with RGC loss and decreased thickness of RNFL [35].

It has been possible to establish correlations between microglia activation, amyloid load and neuronal damage in the brain of AD patients using PK11195-PET as a marker of activated microglia and [11C]PIB-PET to detect raised amyloid load [100, 101]. However, these techniques, because of their low resolution, and the small size of the retina, cannot be applied to the retina. The development of techniques with the resolution required to analyze in vivo the glial reactivity

in the retina would be of utmost importance to uncover the role of neuroinflammation in the retina of AD patients.

In conclusion, it is well established that brain neuroinflammation has a central role in the pathophysiology of AD. In the retina, in the context of AD, there are just a few studies analyzing glial reactivity and neuroinflammation. To better understand their role in retinal pathology in AD, more studies are needed, particularly in vivo studies, to assess not only the early stages of the disease but also its progression. However, to disentangle these questions, we need new tools and techniques to perform in vivo assessments.

Neurodegeneration and Optic Nerve Changes

Neurodegeneration and changes in the ONH have been described in post-mortem retinas from AD patients. Analysis of post-mortem ON obtained from AD patients showed axonal degeneration, concomitant with a decreased number of RGCs and thinning of the RNFL [102]. RGC degeneration was characterized by vacuolated cell cytoplasm and cell shrinkage [91]. The total number of neurons lost in the GCL was reported to be 25% in the central retina (fovea/foveola/parafoveal retina) of AD patients as compared with age-matched controls. Throughout the entire retina, the overall neuronal loss was estimated to be 36.4% [35]. Moreover, after morphometric analysis of the ON and the retina, the M cells, which are RGCs forming large caliber ON fibers, were partially lost [103]. Additional findings also demonstrate a significant loss of large and small RGCs in the macula of post-mortem retinas of AD patients [34]. A reduction in the number of ON fibers as well as a larger optic cup-to-disc ratio was detected by scanning laser ophthalmoscopy (SLO) in patients with AD comparing with controls [32]. Also, a higher proportion of patients with AD had detectable nerve fiber damage [104]. More recently, post-mortem analysis of AD retinas and optic nerves showed abnormal mRGC dendritic morphology and size and axon loss. The mRGCs from AD patients displayed smaller cell bodies, a patchy distribution of the melanopsin photopigment within their cytoplasm and a thinning of dendrites [93].

Regarding RGC and ON degeneration, the findings obtained in AD patients are more consistent, comparing to studies evaluating retinal structure and function and psychophysical studies, in which more conflicting results have been obtained. Therefore, since the ON can be visualized by non-invasive techniques, it may be screened. In addition, real-time imaging of RGCs undergoing apoptosis is also possible. The DARC (detection of apoptosing retinal cells) technique has been used to detect in vivo RGC death in glaucoma [105, 106], but it has been claimed that it can be also applied to AD (Yap et al.). In summary, using OCT and DARC techniques to assess in vivo changes in ON and RGCs might be very useful as complementary tools to facilitate the diagnosis of AD.

Vascular Changes

The brains of AD patients present changes in the vasculature [107], namely a narrowing of the retinal vessels and reduced venous blood flow rate [108, 109]. AD patients also present a sparser retinal microvascular network [110] and more tortuous retinal vessels compared with matched controls [111]. Interestingly, the fact that MCI patients present decreased retinal blood flow, but unchanged RNFL thickness, put forward the possibility that blood flow changes may precede neurodegeneration in AD pathology [109].

It was also found that islet amyloid polypeptide (IAPP), which forms toxic aggregates in the brain of AD patients, is present in the retina. Total IAPP levels and pericytes numbers in the retina mirrored comparable measurements in the hippocampus of AD patients. This study suggested that IAPP may be implicated in vascular changes associated with AD [112].

There are many studies that assessed the vascular changes in the brains of AD patients. However, there are just a few studies evaluating alterations in retinal vasculature. As mentioned above, these studies suggest that vascular changes also occur in the retina, and might even precede structural retinal changes, but this needs to be better clarified with additional studies, preferentially evaluating, at the same time, retinal and brain vasculature in order to try to establish correlations between them.

The molecular and cellular findings reported in studies that only assessed the retina, and those assessing both the retina and brain simultaneously, are summarized in Tables 3 and 4, respectively.

Structural and Functional Changes in the Retina of Alzheimer's Disease Mouse Models

Several animal models have been used to assess retinal changes in AD [113]. The use of animal models that recapitulate some features of AD is useful to understand the pathophysiology of AD since the early stages. Moreover, findings obtained from animal models of AD might help to identify molecular targets or biomarkers that may have clinical application in humans [2]. Nevertheless, since animal models of AD are generated using genes associated with familial AD, attention must be taken when trying to apply the conclusions obtained from these models to sporadic AD cases [114–116]. Herein, we summarize findings concerning structural and functional retinal changes in AD animal models. In fact, this manuscript is focused on retinal changes, and not on brain changes, which are very well documented. It must be emphasized that most studies carried out in animal models of AD that assess retinal changes do not assess brain changes. However, there are a few studies focused on the retina that also analyzed some

Table 3 Retinal molecular and cellular changes detected in AD patients—studies assessing only the retina

