



Optical Coherence Tomography in Alzheimer's Disease

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Abbreviations

AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease assessment scale
aMCI	Amnesic type of mild cognitive impairment
APP	Beta-amyloid precursor protein
ERG	Electroretinogram
GCL	Ganglion cell layer
HRT	Heidelberg retina tomograph
IPL	Inner plexiform layer
OCT	Optical coherence tomography
ON	Optic nerve
PERG	Pattern electroretinogram
PS1	Presenilin 1
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RNFL	Retina nerve fiber layer
VEP	Visual evoked potential

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13.1 Introduction

Alzheimer's disease (AD) is the most common cause of dementia with an incidence that increases with age exponentially. According to the World Health Organization the worldwide prevalence of Alzheimer's disease (AD) is increasing yearly and receives growing attention because it affects quality of life, and also because has a significant economic impact, being a major public-health problem [1] and a substantial financial burden on families [2]. The recent publication of the Global Burden of Disease survey 2016 shows that among neurological conditions, the global number of individuals who lived with dementia has doubled compared to 1990 and dementia was the fifth leading cause of death globally [3].

AD is a brain degenerative disorder, where inherited susceptibility and environmental factors are probably interrelated [4, 5]. The clinical evolution of AD is a slowly progressive and episodic memory loss as the predominant symptom, with various accompanying signs including aphasia, apraxia, and agnosia, and general cognitive symptomology, such as impaired judgement, decision-making, and orientation [4]. Because of the slowness of the disease's progression, the neurodegenerative processes are likely to start 20–30 years before the clinical manifestations of AD. This transitional phase is recognized as mild cognitive impairment (MCI), which has some memory deficit, preservation of general cognitive and functional abilities, and absence of diagnosed dementia as cardinal features [6]. The amnesic type of MCI (aMCI) shows the highest annual incidence conversion rate to AD [7]. Nonetheless MCI can be comorbid with other neurological disorders, such as nondemented Parkinson's disease (PD) patients and increased the risk of progressive cognitive decline and dementia [8].

Despite great advances in the understanding of AD pathophysiology in the last few years, the exact pathogenesis of AD and its precursor MCI is still not comprehensively understood.

At the histopathologic level, neuronal loss, beta-amyloid plaques, neurofibrillary tangles made of hyperphosphorylated tau and neuritic plaques, and granulovacuolar degeneration characterize the brain of AD [4]. These lesions have been seen in the hippocampus and other limbic structures, as well as in the visual associative areas [9, 10], the primary visual cortex [11, 12], and in subcortical structures including the lateral geniculate nuclei and the superior colliculi [13–15], and within the retina [16–18].

AD patients may be affected by various visual disturbances, such as deficits in contrast sensitivity [19–21], motion perception [22, 23], and color discrimination [24–26]. Historically, these visual dysfunctions in AD have been attributed to damage in the primary visual cortex and to degenerative processes in primary and associative visual cortical areas, but cortical dysfunction alone cannot explain the pattern of observed defects. Multiple forms of evidence points toward the involvement of retinal ganglion cells and their axons in the optic nerve as a basis of the visual dysfunction in AD [16, 27]. This peripheral involvement in AD and MCI could be independent from the central one [28].

In the last two decades, several studies have considered the retinal involvement in AD pathophysiology. Sophisticated imaging techniques have been used, such as optical coherence tomography (OCT), scanning laser polarimetry, and pattern electroretinography (PERG), to assess the morphologic and functional changes of the retina in AD [29].

Optical Coherence Tomography (OCT) permits the objective quantification *in vivo* of the retinal nerve fiber layer (RNFL) that consists of axons that form the optic nerve and contributes partially to the retinal thickness. This method consists of a non-invasive technology allowing cross-sectional imaging of the eye [30, 31]. The implementation of Spectral-Domain OCT provides advantages in signal-to-noise ratio, permitting faster signal acquisition [32, 33]. Taking in mind that the human eye is an embryological protrusion of the brain, and the nerves and axons of the retinal nerve fiber layer (RNFL) are similar to those in the brain, it is not surprising that OCT has been widely employed in assessing RNFL thickness in several neurologic as well as neuro-ophthalmologic disorders [34–38].

The intent of this chapter is to provide a comprehensive overview of the results provided by the OCT technique as used to understand morphological retinal changes that occur due to the degenerative processes associated with Alzheimer's disease and other dementing disorders.

13.2 Retina and Alzheimer's Disease

As an integrated part of the nervous system, the retina is physiologically under senescence processes, the majority of them still under intense scrutiny. Therefore, in order to better evaluating AD patients, it is important to quantify the degree of thinning arising with age in the absence of pathological processes. It is also important to determine whether age-related loss is uniformly distributed across the optic disc or has any tendency to be sectorial and might therefore be a confounding factor for a correct evaluation of disease-related processes.

In the quest for understanding the degenerative changes accompanying AD, researchers performed both histological and *in-vivo* studies on healthy subjects.

Using immunohistochemical techniques, Löffler and colleagues examined the presence and expression of amyloid-related proteins, the same that have been found in specimens of AD patients' brains, in the human retina collected from cadaver eyes at various ages [17]. They did not find any abnormal deposits or immunoreactivity changes in the outer neural retina. On the other hand, they demonstrated the presence of tau proteins and amyloid precursor protein in the inner retina layers, including retinal ganglion cells and nerve fiber layer, of the human retina in older persons. Small amounts of beta-amyloid were detected in the sub-retinal pigment epithelium space [17]. Intracellular and extracellular A β deposits were recently detected in immunoreactive melanopsin retinal ganglion cells (mRGC) in AD retinas with abnormal morphology [18].

The analysis of normal *in-vivo* human retinal nerve fiber layer thickness, as measured by time-domain OCT, has been repeatedly confirmed as an age-related

reduction of RNFL thickness in normal subjects [39–42]. This thinning mainly involved the superior and inferior optic disc areas [43–45].

13.2.1 Animal Model of AD

One of the most recognised theories for the genesis of AD, the “amyloid cascade hypothesis”, postulates that APP dysmetabolism and beta-amyloid deposition are the primary events that facilitate the disease process of AD [46].