Retina	References
AD hallmarks	
Absence of NFT within RGCs and no neuritic plaques/amyloid angiopathy in the retinas/ON	[91]
Presence of retinal Aβ plaques	[18, 19, 21]
Presence of retinal Aβ fibrils and protofibrils ↑ Aβ42-containing deposits	[21]
Presence of neuritic-like plaques and NFT-like structures	
Presence of hyperphosphorylated tau/ Absence of fibrillar tau or Aβ aggregates	[22]
Aβ accumulation inside and around mRGCs	[93]
Glial reactivity	
Hypertrophy of microglia and perivascular macrophages ↑ MHC class II levels in endothelial cells	[99]
↑ ratio of astrocytes to neurons ↑ GFAP immunoreactivity of astrocytes in the GCL and of Müller cell end-feet/radial processes	[35]
↑ MHC class II and CD68 microglia activation markers	[98]
Neurodegeneration/cell loss	
Loss of RGCs	[34, 35, 93, 102, 103]
Loss of mRGCs; abnormal mRGC dendritic morphology	[93]
Reduction of ON fiber number	[32, 104]
Vascular changes	
Sparse retinal microvascular network and tortuous retinal vessels	[110, 111]
Decreased retinal blood flow	[108, 109]
Narrow venous blood column diameter in the major superior temporal retinal vein	[108]

NFT neurofibrillary tangles, *RGCs* retinal ganglion cells, *ON* optic nerve, *Aβ* amyloid beta, *mRGCs* melanopsin ganglion cells, *MHC II* major histocompatibility complex, *GFAP* glial fibrillary acidic protein, *GCL* ganglion cell layer

parameters in the brain. In this section, studies assessing only the retina and those assessing the retina and brain were separated in two sub-sections.

Main Findings of Studies Assessing Only the Retina

There is lack of studies regarding in vivo assessment of retinal structure/thickness in AD animal models. To date, there is only one study reporting a decrease of GCL/RNFL thickness in the retina of TgCRND8 mice, at 4 months, evaluated by OCT [117]. On the other hand, others reported no alterations in the thickness of nuclear retinal layers of APP/PS1 mice, at 12–16 months, evaluated by hematoxylin–eosin staining, suggesting that no neurodegenerative process is occurring in the retinas of this animal model [118].

Regarding retinal physiology, controversial results related with ERG responses have been obtained in APP/PS1 mice. Some studies reported a decrease in the ERG amplitude at 12–16 months [118, 119] as well as a delay in the latency at 11–24 months [120]. However, others reported

Table 4 Retinal molecular and cellular changes detected in AD patients—studies assessing the retina and brain simultaneously

Retinal molecular and cellular changes in AD patients		
Retina	Brain	References
AD hallmarks		
Absence of amyloid deposits or abnormal tau accumulation	Presence of Aβ and p-tau staining	[92]

Aβ amyloid beta, *p-tau* phosphorylated tau

no changes in the ERG response under dark-adapted conditions (rod response) in APP/PS1 mice, but there was an increase in the amplitude at 10.5–11 and 13 months under light-adapted conditions (cone response), which suggests that cone responses are more preserved or are larger in APP/PS1 mice than in controls [121]. Concordantly, others reported no significant changes in the ERG response in APP/PS1 mice at 13–15 months of age, apart from a slight decrease in the latency of rod pathway [122]. Unaltered ERG recordings were also reported in other animal models of AD, namely in 5xFAD mice, at 1, 2, and 6 months [123], and in P301L mice, at 1, 3, and 5 months [124]. Interestingly, in PERG studies, it has been reported a decreased amplitude in APP/PS1 mice at 13 months [125], in 5xFAD mice at 5 months [123], and in P301L mice since 1 until 6 months [124], suggesting altered RGCs activity in several AD animal models.

In animal models of AD, studies assessing structural and physiological alterations in the retina are not abundant. Moreover, those studies have been performed in different animal models, at different time points, and under different experimental conditions. Therefore, it is not a surprise the existence of conflicting results. Despite of that, and the limitations of the animal models of AD, several studies demonstrate clearly there are structural and physiological alterations in the rodent retina, which is in agreement with several reports in human studies. The structural and functional assessments reported in studies that only assessed the retina in animal models of AD are summarized in Table 5.

Main Findings of Studies Assessing the Retina and the Brain

In animal models of AD, there are no studies assessing simultaneously the structure of the retina and brain to understand possible correlations between both regions.

Concerning studies assessing retinal and brain function in the same animals, there are only two studies that evaluated the retina by PERG and the brain through VEP at the same time point, but no correlations were performed. These studies reported a decrease in PERG amplitude with a delay in VEP latency in APP/PS1 mice, at 13 months [125], and a decrease in VEP amplitude in 5xFAD mice, at 2 and 6 months [123] (Table 6).

Molecular and Cellular Changes in the Retina of Animal Models of AD

Herein, we summarize data from studies that have been published to date analyzing only the retina in different AD animal models (Table 7).

Main Findings of Studies Assessing Only the Retina

Aβ and Tau

The presence of Aβ in the retina of AD animal models is controversial. A recent study demonstrated the absence of Aβ or amyloid plaques in the retina of APP/PS1 mice at 13 months. Although Aβ was not detected, the authors found that APP, and the small membrane-bound-C terminal fragment (CTF) α and β were more abundant in the retina of APP/PS1 than in wild-type (WT) age-matched animals. Despite the upregulation of APP (~500%) in the retina, the CTFβ/CTFα ratio was small, suggesting that the increase in APP is processed mainly by the α-secretase which may limit the formation of toxic Aβ [121]. Conversely, other studies in the same animal model reported the presence of Aβ in the retina (thioflavine-S staining) at 13–16 months [126]. Accordingly, others detected the presence of Aβ plaques in the IPL and OPL. The appearance of the first Aβ plaques, with 5–20 μm length, was found at 12–13 months [118] and Aβ plaques with greater dimensions at 15–16 months [118]. Another study reported the existence of extracellular deposits of Aβ and robust APP immunoreactivity at the NFL and GCL at 27 months old, whereas at 7.8 months, it was only detected a sparse immunoreactivity of APP in the GCL and inner nuclear layer (INL) [127].