In the past decade, through the use of genetic engineering techniques, transgenic (Tg) animal models over-expressing mutant forms of amyloid precursor protein (APP) and/or presenilin 1 (PS1) have been generated to mimic various aspects of AD pathology, including A β deposition, cognitive deficits, inflammation, and synaptic dysfunction, to test newly proposed therapeutic agents [47]. Recent publications have shown the accumulation of A β -plaques within the retina [48–51] and its microvasculature [52], retina ganglion cell death [53], and local neuroinflammation [52] in different Tg animal models. Nevertheless, these transgenic models only mimic part of the pathological features of AD.

An interesting Tg AD rat model, TgF344-AD, expressing mutant human amyloid precursor protein (APP^{sw}) and presenilin 1 genes, seems to more faithfully encapsulate most of the features of AD. This animal model is characterized by an otherwise healthy long lifespan, but the rats suffer from later age cognitive decline, age-dependent cerebral amyloidosis, taupathy, gliosis, and frank neuronal loss that seems to parallel those in humans [54]. Tsai and colleagues investigated a group of TgF344-AD rats and age-matched wild type rats [55]. When compared with age-matched controls, the retinas of Tg rats demonstrated the presence of A β plaques, hypertrophic retinal pigment epithelial cells, signs of neuroinflammation, and a significant thinning of retinal choroid [55].

In mice models, non-mutant human Tau (hTau) gene expression may be sufficient to initiate AD and may thus be a more relevant model to study the disease [56]. In hTau mice at 5 and 17 months of age researchers examined functional, histological and molecular changes occurring in the visual system. They unexpectedly observed that hTau expression is not toxic for retinal cells at least in-so-far as the electroretinogram response was not altered in hTau compared with mTKO littermates, but even more pronounced in amplitude in hTau than in KO mice deprived of Tau retinae, suggesting a protective role of hTAU in visual physiology [57].

13.2.2 Histological Studies in Post-Mortem AD Eyes

In 1986, histological examination in a human post-mortem study revealed depletion of axons in the optic nerves from AD patients [16]. Sadun and colleagues were the first to demonstrate this primary AD-associated optic neuropathy and further, to characterize, by morphometric analysis, that the predominant effect was on the largest retinal ganglion cells (M-cells) that contribute their large caliber fibers to the

optic nerve [27]. Other studies [58, 59] failed to confirm the selective large axon losses. This discrepancy has been attributed, at least in part, to methodological biases such as different *post-mortem* delays, different techniques in axonal counting and/or difficulties in obtaining well-preserved myelinated axons.

Extensive retinal ganglion cell loss in the central retina in AD was also observed in histological studies [16] or by other methods of evaluating the RNFL *in vitro*. Morphometric analysis of the central retina (fovea/foveola/parafoveal retina) in eyes from 9 AD and 11 age-matched controls revealing an overall decrease of 25% in total numbers of neurons in the ganglion cell layer (GCL) (fovea/parafoveal retina) in AD as compared with control eyes [60]. Moreover, the most severe decrease was observed in the foveal region (−43%) over the far temporal region. Similar results were obtained in AD patients with the evaluation of the peripheral retina: the neuronal loss was more pronounced in the superior and inferior quadrants (50–59%) and a significantly increased ratio of astrocytes to neurons was detected when compared with control eyes [61]. Moreover, histological signs of degeneration in the retinal ganglion cells (RGCs) were described to include a vacuolated, “frothy” appearance of the cytoplasm in the absence of neurofibrillary tangles within the RGCs, or of neuritic plaques or amyloid angiopathy in the retinas or optic nerves in AD [62].

Koronyo-Hamaoui and colleagues recently identified retinal A β plaques in *post-mortem* eyes from 8 AD patients and in 5 suspected early stage cases, but not in five age-matched non-AD individuals [50].

Plaque-like structures were seen in two retinas from two AD patients, with thickening of retinal choroid and no changes in the retinal pigment epithelial cells [55]. Fibrillar tau or A β aggregates were seen in *post-mortem* retinas from the same AD patients that had been previously observed by using an *in-vivo* imaging technique [63].

In a recent post-mortem study [18], researchers identified mRGCs with antibody targeting melanopsin from 14 AD patients with preserved retinal anatomy, and 13 controls. In AD patients, they revealed preserved retinal layers as compared to controls, but smaller somas and thinner dendrites, focal attenuations of melanopsin immunostaining, signs of optic neuropathy with axonal loss predominantly affecting the larger fibers in the superior quadrant. Melanopsin RGC number was significantly correlated with age in controls but not in AD patients, meaning that the degenerative processes at the basis of AD are, at least in part, independent from age related changes. Finally, in a subgroup of subjects, they found evidence of consistent accumulation of A β inside immunoreactive mRGCs soma and extracellular/abluminal areas in AD patients, while they were absent in controls [18].

13.2.3 Clinical Studies Based on the Subjective Evaluation of Fundus Photographs

The RNFL consists of the RNFL axons of retinal ganglion cells, converging at the optic disc forms the origin of the optic nerve.

That retinal ganglion cell degeneration occurs in AD is further evident by means of the use of a boundary-tracking program and RNFL photographs. A higher proportion of AD patients showed signs of optic neuropathy manifesting as optic disc atrophy, pathologic optic disc cupping, and thinning of the neuroretinal rim and of the RNFL [64, 65]. Tsai et al. [65] observed an increased cup-to-disc ratio, cup volume, and decreased optic disc rim area in AD patients by optic nerve analyser.

Analyzing mild to moderate AD patients with RNFL fundus photographs, Lu and colleagues found that all the AD patients had different types of RNFL abnormalities, including diffuse and wedge shape nerve fiber layer drop-out [66]. These abnormalities in AD patients were associated with a higher cup–disc ratio of 39–43% when compared to that in the control group.

However, these studies required the subjective evaluation of fundus photographs with the inherent observer bias.

13.3 *In-Vivo* Morphological Analysis in AD and MCI Patients

One confounding factor in analysing MCI and AD-related late-onset progressive changes is that there are anatomical and physiological changes normally found in aging eyes. In animal [67] and human [67, 68] studies, a physiological age-dependent progressive loss of optic nerve fibers, with progressive decrease of mean axonal diameter, has been demonstrated [69–71].

Optical coherence tomography (OCT) is a technique that can also be used in ophthalmology for the measurement of the macular thickness and volume. OCT can determine RNFL thickness of the peripapillary region reflecting axons and would allow quantification of axonal loss, measurement of macular thickness and volume would reflect retinal neurons, allowing quantification of neuronal loss [30].

Several previous studies using OCT techniques have examined the relationship between age and RNFL measurements. These have consistently shown that optic nerve, RNFL, and macular measurements with OCT all varied with age [41, 72], with the greatest decrease in mean RNFL occurring in the superior [44] and inferior quadrants [42], especially after age 50 years [43]. There was less loss in RNFL thickness in the nasal and temporal quadrants [73, 74]. This age-related decline in normal RNFL measurements needs to be considered when considering or monitoring ocular disease.

However, as described below, the reduction in RNFL thickness observed in most studies on AD patients was significantly greater than that observed in the age-matched controls and thus cannot be exclusively ascribed to aging (see some illustrative OCT imaging in Fig. 13.1 and a synopsis of published OCT studies in AD and MCI in Table 13.1).

Parisi and colleagues were the first who used OCT to study a group of 17 AD patients affected from mild severity cognitive impairment and compared them with a group of 14 age-matched controls. In AD patients, OCT results showed thinning of the average peripapillary RNFL and in all quadrants examined, showing the involvement of the neuroretinal tissue in AD [75, 76].

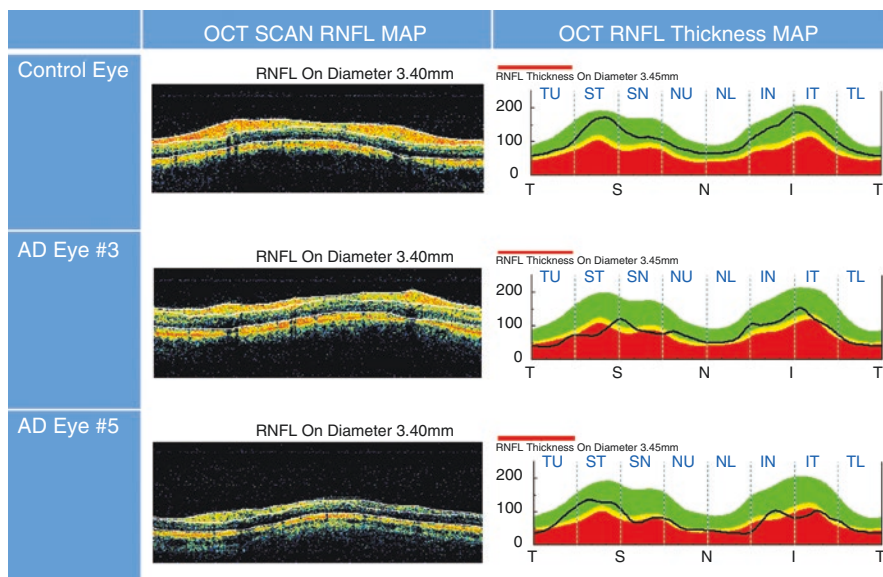


Fig. 13.1 Optical Coherence Tomography (OCT) imaging taken in cylindrical section of tissue surrounding the optic disc of a control eye and of 2 AD patients eyes. The images in the left panel are raw OCT data, while the maps in the right panel are quantitative data curve. In AD patients eyes OCT shows a decrease of RNFL reflection (reduced RNFL thickness) in each examined quadrant, with particular prevalence of the temporal ones

The mean RNFL thickness was corroborated to be reduced in AD patients by several independent groups [18, 66, 77–89]. Patients affected with MCI have also shown some RNFL thinning [81, 86, 88–90]. Individual examination of the quadrants was even more revealing. Most studies observed a significant reduction of RNFL thickness in the superior quadrant [18, 66, 75, 76, 79, 80, 83–88, 90–92], but for some also in the inferior quadrant [66, 75, 76, 79, 80, 84–88, 90–92], and for a less extent also in the nasal [75, 76, 80, 84, 86] and temporal [75–77, 79, 80, 84–86, 88] quadrants. In contradistinction, the preferential involvement of each quadrant is more inconsistent in MCI patients [86, 88, 90]. For the sake of completeness, some researchers did not observe reduced RNFL thickness both in AD [93–96] and MCI [87, 92–94, 96] patients in comparison with controls.

When assessed, the mean ganglion cell layer plus inner plexiform layer thickness (GCL-IPL) thickness was found to be reduced in AD eyes by several independent groups [77, 81, 87], and even in some patients affected with MCI [28]. In one study GCL-IPL thickness was reduced in moderate AD and in frontotemporal dementia, but not in MCI and mild AD patients [81].

Some researchers studied optic nerves of AD patients by using confocal scanning laser ophthalmoscopy (cSLO). Ophthalmoscopy in combination with cSLO, revealed an enlargement in the mean vertical cup-to-disc ratio (clinician and instrument derived), rim volume, rim area, and reduced RNFL thickness in patients with AD with respect to controls [97]. Compared with individuals in the lowest quarter

Table 13.1 Demographic data and RNFL thickness measurements in patients and controls as determined by OCT