In 3xTg-AD mice, it was detected the presence of some Aβ deposits in the retina at 9 months [129], while in another study, the presence of Aβ deposits was detected already at 5–20 weeks, with an increase of these deposits at later time points [128].

In 5xFAD mice, large amounts of intracellular Aβ were found in the retina at 8-months [130]. It has been claimed that the intraneuronal Aβ can be the source of the extracellular Aβ in the brain of 5xFAD mice [135], and the same could occur in the retina. Although the classical view is that Aβ forms deposits extracellularly, emerging evidence indicates that this peptide can also accumulate inside neurons and contribute to disease progression. Therefore, it is important to understand the dynamic interrelationship between intra- and extracellular Aβ [136].

In Tg2576xTg1 mice, extracellular deposits of Aβ were found in the retina, specifically at the RNFL and surrounding the cells in the GCL, at 27 months, but not at 7.8 months [127].

The studies mentioned above indicate that different animal models of AD present distinct amounts of Aβ in the retina. In fact, a study assessed and quantified the amount of Aβ40 and Aβ42 in the retina of several animal models of AD. It was found that the amount of Aβ40 is higher in 5xFAD and lower in 3xTg-AD mice (5xFAD > APP/PS1 > Tg2576 > 3xTg-AD), while the amount of Aβ42 is also higher in 5xFAD and lower in APP/PS1 (5xFAD >

Table 5 Retinal structural and functional changes detected in AD animal models—studies assessing only the retina

Retinal structural and functional changes in AD animal models				
Animal model	Age	Retinal structure		References
TgCRND8 mice	4–8 M	↓ RNFL and GCL thickness		[117]
Animal model	Age	Retinal function		References
		PERG	ERG	
APP/PS1 mice	12–16 M	–	↓ Amplitude	[118]
APP/PS1 mice	13–16 M	–	↓ Amplitude	[119]
APP/PS1 mice	10.5–11 M 13 M	–	No changes in rods response but ↑ amplitude under light-adapted conditions (cones response)	[121]
P301L mice	1, 3, and 5 M	↓ Amplitude ↑ Latency	No changes	[124]

PERG pattern electroretinogram, *ERG* electroretinogram, *RFNL* retinal fiber nerve layer, *GCL* ganglion cell layer, – not assessed

Tg2576 > 3xTg-AD> APP/PS1). The 5xFAD mice exhibit the highest expression of Aβ in the CNS. Its genome is altered with five human genes and this prompts a more aggressive brain and retinal AD-pathology [137]. More recently, it was reported the presence of Aβ42 in the retina of another AD animal model, the TgCRND8 mice, at 4 months, with a stronger deposition of APP and Aβ aggregates in RGCs, suggesting that these cells might be the most susceptible to degeneration [117].

Besides the Aβ plaques, another hallmark of AD is the presence of aberrant aggregates denominated neurofibrillary tangles (NFTs) resulting from the hyperphosphorylation of tau protein, which contribute to the destabilization of microtubules, impairment of axonal transport, and neuronal death [138]. Most animal models of AD have genome modifications that trigger Aβ deposition, aggregation, and plaque formation, but without the development of neurofibrillary tangles. However, it has been reported an increase in the amount of p-tau and NFTs in the retina of APP/PS1 mice [126], 3xTg-AD mice [128], as well as in two models of tauopathy, Htau mice [139] and P301L mice [131]. Interestingly, the presence of hyperphosphorylated tau in the RNFL and tau inclusions in RGCs were found in the retinas of P301S tau transgenic mice at 1 and 2 months, respectively [131].

Glial Reactivity

AD pathology comprises a neurodegenerative process accompanied by an immune/inflammatory response [94]. The involvement of glial cells in the AD pathophysiology, particularly in the retina of several animal models of AD, will be highlighted here.

Microglial cells are the immune cells of CNS. In the retina, microglia are mainly localized in the inner retinal layers. Under physiological conditions, they are highly ramified and exhibit a dynamic behavior, using their processes to scan the retina parenchyma. However, with the aging process, this dynamic behavior and their morphology change to a senescent phenotype [140]. Retinal microglial cells have been assessed since microglial changes have been correlated with several neurodegenerative diseases, namely AD.

Table 6 Retinal functional changes detected in AD animal models—studies assessing the retina and brain simultaneously

Retinal functional changes in AD animal models					
Animal model	Age	Retinal function		Brain function	References
		PERG	ERG	VEPs	
APP/PS1 mice	11–24 M	–	↑ Latency	↑ Latency	[120]
APP/PS1 mice	13–15 M	–	Mostly no changes, although better outcome in rods response (↓ latency)	No changes	[122]
APP/PS1 mice	13 M	↓ Amplitude	–	↑ Latency	[125]
5xFAD mice	1, 2, and 6 M	↓ Amplitude	No changes	↓ Amplitude	[123]

PERG pattern electroretinogram, *ERG* electroretinogram, *VEPs* visual evoked potentials, – not assessed

Table 7 Retinal molecular and cellular changes detected in AD animal models—studies assessing only the retina

Animal model	Age	Retina	References
AD hallmarks			
APP/PS1 mice	13 M	Absence of Aβ or amyloid plaques	[121]
APP/PS1 mice	12–16 M	Presence of Aβ	[118, 126, 127]
APP/PS1 mice		Presence of p-tau tangles	[126]
3xTg-AD mice	5–20 post-natal weeks	Presence of Aβ Presence of p-tau tangles	[128]
3xTg-AD mice	9 M	Presence of Aβ	[129]
5xFAD mice	8 M	Large amount of intracellular Aβ	[130]
Tg2576xTg1 mice	7.8 M	Absence of Aβ	[127]
Tg2576xTg1 mice	27 M	Presence of Aβ	[127]
TgCRND8 mice	4 M	Presence of Aβ	[117]
P301L	1 and 2 M	↑ p-tau in RNFL and tau inclusions in RGCs	[131]
Glial reactivity			
APP/PS1 mice	13 M	No changes in the number of microglia and in the number of their processes	[121]
APP/PS1 mice	13 M	↑ Number of microglia ↑ Reactive microglia	[125]
APP/PS1 mice	12–16 M	↑ Microglia immunoreactivity	[118]
Tg2576 mice	14 M	↑ Astrocytes and microglia reactivity	[132]
3xTg-AD mice	5–20 and 30–40 post-natal days	No changes in microglia density and morphology	[128]
3xTg-AD mice	50–80 post-natal days	↑ Microglia density Microglia become less ramified and present a pro-inflammatory phenotype	[128]
P301L mice		↑ Microglia reactivity	[133]
Tg2675xTg1 mice	27 M	↑ Microglia reactivity	[127]
APP/PS1 mice	5 and 13 M	No changes in the expression and distribution of Müller cells	[121]
APP/PS1 mice	13 M	↑ Müller cells reactivity	[125]
APP/PS1 mice	12–16 M	No changes in GFAP staining	[118]
3xTg-AD mice	9 M	No changes in GS expression (Müller cells marker) ↑ Number of GFAP-positive Müller cells processes Astrocytes with hypertrophic-like phenotype	[129]
3xTg-AD mice	5–10 and 30–40 post-natal days	↑ Astrocyte reactivity	[128]
Tg-SwDI mice	6.5–8, 9–10 and 14–15 M	No changes in GFAP immunoreactivity (6.5–8 M) ↑ GFAP immunoreactivity (9–10 and 14–15 M)	[134]
Neurodegeneration/cell loss			
APP/PS1 mice	5 and 13 M	No changes in the number of RGCs	[121]
APP/PS1 mice	10.8 M	↑ TUNEL-positive RGCs	[127]
APP/PS1 mice	13–16 M	↓ Cell density in the inner layers Presence of TUNEL-positive cells ↓ Axonal density in the ON	[119, 125]
APP/PS1 mice	13–16 M	↓ Number of amacrine cells	[125]
Tg2675xTg1 mice	7.8 and 27 M	Presence of TUNEL-positive cells	[127]
Tg-SwDI mice	6.5–8 and 9–10 M	↓ Cell density in the inner retinal layers	[134]
Tg-SwDI mice	9–10 and 14–15 M	Loss of cholinergic cells	[134]
TgCRND8 mice	4 M	↓ Number of RGCs	[117]
P301L mice	5 M	Abnormal axonal enlargements No changes in the number of RGCs	[131]

Aβ amyloid beta, *p-tau* phosphorylated tau, *GFAP* glial fibrillary acidic protein, *GS* glutamine synthetase, *ON* optic nerve, *RGCs* retinal ganglion cells

The number of microglial cells in the retina of APP/PS1 mice is increased at 13 months, comparing with 5 months-old animals. However, these changes were detected between time points, and not between phenotypes, i.e. APP/PS1 vs WT mice, suggesting that these changes are associated with the aging process and not necessarily with AD pathology [121]. However, in the same animal model, another study reported changes in microglia, comparing to WT animals, suggesting that these changes are related with AD. The number of microglia and reactive microglia increased in the retina at 13 months [125]. Concordantly, others reported an increase in microglia immunoreactivity in the retina, with a "dendritic-like" appearance and thicker processes, at 12–16 months [118].

In 3xTg-AD mice, the density of microglial cells in the retina remains equal to the age-matched WT mice at 5–20 and 30–40 post-natal weeks, which are considered, respectively, pre-symptomatic and early symptomatic AD stages. At later stages, 50–80 weeks, increased microglia density was found in the retina of 3xTg-AD. Regarding microglia morphology, it acquires different morphologies depending on the AD stage: in the pre-symptomatic stage, microglial cells present a more ramified morphology and express typical anti-inflammatory components; at early-symptomatic stage, the morphology of microglial cells did not differ between 3xTg-AD mice and controls; in later symptomatic stage, microglial cells became less ramified comparing with control animals and presented a pro-inflammatory phenotype [128].

In the retina of the P130L mice, a model of tauopathy, a significant increase in microglia reactivity was detected, co-localizing with tau oligomers, suggesting the engulfment of tau oligomers by these cells [133]. In Tg2675xTg1 mice, there is only one study reporting an increase of microglia reactivity surrounding RGCs, at 27 months [127].