No. of subjects and diagnosis	Mean MMSE/AD stage	Mean age \pm SD	OCT machine	Mean RNFL (μ m)	Superior quadrant (μ m)	Inferior quadrant (μ m)	Nasal quadrant (μ m)	Temporal quadrant (μ m)	Note
Reference Parisi et al. [75, 76] 17 AD 14 controls	70.37 \pm 6.1		Humphrey	59.5 \pm 16.70 ^a 99.9 \pm 8.95	72.1 \pm 21.4 ^a 104.6 \pm 12.1	77.9 \pm 26.4 ^a 116.2 \pm 9.87	50.4 \pm 23.2 ^a 93.4 \pm 13.7	37.9 \pm 17.60 ^a 85.6 \pm 8.21	RNFL overall values correlated with PERG
Iseri et al. [91] 14 AD 15 controls	18.5/mild to moderate 29.4	70.1 \pm 9.7 65.1 \pm 9.8	Carl Zeiss Meditec, Model 3000	87.4 \pm 23.7 ^a 113.1 \pm 6.7	112.6 \pm 35.3 ^a 137.1 \pm 16.4	103.1 \pm 33.6 ^a 141.5 \pm 19.1	63.5 \pm 19.1 ^a 96.0 \pm 34.4	64.9 \pm 17.7 72.3 \pm 16.4	Decline in both peripapillary and macular thickness and volume in AD eyes
Berisha et al. [101] 9 AD 8 HV	23.8/mild to moderate 29.5	74.3 \pm 3.3 74.3 \pm 5.8	Carl Zeiss Meditec, Model 3000	92.2 \pm 21.6 ^a 113.6 \pm 10.8		117.0 \pm 15.3 128.1 \pm 11.4	67.0 \pm 15.0 69.5 \pm 11.1	65.7 \pm 15.1 64.1 \pm 7.3	Narrowing of the retinal microvasculature
Paquet et al. [82] 23 MCI 14 AD 12 AD 15 controls	28.8 22.6/mild 16.6/severe 28.9	78.7 \pm 6.2 78.3 \pm 5.1 78.8 \pm 4.9 75.5 \pm 5.1	Carl Zeiss Stratus OCT 3	89.3 \pm 2.7 ^a 89.2 \pm 2.9 ^a 76.6 \pm 3.8 ^a 102.2 \pm 1.8					The involvement of retina is an early event in the course of this disorder
Lu et al. [66] 22 AD 22 controls		73 \pm 8 68 \pm 9	Carl Zeiss Meditec, Model 3000	90 \pm 18 ^{a,b} 98 \pm 12	107 \pm 30 ^{a,b} 124 \pm 16	116 \pm 35 ^{a,b} 128 \pm 18	66 \pm 26 70 \pm 17	70 \pm 20 71 \pm 13	Enlarged optic cup to disc ratio in AD
Kessler et al. [90] 24 MCI 30 AD 24 controls	28.1 23.6	71.0 \pm 10.0 73.7 \pm 9.9 70.9 \pm 9.2	Carl Zeiss Stratus OCT 3	85.8 \pm 10.0 ^a 84.7 \pm 10.6 ^a 94.3 \pm 11.3	101.3 \pm 15.2 99.0 \pm 18.0 ^b 110.0 \pm 16.7	111.9 \pm 16.1 ^a 110.1 \pm 19.1 ^a 127.0 \pm 15.5	65.9 \pm 15.1 66.8 \pm 14.5 76.4 \pm 21.8	64.2 \pm 13.9 61.7 \pm 10.9 67.8 \pm 15.1	RNFL thickness not correlated with MMSE
Kromer et al. [119, 120] 22 AD 22 controls	22.6/mild to moderate	75.9 \pm 6.1 64.0 \pm 8.2	Spectralis Heidelberg Engineering	80 ^{b,c}	46 ^{b,c}		47 ^{b,c}		The RNFL of the AD patients did not correlate with pattern VEP latencies
Moreno-Ramos et al. [105] 10 AD 10 LB 10 PD 10 controls	16.4 14.9 16.4 29.2	73.0 \pm 6.5 74.2 \pm 5.1 74.3 \pm 5.0 70.2 \pm 5.5	TOPCON 3D OCT-1000	94.5 \pm 2.2 ^a 93.3 \pm 1.5 ^a 94.8 \pm 2.0 ^a 108.0 \pm 2.2					Retinal involvement measured by OCT may also be present in non-AD dementias

Marziani et al. [84]	21 AD 21 controls	19.9/mild to moderate 27.9	79.3 ± 5.7 77.0 ± 4.2	(1) Optovue RTVue-100 and (2) Spectralis Heidelberg Engineering Central sector	244.1 ± 17.9 ¹ 277.5 ± 21.7 ² 252.3 ± 19.2 ¹ 283.8 ± 27.3 ²	274.8 ^{in,d} 304.3 ^{2a,d} 288.9 ^{id} 319.3 ^{3d}	273.25 ^{ia,d} 301.7 ^{2a,d} 286.25 ^{id} 314.75 ^{3d}	278.4 ^{ia,d} 309.35 ^{2a,d} 290.85 ^{id} 323.55 ^{3d}	271.8 ^{in,d} 291.95 ^{2a,d} 286.25 ^{id} 304.45 ^{3d}	Reduced RNFL in AD patients using 2 different OCT instruments
Kirbas et al. [83]	40 AD 40 controls	21.5	69.3 ± 4.9 68.9 ± 5.1	Spectral domain OCT	65 ± 6.2 ^a 75 ± 3.8	76 ± 6.7 ^a 105 ± 4.8	106 ± 11.5 108 ± 8.7	75 ± 2.8 76 ± 2.7	74 ± 6.7 77 ± 7.3	No correlation between MMSE and OCT results
Larrosa et al. [85]	151 AD 61 controls	18.31	75.29 74.87	(1) Carl Zeiss Meditec Cirrus and (2) Spectralis Heidelberg Engineering	97.5 ± 14.1 ¹ 98.2 ± 17.1 ^{2a} 100.5 ± 13.0 ¹ 102.7 ± 6.7 ²	113.2 ± 18.7 ^{1a} 117.8 ± 19.0 ^{1a}	120.4 ± 20.1 ^{1a} 127.4 ± 21.0 ¹	72.7 ± 17.3 ¹ 74.5 ± 17.2 ¹	64.5 ± 21.7 ^{1a} 67.8 ± 20.0 ¹	RNFL measurements were a very useful and precise tool for AD diagnosis.
Ascaso et al. [86]	21 aMCI 18 AD 41 controls	19.3 28.8	72.1 (AD + aMCI) 72.9	Stratus OCT 3	86.0 ± 7.2 ^a 64.7 ± 15.2 ^{a,e} 103.6 ± 8.9 (data showed from the right eye only)	96.7 ± 14.6 ^a 73.2 ± 22.0 ^{a,e} 126.6 ± 13.8	110.1 ± 17.7 ^a 86.2 ± 25.7 ^{a,e} 135.6 ± 17.6	71.0 ± 16.7 ^a 43.3 ± 20.4 ^{a,e} 77.8 ± 16.7	66.3 ± 12.1 ^a 56.7 ± 14.9 ^{a,e} 75.8 ± 16.6	A significant association between RNFL thickness in superior and nasal quadrants, and MMSE score
Cheung et al. [87]	41 MCI 100 AD 123 controls		70.4 ± 10.2 ^a 73.5 ± 6.23 ^a 65.7 ± 3.77	Carl Zeiss Meditec Cirrus HD-OCT	RNFL 89.21 86.83 ^a 90.37 GC-IPL 73.73 ^a 72.73 ^a 77.79	110.9 105.7 ^a 113.5 73.48 ^a 72.66 ^a 77.65	112.2 108.2 ^a 114.3 70.87 ^a 70.61 ^a 76.83	68.93 68.54 68.10 75.95 ^{a,f} 74.75 ^{a,f} 79.86 ^f	65.10 64.89 65.25 72.99 ^{a,f} 71.88 ^{a,f} 76.31 ^f	In the model adjusted for optic disc areas, hypertension, diabetes and, history of myocardial infarction, only superior quadrant reached the significance level