In summary, there are some studies assessing the microglia in the retina of animal models of AD. In some of those studies, no changes were detected in microglia morphology and reactivity, but others revealed alterations in these cells. These potential discrepancies are related with the animal model used, as well as with the time point assessed. However, there is no doubt that at least for some animal models and later time points there is change in microglia profile in the retina, similarly as in the brain. However, we must keep in mind that it is not easy dissecting changes in microglia due to the natural aging process or due to AD pathology, and further studies are needed to clarify this question.

Müller cells are the predominant glial element of the retina (90% of total glia) and are oriented radially, while astrocytes are located mainly in the inner part of the retina. Both cell types are important for neurotrophic support, blood–retinal barrier (BRB) maintenance and homeostatic functions, among others (reviewed by [141]). The most common markers used to detect Müller cells are glutamine synthase (GS), vimentin, and cellular retinaldehyde-binding protein (CRALBP). GFAP is the major constituent of the astrocytic intermediate filament usually used to detect astrocytes [141]. However, Müller cells end feet can also express GFAP [142].

In APP/PS1 mice, the GS and CRALBP immunoreactivity and the distribution of Müller cells are unchanged in the retina, at 5 and 13 months [121]. However, others reported an increase in Müller cells immunoreactivity (GS staining) at 13 months [125]. Regarding astrocytes, no differences in the GFAP staining were detected between APP/PS1 and WT mice at 12–16 months [118].

In 3xTg-AD mice, no changes in the GS expression were observed at 9 months. However, the number of GFAP-positive Müller cell processes increased in the retina, comparing with WT animals. Importantly, aging per se increases the number of Müller cell processes expressing GFAP in the retina of 3xTg-AD mice, 10 times more comparing 3xTg-AD at 18–24 months with 9 months old. Regarding astrocytes, some presented a hypertrophic-like phenotype, with more and longer processes in the retinas of 3xTg-AD mice at 9 months [129]. Concordantly, a recent study reported a marked astrogliosis in the retina of the 3xTg-AD mice at early stages [128]. Although these results suggest a possible involvement of macroglia in the pathological process of AD at early stages, at least in the 3xTg-AD animal model, it is important to highlight that macroglial changes also occur within the normal aging process. Therefore, it is important to distinguish changes in macroglia due to aging from those specific of AD.

In Tg-SwDI mice, there is astrocytic gliosis in the RNFL, demonstrated by the increase of GFAP immunoreactive area comparing with controls. This gliosis was detected only in animals with middle (9–10 months) and old age (14–15 months), since no evidence of astrogliosis was found in young (6.5–8 months) animals. However, this increase in GFAP immunoreactivity was also observed in the old control animals (14–15 months) when comparing with younger animals (6.5–8 and 9–10 months), suggesting that aging also contributes for the AD-dependent gliosis [134].

As for microglia, these findings suggest that macroglia reactivity in the retina is not consistent among the animal models of AD. Besides the animal model used, glial changes are also related with the age of the animals, as well as with the type of glial cells analyzed, Müller cells or astrocytes. Further studies are needed to detangle the glial changes related with the normal aging versus AD-specific ones.

Neurodegeneration/Cell Death

Brain neurodegeneration is a hallmark of AD and has been associated with Aβ toxicity [143]. Retinal cell death has been also assessed in animal models of AD. In the retina of APP/PS1 mice with 5.5 and 13 months, no changes were detected in the number of RGCs (RBPMS staining), namely the

intrinsically photosensitive RGCs and αRGCs, the two subpopulations mostly affected in AD patients [121]. However, in the same animal model, others reported a reduction in the cell density in the GCL [119, 125], as well as the presence of TUNEL-positive cells in the inner part of the retina [119, 125] and a reduction of axonal density in the ON, at 13–16 months [119]. Accordingly, it was observed an increase in the number of TUNEL-positive RGCs at the age of 10.8 months [127]. The number of amacrine cells was also assessed by choline acetyltransferase (ChAT) staining, and it was detected a decrease in the number of these cells in APP/PS1 mice, which was associated with an increase in cell death by apoptosis (co-labeling of TUNEL and ChAT) [125].

In the Tg2675xTg1 mice, TUNEL-positive cells were detected only in the GCL, at two time points, 7.8 and 27 months, and the number of apoptotic cells increased with age [127]. In Tg-SwDI mice retina, a reduction in the number of cells in the GCL was detected at 6.5–8 months that persisted until 9–10 months. This animal model also presented a loss of cholinergic cells in the GCL at 9–10 months and in the INL at 14–15 months [134]. In TgCRND8 mice, death of RGCs was reported very early, at 4 months. However, the authors only counted DAPI-positive cells in the GCL and did not use a specific marker for RGCs. Thus, the cell death measured in the GCL could also include displaced amacrine cells and endothelial cells that are also present in this layer [117]. In P301S mice, there are no changes in the number of RGCs. However, it was reported an abnormal axonal swelling, with axons presenting dilations containing disorganized filaments and degenerative mitochondria [131].

This group of findings suggests that retinal cell death is a common feature in different animal models of AD, in some cases even at early stages, and affecting particularly RGCs, which form the ON. However, these evidences were not found in all studies, which might be related with the different techniques used to assess retinal cell death, the animal models used, as well as the time points at which the assessment was performed.

Tight Junctions/Blood–Retinal Barrier Permeability

The retina is an immune privileged tissue protected by the BRB, which is composed by an outer part that comprises the retinal pigment epithelial (RPE) cells, and an inner part at the level of the retinal capillary endothelial cells [144]. In both RPE and retinal endothelial cells, tight junctions are major molecular components of the BRB. However, there is only one study addressing and reporting changes in the tight junction proteins in an animal model of AD. In 5xFAD mice, at 8 months, there was an increase in the accumulation of Aβ in the RPE, which was associated with a decreased expression and disorganization of ZO-1 and occludin [130].

Main Findings of Studies Assessing the Retina and the Brain

Studies addressing alterations in both the retina and the brain, at similar time points (Table 8), may help clarifying whether the retina is indeed a window to or a mirror of the AD brain. However, there are only a few studies reflecting this dual analysis of the retina and brain at similar time points, and herein, we summarize data from those studies. However, it is important to highlight there are several differences among the studies mentioned below, particularly regarding the type of changes analyzed in the retina and the use of different animal models of AD. Moreover, most studies only analyzed retinal sections and not the entire retina. The use of retinal whole-mounts would give a better clue about potential changes in the retina. Lastly, some discrepancies may also arise because different histological techniques and criteria have been used.

Aβ and Tau

There is still controversy regarding the mechanisms underlying retinal dysfunction and the period that retinal changes related to AD hallmarks start, and therefore, a better insight into these questions is needed. Using the APP/PS1 animal model, Chidlow and colleagues evaluated the retinal pathology, concomitantly with changes in the brain. As it was expected, there was a consistent increased expression of APP in the cortex and hippocampus of transgenic animals at all time points analyzed, from 7 to 12 months. In the retina, at all time points, the expression of APP was higher than in WT animals, not only in the RGCs but also in other retinal neurons. The increased expression of APP in the brain naturally contributed for increasing the Aβ peptides and consequently for the deposition of plaques. However, in the retina, no amyloid deposits and no signs of p-tau were observed at 12 months [145]. Being both Aβ deposits and p-tau major features of AD pathology, these observations suggest that retinal pathology does not occur simultaneously with the amyloid deposition in the brain, which is in agreement with what was found in AD patients [92].

On the contrary, others reported the presence of Aβ plaques in the retina of APP/PS1 mice, by using curcumin retinal in vivo imaging, with the first plaques appearing early (2.5 months) than in the brain, and accumulating along with disease progression [18]. In fact, the accumulation of the intracellular Aβ in the RGCs, and in the INL and ONL, as well as in the brain of the APP/PS1 mice is only evident in later time points, at 11 and 24 months [120]. Moreover, the presence of intracellular Aβ in the RGCs and INL in APP/PS1 mice, at 9 months, is in agreement with the previous studies, but no Aβ aggregates were found in the retina, despite being found in the brain of the same animals [146]. In the retinas of Tg2576 mice, at 14 months, Aβ aggregates were found, but without the appearance of "plaque-

Table 8 Retinal molecular and cellular changes detected in AD animal models—studies assessing the retina and brain simultaneously

Retinal molecular and cellular changes in AD animal models				
Animal model	Age	Retina	Brain	References
AD hallmarks				
APP/PS1 mice	7–12 M	↑ APP expression Absence of Aβ and no signs of p-tau	↑ APP expression Presence of amyloid plaques	[145]
APP/PS1 mice	9 M	Absence of Aβ aggregates	Presence of Aβ aggregates	[146]
APP/PS1 mice	2.5 M, 12 and 24 M	Presence of Aβ plaque early than in brain (2.5 M)	Presence of Aβ in later stages (11 and 24 M)	[120]
APP/PS1 mice	3 M	↑ BACE1 expression than in brain (3 M)	↑ BACE1 plaques (6 and 8 M)	[147]
APP/PS1 and Tg2576 mice	6 M	Absence of Aβ plaque-like structure ↑ CTFα and ↓CTFβ levels	Presence of Aβ plaques Similar CTFα and CTFβ levels	[146]
Tg2576 mice	14 M	Presence of Aβ aggregates without appearance of "plaque-like"	Presence of Aβ plaques	[132, 146]
3xTg-AD mice	3–6 M	Abnormal tau accumulation (3 M)	Abnormal tau accumulation (6 M)	[148]
5xFAD mice	1.5 M	Presence of Aβ	Presence of Aβ	[149]
TgF344-AD rat	19 M	Amyloid plaques with variable sizes	Amyloid plaques with variable sizes	[19]
Glial reactivity				
APP/PS1 mice	7–12 M	No changes in microglial markers and pro-inflammatory cytokines No changes in GFAP levels (until 12 M)	↑ Microglial markers ↑ GFAP levels (at 7 M)	[145]
5xFAD mice	1.5 M	↑ Pro-inflammatory biomarkers	↑ Pro-inflammatory biomarkers	[149]
Htau and P301L mice	3–24 M	↑ Microglia reactivity and astrocytes co-localizing with tau (P301L mice)	↑ Microglia reactivity and astrocytes co-localizing with tau (Htau mice)	[133]
Neurodegeneration/cell loss				
APP/PS1 mice	9–12 M	No changes in synaptic density (9 M) Absence of dystrophic neurites (11 M) Absence of RGCs loss (12 M)	Presence of dystrophic neurites (11 M)	[145]
Tg2576 mice	14 M	Absence of RGCs loss ↓ RGC dendritic integrity	↓ Frequency of dendritic spines in hippocampal neurons	[150]
3xTg-AD mice	5 post-natal weeks	↑ Caspase-3-positive cells	↑ Caspase-3-positive cells	[128]