(continued)

Table 13.1 (continued)

	No. of subjects and diagnosis	Mean MMSE/AD stage	Mean age \pm SD	OCT machine	Mean RNFL (μ m)	Superior quadrant (μ m)	Inferior quadrant (μ m)	Nasal quadrant (μ m)	Temporal quadrant (μ m)	Note
Reference Fekete et al. [93]	21 MCI 10 AD 21 controls		74.3 \pm 12.2 74.4 \pm 10.5 69.1 \pm 6.7	Stratus OCT 3000 (Carl Zeiss Meditec)		118.2 \pm 13.4 108.8 \pm 13.3 117.7 \pm 15.2				No differences between the RNFL thicknesses measured in all retinal quadrants. Solely in AD patients, venous blood flow positively correlated with superior RNFL thickness
Gao et al. [88]	26 MCI 25 AD 21 controls	25.77 19.24 28.57	73.42 \pm 1.54 74.72 \pm 1.39 72.05 \pm 1.02	Cirrus HD-OCT 4000, Carl Zeiss Meditec	92.38 ^a 85.99 ^a 98.60	112.12 ^a 106.10 ^a 122.25	123.87 108.64 ^a 127.59	68.54 66.16 69.71	66.56 ^a 63.14 ^a 74.60	No correlation with MMSE test. AD data still significant after adjusting for age, sex, hypertension and diabetes
Oktem et al. [89]	35 MCI 35 AD 35 controls	28 18 29	74.1 \pm 6.3 75.4 \pm 6.9 70.2 \pm 8.0	Zeiss Cirrus HD 5000 model OCT device	82.5 \pm 7.3 ^a 80.6 \pm 9.6 ^a 91.5 \pm 7.1					In all study participants, a significant correlation was present between MMSE test and RNFL thickness

Garcia-Martin et al. [77]	150 AD 75 controls	18.35 29.78	75.33 74.79	Spectralis OCT	<p>RNFL 95.67 ± 15.22^a 99.23 ± 16.48 GC-IPL 6.27 ± 1.76^a 6.45 ± 1.77</p>	<p>RNFL 77.02 ± 16.80 77.54 ± 18.88</p>	<p>RNFL 66.90 ± 15.34^a 71.09 ± 15.52</p>	The thickness of the RNFL, ganglion cell and inner plexiform layers were significantly decreased in AD patients with longer disease duration
Cunha et al. [79]	24 AD 24 controls	17.02 29.08	74.8 ± 6.25 72.25 ± 7.31	3D OCT-2000, Topcon Corp	<p>93.75 ± 13.42^a 102.96 ± 9.19</p>	<p>112.38 ± 23.25^a 130.10 ± 12.78</p>	<p>66.91 ± 16.66 72.69 ± 9.16</p>	Significant correlation between most OCT parameters and MMSE scores
Pillai et al. [94]	21 aMCI 21 AD 20 non-AD 20 PD 34 controls		68.2 ± 6.7 65.8 ± 11.1 68.7 ± 8.4 62.6 ± 9.5 65.1 ± 8.3	Cirrus 4000 HD-OCT (Zeiss)	<p>89.9 ± 2.1 88.9 ± 2.1 89.9 ± 2.1 88.5 ± 2.1 85.3 ± 1.6</p>	<p>117.0 ± 3.6 114.4 ± 3.6 114.3 ± 3.7 111.9 ± 3.7 108.7 ± 2.8</p>	<p>63.4 ± 2.5 61.8 ± 2.5 59.5 ± 2.6 59.2 ± 2.6 59.1 ± 2.0</p>	No retinal involvement in AD and non-AD dementias
Trebbastoni et al. [95]	36 AD 36 controls	22.7 28.6	72.0 ± 7.3 71.7 ± 6.0	Heidelberg Spectralis (Heidelberg Engineering)	<p>96.7 ± 6.3 97.6 ± 8.3</p>	<p>126.3 ± 11.7 125.1 ± 11.6</p>	<p>74.1 ± 8.9 70.9 ± 12.5</p>	After 12 months AD patients had a significant reduction of the total RNFL thickness, as well as the RNFL thickness of the inferior and superior quadrants

(continued)

Table 13.1 (continued)

Reference	No. of subjects and diagnosis	Mean MMSE/AD stage	Mean age \pm SD	OCT machine	Mean RNFL (μ m)	Superior quadrant (μ m)	Inferior quadrant (μ m)	Nasal quadrant (μ m)	Temporal quadrant (μ m)	Note
Liu et al. [28]	50 CIND 27 AD 47 controls	25.2 16.6 27.4	69.7 \pm 8.2 75.2 \pm 7.8 67.3 \pm 6.2	Cirrus HD-OCT (Carl Zeiss Meditec)	GC-IPL 76.92 \pm 6.29 ^a 78.41 \pm 5.85 80.19 \pm 5.89					Correlation was observed between GC-IPL thickness and WM microstructure and GMV of healthy controls in several brain area. This correlation was absent both in CIND and in AD patients
La Morgia et al. [18]	21 AD 74 controls	18.3	71.2 \pm 10.5 69.1 \pm 8.1		88.8 \pm 8.4 ^a 95.8 \pm 12.3	104.4 \pm 13.4 ^a 117.1 \pm 17.6	116.5 \pm 15.5 122.4 \pm 18.1	66.6 \pm 13.9 74.3 \pm 15.3	67.2 \pm 10.4 69.3 \pm 10.5	Inverse correlation between average RNFL thickness and age
Cunha et al. [80]	50 AD 152 controls		73.1 \pm 5.36 71.0 \pm 4.62	SD-OCT (Spectralis Heidelberg Engineering)	85.72 \pm 14.42 ^a 96.51 \pm 9.36	114.44 ^{a,f} 133.14 ^f	96.27 ^{a,f} 106.75 ^f	68.76 \pm 16.99 ^a 74.77 \pm 13.73	64.22 \pm 13.01 ^a 71.38 \pm 12.66	AD patients showed thickness reduction in global and temporal quadrants in the peripapillary RNFL and in the superior sector of the macula