Aβ amyloid beta, *p-tau* phosphorylated tau, *BACE* β-secretase 1, *CTF* C-terminal fragments, *GFAP* glial fibrillary acidic protein, *RGCs* retinal ganglion cells

like" structures like those found in the brain [132, 146]. The levels of $A\beta_{42}$ in the retina were 75 times less than in the brain, which might explain this discrepancy [146]. In addition, differences regarding APP proteolytic products were also found in the retina and brain of APP/PS1 and Tg2576 mice, suggesting that retinal APP may undergo an alternative processing due to the low expression of BACE1 in the retina and consequently a minimal activation of the amyloidogenic pathway [146]. However, in opposition to this theory, Li and colleagues reported an upregulation of BACE1 in the RGCs, as early as 3 months, prior to the changes in the brain [147].

Importantly, a study evaluating four transgenic models of AD reported clear differences in the amyloidogenic pathology onset and severity among those models. The first appearance of senile plaques in the retina was observed in the 5xFAD model at 2 months, followed by the 3xTg-AD and APP/PS1 models at 6 months, and in the Tg2576 at 10 months. Again, the content of Aβ in the retina was much lower than the content in the brain. Given that the 5xFAD model expresses five mutations, all responsible for accelerating Aβ generation and deposition, the highest concentration of Aβ in both brain and retina was found in this model [137]. Posterior studies in this model analyzing both regions also demonstrated a substantial increase of Aβ peptides in the brain and retina at very early stages (starting at 1.5 months) showing that the 5xFAD model displays the most rapid accumulation of Aβ peptides of the transgenic AD models studied to date [149]. Other findings also demonstrate the presence of amyloid plaques with variable sizes in the TgF344-AD rat model, not only in the cortex and hippocampus, but also in the IPL and OPL at 19 months [19].

Regarding the tau pathology, only one study assessed simultaneously the brain and retina. Recently, it was reported an increase in tau phosphorylation at AT8 epitopes (S202/T205) in the retina in 3xTg-AD mice at 3 months, whereas an increased phosphorylation at S199 site appears at a later stage (6 months), suggesting that retinal tau undergoes epitope-

specific changes throughout the disease progression. In addition, p-tau accumulates in RGCs soma and dendrites contributing to anterograde axonal transport impairments, preceding neuronal death. Surprisingly, retinal tau accumulation appeared before brain pathology [148].

Glial Reactivity

The accumulation of Aβ peptides with age in the brain of a transgenic model of AD is usually accompanied by an increase of the inflammatory state [151]. In the APP/PS1 model, there was a lack of identifiable retinal inflammatory markers. While in the cortex and hippocampus, at 7 months, it was evident an increase of microglial markers and an upregulation of GFAP surrounding Aβ deposits, no changes were found in the retina until 12 months. Moreover, in the retina no difference was detected in the Iba1-labeling between transgenic and control mice, no evidence for increased mRNAs levels of proinflammatory cytokines, such as TNF-α, IL-1β and IL-6, and GFAP, nestin, and glutamine synthase levels remained unchanged, further suggesting that gliosis was not present at the time points under study [145]. Nevertheless, in the retina of Tg2576 mice, at 14 months, there is an increase in astrocytes and microglia reactivity across the retina [132]. However, the authors did not assess microglia and astrocytes in the brain, only the presence of Aβ in both regions. Another study analyzing both retina and brain in 5xFAD mice presented evidence, in both regions, of the presence of Aβ peptides accompanied by an increase in C-reactive protein and cyclooxygenase-2, two pro-inflammatory biomarkers, starting at 1.5 months [149].

Deficits in the expression of the innate immune-repressor complement factor H (CFH) may contribute for neuroinflammation in AD. The levels of βAPP, Aβ42 peptide, and CFH were evaluated in the whole retina, superior colliculus (SC), and primary visual cortex (PVC) of four transgenic animal models of AD. In 5xFAD and Tg2576 mice, models with the highest Aβ42 peptide abundance, there was an inverse relationship between the abundance of detectable Aβ42 peptides and CFH in the retina, which was also perceptible along the retina/SC/PVC pathway. This study suggests that high levels of Aβ42 across the visual pathway may correlate with deficiencies in CFH, increasing the potential for pro-inflammatory signaling along this circuit [137].

More recently, a significant increase in reactive microglia and astrocytes co-localizing with tau oligomers was observed in the retina and brain. However, these findings were not described in the same animal model, since the cortex was analyzed in the Htau mice and the retina in the P301L mice, two different tauopathy animal models [133].