Ferrari et al. [81]	27 MCI 20 mild AD 17 moderate AD 17 FTD 49 controls	26.62 23.0 16.59 21.64	70.45 ± 5.51 69.75 ± 7.51 71.23 ± 6.95 65.59 ± 6.89 68.32 ± 6.96	Fourier-domain OCT Heidelberg Spectralis™	RNFL 92.79 ± 10.31 ^a 94.55 ± 6.84 91.33 ± 13.16 ^a 87.47 ± 7.34 ^a 97.49 ± 8.52 GCL-IPL 55.61 ± 8.17 57.52 ± 0.27 50.07 ± 7.21 ^a 51.83 ± 7.48 ^a 58.18 ± 7.94						GCL-IPL was significantly correlated with raw MMSE in AD
Kwon et al. [92]	30 MCI 30 AD 30 controls	24.17 17.2 27.47	72.17 ± 4.98 73.60 ± 3.67 70.93 ± 4.68	Carl Zeiss Meditec cirrus HD-OCT	115.0 ± 13.19 106.78 ± 13.5 ^e 115.30 ± 14.78	120.84 ± 17.59 113.82 ± 16.14 ^a 113.70 ± 12.02	68.22 ± 9.40 64.47 ± 7.75 66.40 ± 7.22	68.75 ± 9.79 63.71 ± 9.91 66.23 ± 12.98			
Golzan et al. [96]	23 pre-AD 28 AD 50 controls		80 ± 4 70 ± 9 79 ± 5		RNFL 101.15 99.17 93.18 GCL-IPL 98 ± 9 91 ± 2 96 ± 9 ^{a,c}						The association between RNFL and RGCL thickness and neocortical Aβ standardized uptake value ratio in the grouped control and preclinical cohort

AD Alzheimer's disease, *aMCI* amnesic mild cognitive impairment, *CIND* patients with cognitive impairment but no dementia, *FTD* frontotemporal dementia, *GC-IPL* ganglion cell-inner plexiform layer, *LB* dementia with Lewy bodies, *MCI* mild cognitive impairment, *MMSE* mini mental state examination, *pre-AD* preclinical AD, *RNFL* retinal nerve fiber layer, *PD* dementia associated with Parkinson's disease

^aSignificantly different from controls

^bData extrapolated from the bar chart

^cStatistics do not clearly show

^dMean of internal plus external sectors

^eSignificantly different from MCI

^fMean of supero-nasal or temporal plus infero-nasal or temporal sectors

¹Optovue RT Vue-100 and

²Spectralis Heidelberg Engineering

of values of cup-to-disc ratios, those with higher values generally had an increased risk of AD [97]. Lu et al. [66] also observed an enlarged cup-to-disc ratio and a thinner RNFL thickness in their 22 mild to moderate AD patients. In contrast, Kergoat et al. [98] found no differences in the regional distribution of RNFL thickness between patients with mild to moderate AD and healthy controls evaluated with scanning laser polarimetry. The same researchers did not observe optic nerve head structural abnormalities in AD by using real-time topographical images obtained with a Heidelberg retina tomograph (HRT) from individuals in the early stages of AD compared with age-matched controls [98]. The same negative results were obtained by Kurna and coworkers in a group of patients with mild to moderate AD [99]. Despite that, Csincsik et al. [100] used ultra-widefield (UWF) scanning laser ophthalmoscopy of the retina to determine phenotypic variations in 59 patients with AD and 48 healthy controls and found significantly higher prevalence of a hard drusen phenotype in the periphery of AD patients compared to controls, as well as changes to the arterial and venular vasculature beyond the posterior pole. The number of optic nerve head drusen increased at the 2 years follow-up measurement in AD patients [100].

Berisha et al. [101] tried to determine whether regional thinning of the RNFL occurred in the nine patients with mild to moderate AD and to determine whether the retinal circulation was abnormal in these patients. AD patients showed a marked narrowing of the retinal venous blood column diameter and a reduction in retinal blood flow rate compared with eight age-matched control subjects. OCT data confirmed a significant thinning of the peripapillary RNFL that was most pronounced in the superior quadrant, which did not correlate with the retinal blood flow [101]. They argued that the mechanisms producing reduced blood flow in the retina are related to those that produce cerebral blood flow abnormalities, which are known to occur in AD, such as increased venous wall thickness due to collagen and β -amyloid deposition [102].

In a cross-sectional study on 150 patients with low-to-moderate dementia and 61 controls, researchers compared the parameters provided by two commercially available spectral domain OCT devices, the Cirrus and the Spectralis OCT instruments [85]. With both devices, they confirmed retinal thinning in AD patients, and they found that the best parameter for distinguishing AD patients from healthy controls using OCT measurements was the Spectralis looking at RNFL [85]. Along these lines, Marziani et al. [84] used both Optovue RTVue-100 and Spectralis instruments to evaluate retinal thickness in 21 patients affected by AD in comparison with 21 healthy controls. Both instruments showed a significant difference in full retinal thickness between patients and controls in all the macular sectors except in the central sector and for the superior external sector [84].

In order to verify whether involvement of the retina is an early event in the course of AD, a few studies compared MCI versus AD patients and healthy aged people. Paquet and coworkers [82] enrolled 23 MCI patients, 14 mild AD, 12 moderate to severe AD patients, and 15 healthy subjects. Overall, mean RNFL thickness was reduced in all patient groups in respect to controls. The subgroup analyses revealed no difference between the results observed in MCI and in mild AD patients, whereas

RNFL thickness assessed in moderate to severe AD patients was significantly reduced in respect with that assessed in MCI patients [82]. Kesler et al. [90] obtained similar results finding that the mean RNFL was significantly thinner in both AD and MCI patients groups compared to controls, and that the MCI group fell in between the other two groups. This difference was particularly prominent in the inferior quadrant, whereas the AD patients had significantly thinner retinal NFL values also in the superior quadrant [90].

Some investigators attempted to identify individuals who might be at a high risk of developing AD, and observed that, despite the reduction in peripapillary RNFL thickness, central 1-mm foveal thickness and macular volume were significantly increased in aMCI patients, but not in AD patients, when compared with age-matched controls. The authors argued that retinal swelling might be the first sign of macular retinal ganglion cell degeneration probably due to inflammation and/or gliosis in the early stages of AD [86]. Other independent research groups found decreased thickness of the RNFL in MCI patients, with values sometime equal to [81, 89] or in between [88] the control and AD groups, sometimes accompanied by a reduced macular volume [88]. However, we noticed that 5 studies were unable to find differences between MCI patients and controls [87, 92–94, 96] challenging the utility of OCT in differentiation MCI from mild-to-moderate AD.

Two studies, relying both on cross-sectional and longitudinal data, recruited individuals in the preclinical stage of the disease to perform a correlation analysis between retinal structural measurements and positron emission tomography (PET) A β binding in the neocortex. In adults with preclinical AD, the A β positive group of participants showed higher volume in the IPL in comparison with the A β negative group [103]. The same research group found that the mean RNFL volume reduction over 27 months was linearly related to neocortical A β accumulation, after controlling for normal aging [104].

Finally, it is worth noting that thinning of RNFL is also present in other types of dementia, such as frontotemporal dementia [81], dementia with Lewy bodies, dementia associated with Parkinson's disease [105] and with cerebral autosomal dominant arteriopathy with subcortical infarcts and leuco-encephalopathy (CADASIL) [106] challenging the specificity of OCT findings in AD patients.

13.4 Structural-Functional Correlations

The functional activity of the visual system can be dissected by the use of electrophysiological techniques such as pattern electroretinogram (PERG) and visual evoked potentials (VEPs) that have the capability of assessing, respectively, the bioelectrical activity of retinal ganglion cells and their fibers, and the functional integrity of the entire visual pathways from retina to the visual cortex.

The implicit times were delayed and/or the amplitudes reduced [75, 76, 107–110] in most of the PERG studies performed in AD patients at various stages, reflecting retinal ganglion cell dysfunction. However, in some studies PERG parameters were within the range of normality [111, 112]. In one study luminance pattern

ERGs were delayed and amplitudes reduced, whereas isoluminant chromatic ERGs were always within the normal ranges [110].

The implicit time of patterned VEP was normal in some studies [107, 110, 113, 114] and in others delayed [109, 112, 115, 116], with the amplitudes within the range of normality. A delayed P2 component of the flash VEP is a common finding across studies in AD patients [107, 113, 117, 118], with one exception [115].

Taken as a whole, these electrophysiological results are consistent with the early histological studies showing retinal ganglion cell dysfunction in AD [25, 118] and supports the notion that this damage in AD preferentially affects the larger, faster-conducting retinal ganglion cells and their retinocortical projections.

Parisi and coworkers [75, 76] used OCT and PERG in a group of 17 mild severity AD patients compared with a group of 14 healthy controls. They observed that the general reduction of peripapillary RNFL thickness was accompanied with delayed N35, P50 and N95 implicit times and reduced N35-P50 and P50-N95 amplitudes in their AD patients. More interestingly, in AD eyes, the RNFL overall values were positively correlated to the PERG P50 and N95 implicit times and PERG P50-N95 amplitude. This was not so in controls [75, 76]. However, Iseri et al. [91] did not find significant differences in VEP P100 implicit times and N75-P100 amplitudes recorded at high spatial frequency in a group of 14 mild to moderate AD patients when compared with a group of 15 controls. Moreover, they saw no correlation between any of the abnormally in RNFL and macular OCT thickness and VEP in AD [91]. This negative correlation, between VEPs parameters recorded at both high and low spatial frequency and OCT peripapillary scans, was later corroborated [119].

Liu et al. [28] for the first time observed that thinner macular GC-IPL is associated with lower integrity of the white matter microstructure, as verified using MRI diffusion tensor imaging, in healthy controls in fronto-parieto-occipital and cingulate regions, as well as with lower grey matter volume in occipital pole and cerebellum. These results in controls were contrast with those obtained in AD and MCI patients where these relationships between macula and brain microstructure and volume were not detectable. The authors suggested that neurodegenerative processes related to the AD and MCI pathology can disrupt the physiological retina-brain coupling [28].

13.5 Correlations with Psychometric Measures

Along with personal history, physical examination and laboratory tests, questionnaires are often used to help test a range of everyday mental skills of persons with symptoms of dementias. Widely used tests include the mini mental state examination (MMSE), the Alzheimer's disease assessment scale- (ADAS-Cog), clinical dementia rating (CDR) score, and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

The previously mentioned parameters of increased cup-to-disc ratio, cup volume, and decreased optic disc rim area, all found in AD patients by optic nerve

analyser, positively correlated with ADAS-Cog scores and disease's duration [65]. In AD patients, a significant relationship between inferior RNFL thickness change and ADAS-Cog scores change as well as CDR scores at 12 months follow-up was observed. Interestingly, the linear regression model revealed that for every 10 μm decrease of RNFL thickness, there was an accompanying ADAS-Cog increase of 5 units [95].

Moreover, the reduced total macular volume in patients with AD was positively correlated with the severity of the disease as assessed by the MMSE [79, 89, 91, 95, 105]. Other studies failed to find the same associations [82, 83, 90, 119, 120]. However, some authors observed that the thinner the RNFL, ganglion cell and inner plexiform layers the longer the AD disease duration, even if the latter were not significantly related to severity of the disease (assessed with MMSE score) [77]. Nonetheless, RNFL thickness of AD or MCI patients was not associated with other patient demographic features, such as age [82, 85], gender, and AD stage [120]. In another study assessing the association between macular GC-IPL and peripapillary RNFL thicknesses with disease progression in MCI and AD, the CDR scale score exhibited significant negative relationships with the average GC-IPL thickness and GC-IPL thickness in the supero-temporal, supero-nasal, and infero-nasal sectors [121]. Furthermore, the composite memory score exhibited significant positive association with the average GC-IPL thickness and the GC-IPL thickness in the supero-temporal, inferonasal, and inferotemporal sectors. A positive association between the central macular thickness and the MMSE score was also observed [121].

More recently, La Morgia et al. [18] with the scope to verify the integrity of a subpopulation of retinal ganglion cells expressing the photopigment melanopsin, observed that clinical parameters (age, age at onset, disease duration, and MMSE score) and OCT data were not correlated to AD patients actigraphic data assessing rest–activity circadian rhythms. There may have been a minimum threshold such that relatively few melanopsin retinal ganglion cells sufficed to maintain circadian rhythms.

In AD patients, but not in aMCI, multiple linear regression models showed a strong association between overall RNFL thickness and MMSE score. The same association was found between MMSE and RNFL thickness in superior and nasal quadrants. Macular thickness and volume were not associated with MMSE score either in aMCI or in AD patients [86].