This group of findings indicates, as for other parameters, there are conflicting results regarding not only glial reactivity in the retina but also the correlation of glial reactivity in the retina and brain. It seems that the brain is more affected, but glial reactivity also occurs in the retina. Again, these discrepancies are likely related with the use of different animal

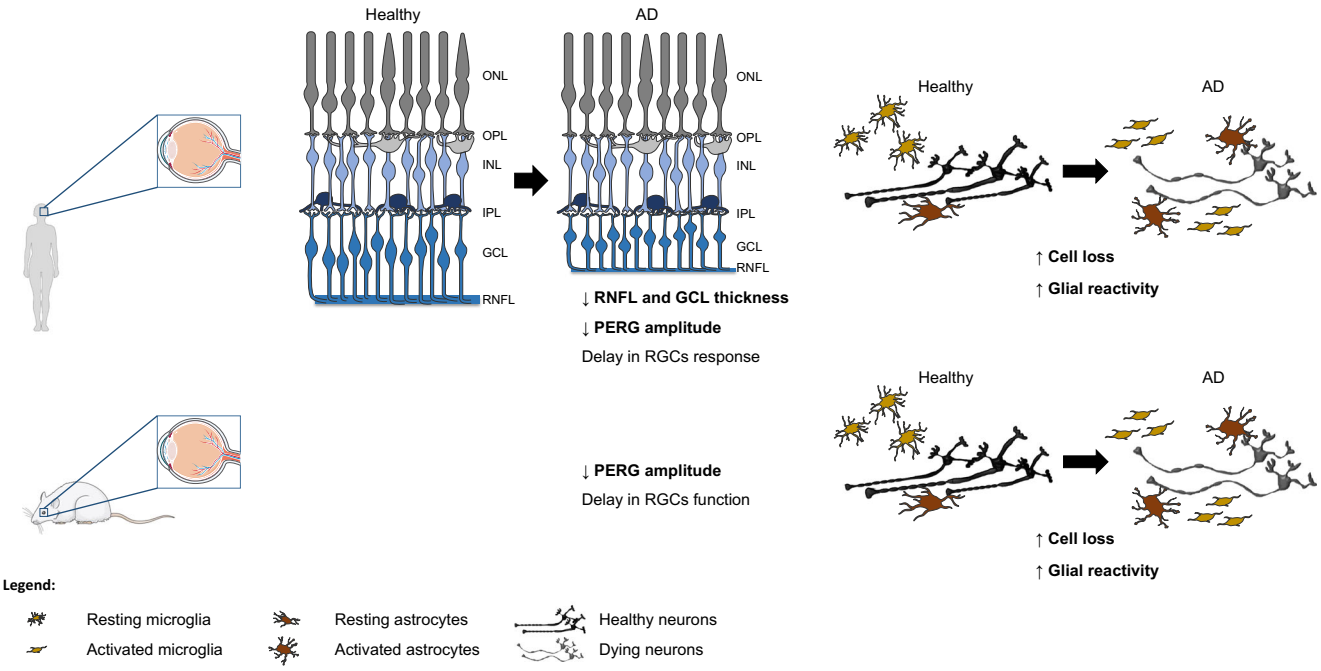

Fig. 1 Main findings in AD patients and animal models. The alterations reported in AD patients are mainly related with a thinning of RFNL and GCL, a decrease of PERG amplitude, a reduction of ON fibers, and an increase of glial reactivity and cell loss in the retina. In the AD animal models, most studies show a decrease of PERG amplitude as well as an increase of glial reactivity and cell loss in the retina of these animals

models and time points, as well as the techniques used to assess each parameter.

Neurodegeneration

The increase of protein aggregates inside and outside the cells promotes a dysregulation of neuronal homeostasis. Yet, the massive neuronal loss usually observed in the brain of AD patients is strikingly absent in mouse models of AD, being only observed at later time points and with low impact for brain functioning.

In a recent study, no changes were observed in the retinal thickness and synaptic density in APP/PS1 mice, at 9 months. Also, no dystrophic neurites were observed in the GCL at 11 months and no RGC loss was detected at 12 months. In contrast, in the same animals, at 11 months, there are dystrophic neurites surrounding the plaques in the cortex and hippocampus [145]. On the other hand, in Tg2576 mice, at 14 months, despite no significant RGCs loss, there was a reduction in the RGC dendritic integrity, which was accompanied by a low frequency of dendritic spines in hippocampal CA1 neurons. These observations suggest that changes in dendrites in the retina may follow similar changes in the brain [150]. In fact, a recent study in 3xTg-AD mice reported an increase of caspase-3-positive cells in the inner part of the retina, as well as in the hippocampus, at five post-natal weeks, suggesting that the neurodegeneration occurs in parallel in the retina and the brain [128].

Since the number of studies that assessed simultaneously the retina and brain are scarce and the animal models used are different, it is difficult to take clear conclusions. Despite of that and of some negative results, the findings suggest that neuronal dysfunction and neurodegeneration can occur at similar time points in the retina and brain.

Conclusions

The concept of the retina as a mirror or a window to look into the brain has been explored in AD, since several AD patients have visual problems, sometimes even before the appearance of the first symptoms of AD. However, it is vital to disentangle whether that measures derived from the retina could be indeed good candidates for an early AD diagnosis, and for that, it is indispensable to unravel whether the retina and brain share similar pathological changes and understand which tissue is firstly and mostly affected in AD. Therefore, it is crucial to assess simultaneously the retina and brain to uncover these issues.

Despite several inconsistent findings, most studies revealed alterations in visual acuity, contrast sensitivity and color perception, a decrease in the RNFL and GCL thickness and the PERG amplitude, a reduction of ON fibers, and an increase of glial reactivity and cell loss in the retina of AD patients. In the AD animal models, most studies show a decrease of PERG amplitude as well as an increase of glial reactivity and cell loss in the retina of these animals (Fig. 1). Taking this into account, and despite some discrepancies, it is clear that the retina is affected in AD patients and animal models, and so retinal molecular, structural, and functional measures can be considered as useful tools to facilitate the early diagnosis of AD.

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