A prospective study attempted to determine whether deterioration of patients' cognitive functions, as verified with the RBANS test, correlated to specific OCT findings [122–124]. These investigators followed, for a period of 25 months, two groups of subjects: 82 participants with a normal cognitive status and 22 MCI patients. The participants who completed the observational period were further categorized as 60 participants experiencing a stable cognitive status and 18 participants who experienced a worsening of their cognitive status. The investigators found that in those participants who remained stable, greater attenuation of RNFL in the superior quadrant could predict specific cognitive deteriorations. In contradistinction, in participants who worsened, less attenuation of RNFL in the inferior quadrant could

predict greater cognitive deterioration [122–124]. These findings suggest that patients who have less reduction in the thickness of the inferior quadrant of RNFL over time may have a higher risk of developing MCI and dementia, leading the authors to put forward RNFL thickness as a potential biomarker of dementia.

13.6 Conclusions

The diagnosis of AD is often based on psychometric assessments by a multidisciplinary team (neurologists, psychiatrists, and psychologist) and a neurological examination. Because of inter- and intra-individual variability, neurophysiological and neuroimaging tests have not yet been considered as criteria on which to base a diagnosis. In fact, neurophysiological as well as other paraclinical tests are recommended only on suspicion of secondary causes of dementia as part of the differential diagnosis of AD. The AD diagnosis is confirmed only with *post mortem* histopathology. Nonetheless, the last few decades have seen the use of structural and functional techniques as potential biomarkers that might also identify factors that may predispose individuals to AD. The optical coherence tomography (OCT) technique for the measurement of the peripapillary RNFL, the macular thickness and volume, has been demonstrated as useful for the demonstration of significant retinal changes in patients that roughly correlate with the severity of the disease (Fig. 13.2).

Particularly intriguing results of recent experiments include:

- In animal models, expressing mutant forms of amyloid precursors, and histological studies on *post mortem* AD eyes, researchers have observed various retinal pathological changes, such as accumulation of A β aggregates within the retina and its microvasculature, retina ganglion cell death and signs of neuroinflammation.
- In evaluations with the optic nerve analyser, a higher proportion of AD patients show signs of optic neuropathy manifesting as optic disc atrophy, pathologic optic disc cupping, and thinning of the neuroretinal rim and of the RNFL.
- In agreement with *post mortem* studies, OCT data studies indicate a significant decline in peripapillary RNFL and also changes in macular thickness and volume that is progressive from MCI to AD eyes.
- Electrophysiological and OCT studies in AD patients show RNFL thickness reduction that is related to neuronal degeneration in the retinal ganglion cell layer that is not a consequence of retrograde degeneration from the post-chiasmatic visual pathway.
- The acquisition in the same patients of OCT and objective measurements of brain microstructure and volume shows that RNFL cannot be used as a surrogate for magnetic resonance imaging measurements of the brain.
- The correlations between morphological and clinical features tend to suggest a potential role for optic nerve head analysis in monitoring the progression of AD and as outcome measures in the assessment of any purported AD treatments.

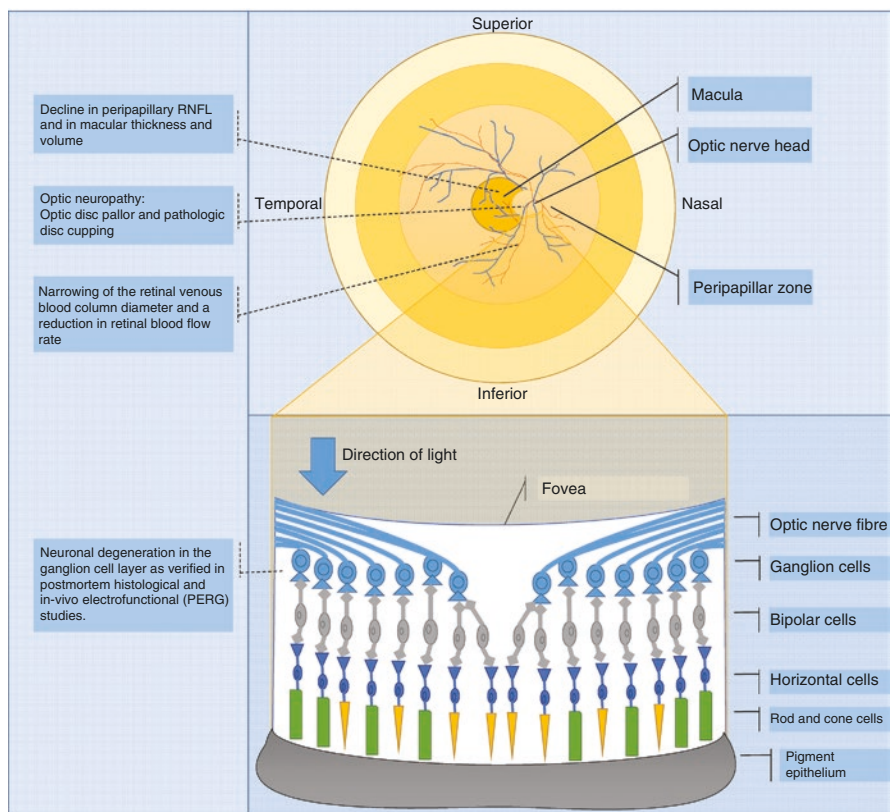


Fig. 13.2 Schematic representation of an entire retina with superimposed anatomic zones (upper panel **a**) and a schematic enlargement of a portion of the retina with the main cell classes (lower panel **b**). On the left panel (**c**) are summarized the findings from the OCT and electrophysiological studies in AD

Overall, these results suggest that degeneration of the retinal ganglion cells should be added to the constellation of neuropathologic changes found in patients with Alzheimer's disease.

Other neurodegenerative disorders, like Parkinson's disease and glaucoma, may enter in the differential diagnosis of RNFL thinning [125]. A particular mention merits the controversial association between primary open angle glaucoma (POAG) and AD. This is based on various indirect evidence of some shared genetic, histopathological and functional features [126, 127]. The association of AD and POAG is poorly supported by epidemiological studies [128, 129]. Nonetheless, for some authors glaucoma could be, in a subgroup of patients, the expression of a neurodegenerative process of the CNS that may be partially influenced by the risk factor of intraocular pressure (IOP) [130, 131]. However, the link between AD and the risk of developing glaucoma persists even without elevated IOP levels [78].

Future research in OCT as a biomarker of AD requires establishing a better specificity of OCT findings in AD. These and similar studies using OCT parameters of retinal changes will be important as objective in vivo outcome measures against which to evaluate new molecules purported to help in the treatment of AD.

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